

Vinylation of Aromatic Halides Using Inexpensive Organosilicon Reagents. Illustration of Design of Experiment Protocols

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Abstract: The preparation of styrenes by palladium-catalyzed cross-coupling of aromatic iodides and bromides with divinyltetramethyldisiloxane (DVDS) in the presence of inexpensive silanolate activators has been developed. To facilitate the discovery of optimal reaction conditions, Design of Experiment (DoE) protocols were used. By the guided selection of reagents, stoichiometries, temperatures, and solvents, the vinylation reaction was rapidly optimized with three stages consisting of ca. 175 experiments (of a possible 1440 combinations). A variety of aromatic iodides undergo cross-coupling at room temperature in the presence of potassium trimethylsilanoate using Pd(dba)₂ in DMF in good yields. Triphenylphosphine oxide is needed to extend catalyst lifetime. Application of these conditions to aryl bromides was accomplished by the development of two complementary protocols. First, the direct implementation of the successful reaction conditions using aryl iodides at elevated temperature in THF provided the corresponding styrenes in good to excellent yields. Alternatively, the use of potassium triethylsilanolate and a bulky "Buchwald-type" ligand allows for the vinylation reactions to occur at or just above room temperature. A wide range of bromides underwent coupling in good yields for each of the protocols described.

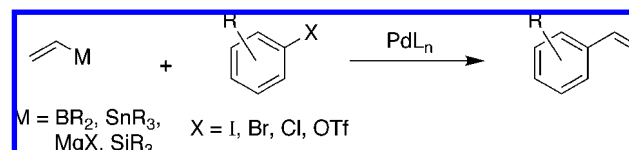
Introduction

Arylethenes (styrenes) are among the most important building blocks in organic synthesis. Substituted styrenes find widespread application in the synthesis of fine chemicals¹ and polymers.² Additionally, substituted styrenes serve as excellent substrates for synthetic endeavors because of the easily tunable electronic and steric properties of the alkene moiety. Many modern enantioselective reactions have been developed using styrenes as the test substrates such as inter alia asymmetric hydroformylation,³ hydroamination,⁴ dihydroxylation,⁵ epoxidation,⁶ and carboamination.⁷ Moreover, styrenes find increasing application

for the development of olefin metathesis, both as substrates and as ligands for metal catalysts.⁸

Although styrenes are classically prepared using the strongly basic conditions of dehydrohalogenation or dehydration,⁹ the advent of metal-catalyzed cross-coupling reactions has provided a range of milder methods for their preparation. This strategy involves the combination of an organometallic donor (generally a vinylmetallic species) with an organic acceptor (generally an aryl halide or pseudohalide) (Scheme 1).

Scheme 1



The simplest vinyl donor, ethylene, is primarily used on industrial scale to prepare substituted styrenes from aryl halides via the Heck reaction.¹⁰ Whereas ethylene is the most atom efficient vinyl donor, it requires special handling that is not generally amenable to laboratory scale synthesis. Thus, a range of organometallic vinyl donors that successfully transfer a vinyl unit to aryl halides have been developed over the past 20 years.

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These donors include boron-,¹¹ tin-,¹² and magnesium-based¹³ reagents and have been demonstrated to react with a range of organic acceptors. Boron-based reagents, including vinylboronic acid,^{11a} its related esters,^{11b,c} and cyclic anhydrides,^{11d} as well as potassium trifluoroborates,^{11e–g} cross-couple with a range of aryl bromides at elevated temperatures. Despite the utility of these vinylboron species, there are difficulties associated with their preparation. For example, the parent vinylboronic acid must be either trapped immediately as one of the aforementioned derivatives or freshly prepared prior to each use.^{11a} Although the vinylboronic acid derivatives are significantly more stable and are commercially available, their greater cost¹⁴ likely reflects the problems associated with their preparation.¹⁵ Additionally, these reagents often require elevated temperatures and/or higher pressures for reaction.¹¹ The vinylboron reagents are generally used with aryl bromides, whereas the vinyltributyltin reagents react with a broader scope of electrophiles, including aryl iodides, aryl and vinyl bromides, aryl and vinyl chlorides, and triflates, to afford high yields of the corresponding vinylated products.¹⁶ Unfortunately, vinyltributyltin suffers from the heavy metal toxicity generally associated with organotin species,¹⁷ which, taken together with its cost,¹⁸ can significantly deter its use on a larger scale. The Kumada-type coupling of vinylmagnesium bromide and chloride is more limited in the scope of electrophilic partner because of the basicity and nucleophilicity of the vinylating agent. For compatible substrates, however, good yields of the corresponding styrene are observed.¹³ Alternatively, dibromoethane has been used as a vinyl bromide precursor for the preparation of styrenes from arylboronic acids, in a process that inverts the acceptor/donor relationship.¹⁹

Each of these vinylmetallic reagents has one or more limitations. An ideal vinylation method would involve an inexpensive and nontoxic donor capable of transferring a vinyl group to a wide range of acceptors under mild conditions and be compatible with many functional groups.

Background

Silicon-based donors, first reported by Kumada and Tamao,²⁰ offer a number of advantages as compared to other organometallic reagents in palladium-catalyzed cross-coupling reac-

tions. In particular, organosilicon reagents are nontoxic²¹ and the silicon containing byproducts are easily removed. Moreover, the organosilicon subunit can be installed by a wide range of reactions, such that the cross-coupling event can be combined with other powerful carbon–carbon bond forming processes, such as ring-closing metathesis,²² silylformylation,²³ and silyl-carbocyclization.²⁴ The initial reports of silicon-based, palladium-catalyzed cross-coupling reactions involved the use of highly reactive, in-situ generated pentacoordinate silicon reagents such as fluorosilicates or bis(catechol)silicates.²⁵ Since those reports, a variety of alternative organosilicon donors have been developed, including trimethyl- and difluoromethyl-alkenylsilanes developed by Hiyama. These donors successfully react with aryl iodides, although they suffered from low reactivity and water sensitivity, respectively.²⁶ Alkenyltrialkoxysilanes^{27,28} and dimethylsilanols²⁹ are inherently more stable, and, with proper activation (typically a fluoride or hydroxide source), do participate in cross-coupling processes. Tetrabutylammonium fluoride trihydrate (TBAF) is the most commonly employed fluoride source because of its solubility in organic solvents.

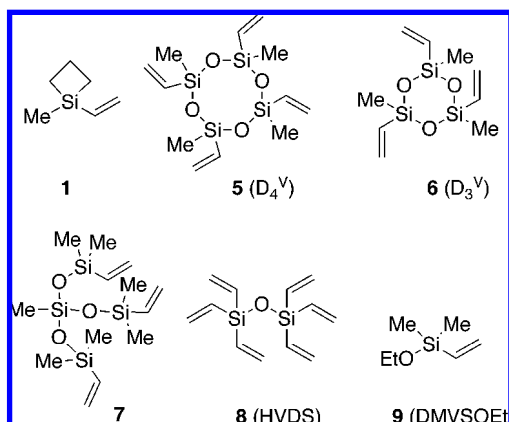
Recently, the use of Brønsted base activation (that avoids the requirement for fluoride activation) of alkenyldimethylsilanols in cross-coupling reactions has been developed in these and other laboratories.³⁰ Initially, potassium trimethylsilanoate (KOSiMe₃) served as the Brønsted base activator that facilitated the palladium-catalyzed cross-coupling between alkenyldimethylsilanols and aryl iodides.³¹ In addition, alkali carbonates^{30a} and alkali hydroxides^{30b} are also competent bases for the cross-coupling reactions. More recently, alkali metal alkenyl-, aryl-, and heteroaryldimethylsilanolates, prepared from the corresponding dimethylsilanols with a metal hydride, have been used directly in cross-coupling reactions without additional activators.³² Alkenylsilanolates cross-couple effectively with aryl iodides, bromides, and chlorides, to afford excellent yields under mild reaction conditions.³³

The transfer of a simple vinyl group using organosilicon-based, palladium-catalyzed cross-coupling was first demonstrated by Hiyama and co-workers.²⁶ The combination of vinyltrimethylsilane and 1-iodonaphthalene provided the corresponding styrene in excellent yield. In this case, the silicon moiety was activated for vinyl transfer using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and HMPA as the solvent. Jeffrey and co-workers have shown that a combination of potassium fluoride and tetrabutylammonium

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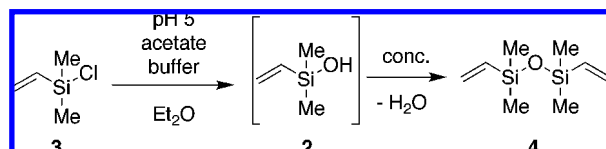
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Chart 1



chloride (TBACl) in toluene also promotes the vinylation reaction under milder conditions in excellent yields.³⁴ Alternatively, methylvinylsiletane (**1**, Chart 1), developed in these laboratories, reacts with a variety of aryl iodides under TBAF activation.³⁵ These reactions proceed at room temperature, provide good to excellent yields, and tolerate a broad range of functional groups. Subsequent mechanistic studies demonstrated that the combination of an alkenylsiletane and TBAF·3H₂O affords the unsaturated propylmethylsilanol in situ.³⁶ Because a dialkylsilanol is the active coupling intermediate, it follows that the use of dimethylvinylsilanol (**2**) would eliminate the requirement for the preparation of the siletane. Although dimethylvinylsilanol can be prepared in situ by the hydrolysis of chlorodimethylvinylsilane (**3**), it spontaneously dimerizes upon concentration, to form divinyltetramethyldisiloxane (DVDS, **4**, Scheme 2).

Scheme 2



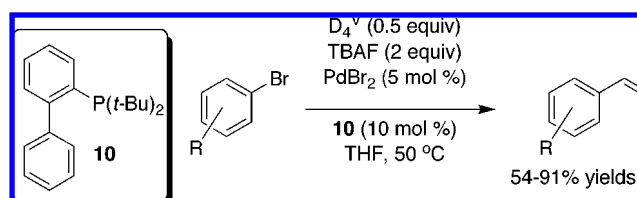
In view of the impracticality of using **2** directly, alternative organosilicon-based vinyl donors that generate dimethylvinylsilanol equivalents in situ must be considered (Chart 1). These donors include the aforementioned vinylsiletane **1**, as well as disiloxanes and polyvinylsiloxanes,³⁷ all of which require fluoride activation.

With the exception of reagent **1**, all of these compounds are commercially available. The poly(vinylsiloxanes) are inexpensive, stable, and widely available (Chart 1, **5–8**) and are competent vinyl donors in fluoride-activated, palladium-catalyzed cross-coupling reactions with aryl iodides.³⁷ Of the available polyvinylsiloxanes, 1,3,5,7-tetramethyl-1,3,5,7-tetra-methylcyclotetrasiloxane (D₄^V, **5**) was chosen because of its low cost and high coupling efficiency, as each of the four vinyl groups is available for transfer.³⁸ D₄^V affords high yields of substituted styrenes from aryl iodides and tolerates a range of

functional groups and steric environments on the aryl halide. Recently, the scope of electrophiles available to couple with D₄^V has been extended to aryl bromides by employing an electron-rich sterically hindered phosphine ligand, 2-(di-*t*-butylphosphino)biphenyl (BPTBP, **10**), to provide substituted styrenes in good to excellent yield (Scheme 3).³⁹

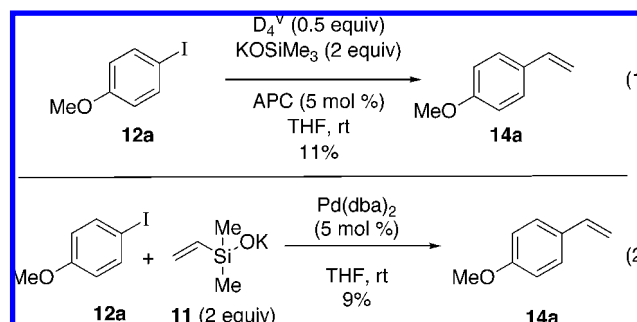
Despite these advances, fluoride activation is still required. To overcome this limitation, we began to investigate a non-fluoride-based vinylation reaction. Specifically, our aim was to develop a method for the vinylation of aryl halides that entailed the use of: (1) an inexpensive and readily available vinylsilicon donor, (2) an inexpensive and readily available activator, and (3) mild conditions that would be amenable to large-scale reactions. Our strategy was to initially develop conditions suitable for the vinylation of a range of aryl iodides and thereafter apply these conditions to aryl bromides (and chlorides) with modifications as needed.

Scheme 3



By analogy with the non-fluoride activation of organodimethylsilanol, the obvious starting point for the current study would have been the examination of dimethylvinylsilanol as a vinyl donor, but because this reagent is excluded (*vide supra*), our studies focused on two alternative approaches: (1) the use of the commercially available potassium dimethylvinylsilanol (11, Scheme 4) and (2) the development of a novel method for generation of **11** from simple precursors. To expedite this discovery process, Design of Experiment (DoE) protocols were enlisted.⁴⁰ The successful incorporation of this tool would allow for the examination of several reaction variables simultaneously and arrive at preparative conditions considerably faster than the standard individual- or parallel-strategy optimization.

Scheme 4



Results

1. Substrate Selection. The investigation began with two orienting experiments that were guided by our existing knowledge of fluoride-free cross-coupling reactions. 4-Iodoanisole

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(38) 1,3,5,7-Tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (Gelest, catalog no. SIT7900.0): \$67/mol.

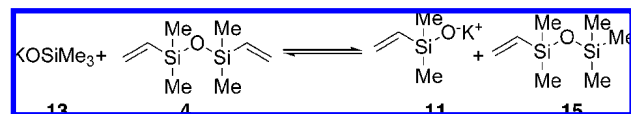
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(40) For an example of DoE in an academic setting, as well as an excellent introduction to the application of Design of Experiment, see: Aggarwal, V. K.; Staibitz, A. C.; Owen, M. *Org. Process Res. Dev.* **2006**, 10, 64–69, and references therein.

(**12a**) was chosen for the model study because it is electron-rich, which should make the model cross-coupling reaction more representative of a larger scope of aryl iodides in contrast to choosing a more reactive, electron-deficient substrate. First, **12a** was treated with D_4^V using 2 equiv of potassium trimethylsilanolate (KOSiMe₃, **13**) as the activator in place of TBAF (Scheme 4, eq 1). These conditions, which employ π -allylpalladium chloride dimer (APC) as the catalyst in THF, provided the corresponding styrene **14a** in only 11% yield after 24 h at room temperature. Second, the viability of the commercially available potassium dimethylvinylsilanolate (**11**) was examined (Scheme 4, eq 2). Unfortunately, even with 2 equiv of the silanolate, only a 9% yield of **14a** was observed after 24 h. A brief examination of KOSiMe₃ as the activator and Cy₃P as the ligand improved the yield of the reaction, but in no case was complete conversion observed. Therefore, it became clear that the simple adaptation of an existing method was not a feasible strategy to accomplish the fluoride-free vinylation.

These initial results suggested that the generation of an alkali dimethylvinylsilanolate was needed but not from deprotonation of the corresponding silanol. One such alternative was the in situ generation by the reaction of KOSiMe₃ and DVDS via silanolate exchange (Scheme 5). The tendency for organodimethylsilanols to form disiloxanes is often an obstacle in the development of their cross-coupling reactions. Disiloxanes are not competent donors under non-fluoride reaction conditions, and their formation unproductively consumes 2 equiv of the starting silanol. Whereas disiloxane formation is generally a “dead-end” under standard Brønsted basic activation, silanolate exchange conditions would employ disiloxane **4** as a starting point. Moreover, the reaction should be close to thermoneutral, wherein one silanolate (KOSiMe₃) would react with a disiloxane (DVDS) to generate another silanolate (potassium dimethylvinylsilanolate) in addition to new, mixed disiloxane. The results of this study are compiled in Table 1.

Scheme 5



The combination of 2.0 equiv each of KOSiMe₃ and DVDS at room temperature provided a marked improvement over the previous conditions. Changing the palladium source provided only a marginal effect (entries 1 vs 2), and increasing the temperature had no effect on the reaction (entries 2 vs 3). A comparison of two ligands provided interesting results. Whereas the bidentate 1,4-bis(diphenylphosphino)butane (dppb) inhibited the reaction (entry 5), the bulky, electron-rich BPTBP markedly improved the yield (entry 4). Differences in relative stoichiometry between KOSiMe₃ and DVDS improved the reaction significantly, but additional increases afforded no further benefit (entries 2 vs 6 and 7).

The moderate improvements that accrued from this preliminary study made it clear that many variables influence the outcome of the reaction. Although we were confident that, given enough time and effort, a systematic investigation of each variable would provide suitable reaction conditions, we nevertheless chose to streamline our investigation by employing Design of Experiment (DoE) protocols.⁴⁰ The implementation

Table 1. Vinylation Using KOSiMe₃ and DVDS^a

entry	DVDS, equiv	Pd source	temp, °C	yield, % ^b
1	2	Pd(dba) ₂	25	16
2	2	APC	25	24
3	2	APC	50	23
4 ^c	2	APC	25	66
5 ^d	2	APC	25	14
6	1	APC	25	40
7	0.5	APC	25	42

^a 0.5 mmol reactions at room temperature. ^b Yield determined by GC analysis versus an internal standard. ^c 5 mol % of **10** used as ligand. ^d 5 mol % of dppb used as ligand.

of DoE protocols would allow us to rapidly screen many reaction variables and determine their impact. Additionally, DoE protocols allow insight into the interaction of the reaction variables with one another.

2. Application of Design of Experiment Protocols. The DoE phase of the study was initiated by employing a rough D-optimal design, involving a limited number of reactions (24) but larger range of reaction variables (Table 2).⁴¹

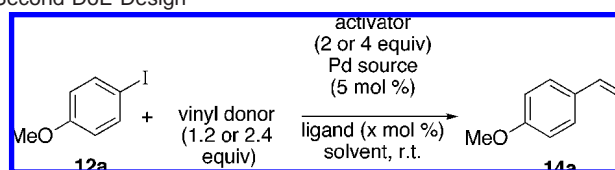
Table 2. Choice of Variables in First DoE Iteration

vinyl donor	activator	palladium source	ligand	solvent	ligand, mol %
DVDS	KOH	PdCl ₂	dppb	DMF	0
D_4^V	CsOH	Pd(dba) ₂	dppbO	dioxane	5
HVDS	KOSiMe ₃	APC	dppbO ₂	toluene	10
DMVSOEt			PPh ₃	THF	
			AsPh ₃		
			10		

In this design, six reaction factors were examined, including the choice of vinyl donor, activator, palladium source, ligand, and solvent. Additionally, the ligand loading was varied between 0, 5, and 10 mol %. On the basis of previous successes, D_4^V , DVDS, vinyl dimethylethoxysilane (DMVSOEt, **9**), and hexavinyl disiloxane (HVDS, **8**) were selected as potential vinyl donors.⁴² Potassium trimethylsilanolate (**13**) and cesium hydroxide (previously shown to promote the cross-coupling of aryl dimethylsilanols)³⁰ along with potassium hydroxide were chosen as activators. In all cases, 2.0 equiv of activator and 1.2 equiv of vinyl donor were used. Two palladium(II) sources (APC and PdCl₂) and one palladium(0) source (bis(dibenzylidene)acetone palladium [Pd(dba)₂]) were chosen, in combination with a range of ligands including dppb, the mono- and bisoxides of dppb (dppbO and dppbO₂), AsPh₃, and BPTBP. In each case, 5 mol % of palladium was used, and the ligand was varied as necessary to examine the palladium/ligand ratio. Dioxane, THF, toluene, and DMF were chosen as solvents. The reactions were

(41) For our first iteration, we employed a trial version of Fusion Pro developed by S-Matrix Corp.

(42) To maintain a level of consistency, we operated under the assumption that each silicon atom would be able to transfer one vinyl group, regardless of the number of vinyl groups attached. Under this assumption, DMVSiOEt could transfer single vinyl donor, whereas HVDS and DVDS could transfer two vinyl units, and D_4^V , four vinyl units.

Table 3. Top Ten Results from the Second DoE Design^a

run	activator	vinyl donor	Pd source	ligand	solvent	ligand, mol %	vinyl, equiv ^b	12 h yield, % ^c
40	KOSiMe ₃	HVDS	APC	dppbO ₂	DMF	5	2	98
89	KOSiMe ₃	DVDS	Pd(dba) ₂	Ph ₃ P	dioxane ^d	0	1	93
7	KOSiMe ₃	DMVSOEt	Pd(dba) ₂	dppb	DMF	0	2	89
31	KOSiMe ₃	DVDS	APC	dppbO	DMF	0	2	86
69	KOSiMe ₃	DMVSOEt	APC	dppbO ₂	DMF	0	1	85
64	KOSiMe ₃	DMVSOEt	APC	dppbO ₂	THF	0	2	85
26	KOSiMe ₃	HVDS	Pd(dba) ₂	dppbO	DMF	0	2	85
86	KOSiMe ₃	DVDS	Pd(dba) ₂	dppbO ₂	DMF	0	1	83
96	KOSiMe ₃	D ₄ ^V	Pd(dba) ₂	AsPh ₃	DMF	1	2	82

^a 0.5 mmol of aryl iodide used in the reaction. ^b The ratio of activator to vinyl equiv is always 2:1.2. ^c Yield determined by GC analysis versus an internal standard. ^d In this reaction, a 2:1 mixture of dioxane/DMF was inadvertently used.

performed (in an argon atmosphere) in a parallel fashion, using an 18-vessel carousel reactor,⁴³ and were monitored by GC analysis at 0.5, 3, and 12 h. The carousel was used to minimize variation in the reaction execution.

Overall, an improvement in the yield of **14a** was observed. The 24 reactions had an average yield of 15%, four of which gave no product. Comparing vinyl donors, DVDS, DMVSOEt, and HVDS each afforded yields greater than 28%, whereas D₄^V provided only 14–17% yield in the best cases. KOSiMe₃ and CsOH were both superior to KOH (average yields using each reagent: 20%, 16%, and 8%, respectively). The palladium sources were equally delineated, as PdCl₂ was inferior to both APC and Pd(dba)₂ (average yields: PdCl₂ – 10%, Pd(dba)₂ – 18%, APC – 18%). The reaction proceeded in all solvents tested, although DMF was slightly superior (average yields: toluene – 11%, THF – 12%, DMF – 20%, dioxane – 15%). The highest yield resulted from the combination of cesium hydroxide and DMVSOEt (**9**) in THF, with Pd(dba)₂/AsPh₃ as the catalyst/ligand system, which afforded a 42% yield of **14a** (GC analysis with internal standard). To verify the results, the reaction under optimal conditions was repeated in a standard reaction apparatus using a small increase in vinyl donor (2.0 equiv) and activator (3.0 equiv). After 12 h, a 51% yield (GC) was obtained.

Although only a modest improvement in the overall yield was observed, the results pointed to two critical features that further directed our efforts. Most notable was the consistent failure of certain reagents (KOH and PdCl₂), which were thus eliminated from future designs.⁴⁴ Second, it was gratifying to observe that the most successful reaction involved a combination of reagents strikingly different from those used in the initial studies. These two features convinced us to undertake a more comprehensive optimization using DoE protocols.

Despite having eliminated some choices, a complete matrix of the remaining variables would have provided 1440 discrete and reasonable combinations. However, by employing DoE

protocols for a second time, a set of 100 reactions that would provide the impact and key interactions of each of the seven categorical factors was identified.⁴⁵ A second, more refined D-optimal design again examined vinyl donor (D₄^V, DVDS, DMVSOEt, HVDS), activator (KOSiMe₃ and CsOH), solvent (DMF, THF, and dioxane), ligands (dppb, dppbO, dppbO₂, AsPh₃, and PPh₃), palladium source (Pd(dba)₂ and APC), and ligand loading (0, 5, and 10 mol %). In this iteration, the role of the vinyl donor stoichiometry was also examined (1.2 and 2.4 vinyl equiv per iodide), whereas the first design had kept the vinyl donor stoichiometry constant. The overall goal of this design was simply the selection of optimal reagents. We hoped the randomization protocols used in the design would allow us to more quickly evaluate the candidates in each aspect of the transformation and the interactions of the various factors.

With the help of the reactor carousel and GC autosampler, the entire design was executed and analyzed in just over 2 weeks. Nine sets of conditions were identified that provided greater than 80% yield (GC analysis) at 12 h reaction times (Table 3), including a best yield of 98% (run 40). Moreover, the ligandless reaction of KOSiMe₃ and DVDS in DMF with Pd(dba)₂ as the catalyst was remarkably fast, providing an 88% yield of **14a** within the first hour (run 7). More satisfying than the high yields, however, was the hierarchical delineation the data provided. From all of the results it was clear that KOSiMe₃ was superior to CsOH (average yield: KOSiMe₃ – 42% vs CsOH – 20%). Additionally, the reactions in DMF were superior to those in ethereal solvents in all head-to-head comparisons (average yields: DMF – 49%, THF – 36%, dioxane – 20%). Equally striking was the failure of a majority of ligands for palladium, which appeared to slow the reaction considerably. Instead, reactions containing either a weakly stabilizing ligand (dppbO₂)⁴⁶ or no ligand at all provided superior yields. Although D₄^V consistently underperformed (average yield: 17%), there was little difference between the remaining three vinyl donors (DVDS (39%), HVDS (42%), and DMVSOEt (42%)). In reactions that allowed for direct com-

(43) See Supporting Information for design of reactor.

(44) Toluene was eliminated because of the poor solubility of the reagent, as well as direction from concurrent work of other members in the group. Additionally, only modest benefit accrued from the use of bulky, electron-rich ligands, and ligand **10** was eliminated from consideration because of cost. Moreover, the literature suggests that these Buchwald-type ligands are required not for cross-couplings of this type.

(45) The calculations and analysis for this and the third iteration used the commercially available Design Expert 7; StatEase, Inc. 2021 East Hennepin Ave., Suite 480, Minneapolis, MN, 55413, 2006.

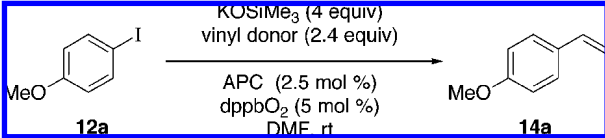
(46) Denmark, S. E.; Smith, R. C.; Tymonko, S. A. *Tetrahedron* **2007**, *63*, 5730–5738.

parison, the yield for each donor was found to be within experimental error. Similarly, the two palladium sources differed only marginally (average yield: APC – 36%, Pd(dba)₂ – 31%).

From these results, the optimal activator (KOSiMe₃), solvent (DMF), and ligand (dppbO₂) could be identified. In contrast, whereas DVDS, DMVSiOEt, and HVDS were clearly superior to D₄^V, they were essentially indistinguishable from each other. To discriminate among these vinyl donors, as well as verify the results of the design, the donors were rescreened in bench top reactions using the conditions (KOSiMe₃/dppbO₂/DMF) suggested by the DoE experiments.

As seen in Table 4, the results were similar to those obtained from the DoE. Again, D₄^V was inferior to the other vinyl donors (but did show an intriguing induction period) (entry 4). DVDS afforded the highest overall yield (95%) and a significantly faster reaction (entry 2), although HVDS and DMVSiOEt also provided respectable yields (87% and 89%, respectively). With both DVDS and DMVSiOEt, product decomposition was observed to varying extents. On the basis of these results and cost considerations,⁴⁷ DVDS was chosen as the optimal vinyl donor.

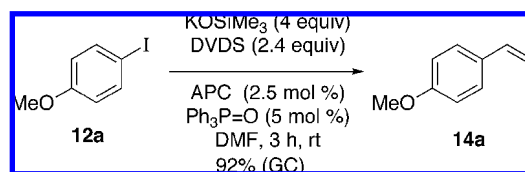
Table 4. Survey of Vinyl Donors

					
entry	vinyl donor	1 h yield, % ^a	3 h yield, % ^a	6 h yield, % ^a	
1	HVDS	65	81	87	
2	DVDS	83	95	91	
3	DMVSiOEt	63	89	68	
4	D ₄ ^V	10	59	65	

^a Determined by GC analysis versus an internal standard.

To minimize costs, the use of triphenylphosphine oxide was evaluated as a replacement for dppb(O)₂. The reactions behaved identically, and Ph₃P=O was deemed to be a suitable, if not preferable, substitute (Scheme 6).

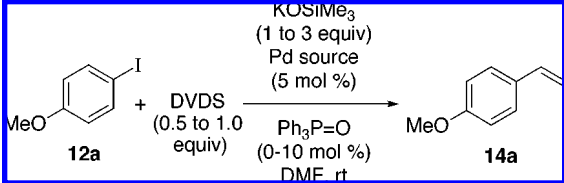
Scheme 6



With a full set of reaction components in hand, a routine reaction optimization still remained. To facilitate this process, a third iteration of DoE protocols was designed to examine the optimal stoichiometries of the vinyl donor, activator, and triphenylphosphine oxide. This iteration consisted of 40 reactions selected using a central composite design, 20 with both Pd(dba)₂ and APC, and was again monitored by GC analysis, at 1 and 3 h time points.⁴⁸ The 10 highest yielding experiments are presented in Table 5.

Gratifyingly, high yields (ranging from 76% to 97%) were observed in all cases with an overall average yield of 81% at 1 h and 88% at 3 h. The reactions using APC showed an average

Table 5. Highest Yielding Results from Third DoE Iteration

						
run ^a	KOSiMe ₃ , equiv	Ph ₃ P=O (x mol %)	vinyl, equiv	Pd source	1 h yield, % ^b	3 h yield, % ^b
22	1.41	2	1.80	APC	74	97
9	2.00	5	1.50	Pd(dba) ₂	90	97
13	2.00	5	1.50	APC	84	96
15	2.00	5	1.50	Pd(dba) ₂	91	96
33	2.59	2	1.20	Pd(dba) ₂	87	96
28	2.59	8	1.20	Pd(dba) ₂	96	96
23	1.41	8	1.80	APC	74	95
24	2.00	5	1.50	APC	80	94
32	2.00	5	1.50	APC	82	94
2	1.41	8	1.80	Pd(dba) ₂	77	92

^a Reaction conditions: 0.5 mmol of iodide reactions at room temperature in a parallel reactor. ^b Yields determined by GC analysis versus an internal standard (naphthalene).

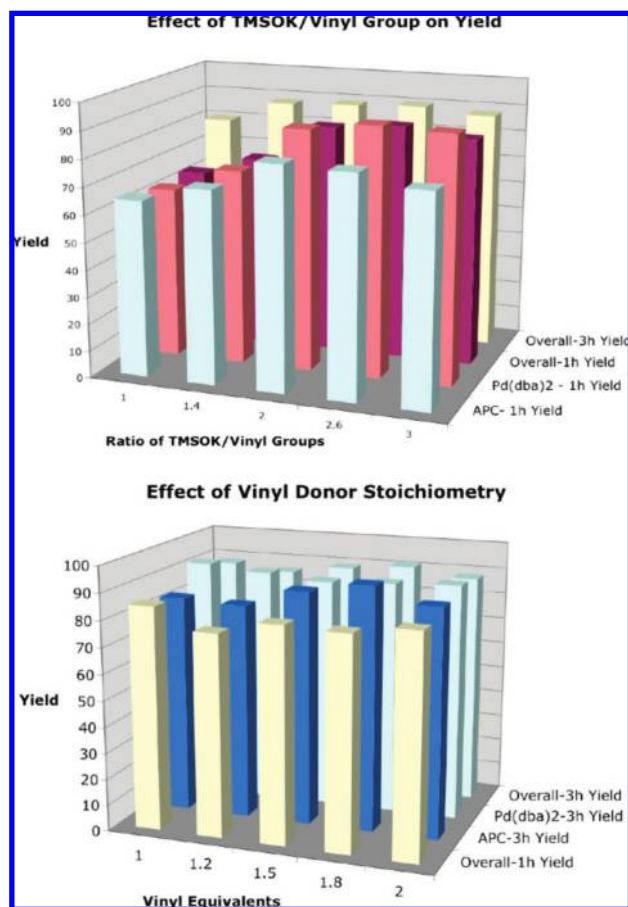


Figure 1. Effect of vinyl donor and activator stoichiometry on yield from the third DoE.

yield of 78% at 1 h and 88% at 3 h, whereas those with Pd(dba)₂ showed 84% at 1 h and 88% at 3 h. From these results, there is still little difference between these two sources, although Pd(dba)₂-catalyzed reactions were slightly faster. The impact of the vinyl groups and KOSiMe₃ stoichiometry was less pronounced. The comparisons of vinyl stoichiometry to yield and KOSiMe₃/vinyl donor ratio to yield are presented in Figure 1.

(47) DVDS, \$52/mol, Gelest cat. # SID4613; DMVSiOEt, \$231/mol, Gelest cat. # SIV9070; HVDS, \$1,320/mol, Gelest cat. # SIH6162.

(48) See Supporting Information for experimental details.

Whereas the maximum yield of **14a** was observed at a ratio of KOSiMe₃/vinyl group between 2 and 2.6 equiv, there was no obvious dependence on the DVDS stoichiometry. On the basis of these results, the optimal conditions were selected as follows: 3.5 equiv of KOSiMe₃, 0.75 equiv of DVDS, 5 mol % of Pd(dba)₂, and 5 mol % of Ph₃P=O in DMF at room temperature. Moreover, these conditions translated well to a preparative scale (2 mmol), affording an 81% yield of **14a** in 1 h.

3. Preparative Vinylations of Aryl Iodides. The optimized reaction conditions were general for a range of aryl iodides (Table 6). The electron-rich 4-iodoanisole and 2-iodoanisole substrates were transformed smoothly to the corresponding styrenes (entries 1, 7) in 80% and 68% yield, respectively. Electron-deficient substrates, including ethyl 4-iodobenzoate, additionally reacted smoothly to provide the corresponding styrenes in 76–81% yields (entries 2, 5, 6). The vinylation of the ethyl ester-containing substrate (entry 2) is notable, as the productive coupling outcompetes ester cleavage known to occur with KOSiMe₃. Additionally, a variety of functional groups are well tolerated, including esters, nitro groups, and cyano groups. There appears to be little effect on the reaction yield due to steric or electron effects as all of the substrates described are between 68% and 81% yield. Further, the preparation of 1-vinylnaphthalene and 2-vinylnaphthalene demonstrates tolerance of moderate steric hindrance in the reaction, without any deleterious effect on yield (entries 2 and 7). Groups bearing an acidic proton, including amines and secondary amides, did not react. The successful examples illustrate the preparation of a range of substituted styrenes under very mild reaction conditions. It is important to note that these reactions exhibited a significant exotherm in some cases (for example, the internal temperature of the reaction of **12a** warmed from 25 to 52 °C) in the first 10 min of the reaction. Decreasing the catalyst loading attenuated the exotherm somewhat, but even using 2.5 mol % palladium, a similar rise in temperature was observed for entry 2. This was not the case for all substrates, however.

Table 6. Preparative Vinylation of Aryl Iodides^a

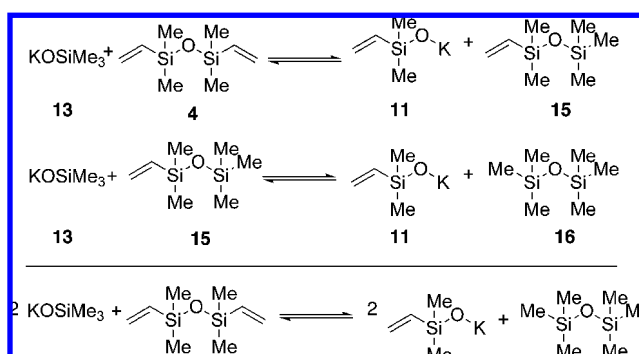
$ \begin{array}{c} \text{Me} \quad \text{Me} \\ \quad \\ \text{Si} - \text{O} - \text{Si} \\ \quad \\ \text{Me} \quad \text{Me} \end{array} + \text{Aryl-I} \xrightarrow[\text{DMF, rt}]{\text{KOSiMe}_3 \text{ (3.5 equiv)}, \text{Pd(dba)}_2, \text{Ph}_3\text{P=O}} \text{Aryl-CH=CH}_2 $					
entry	aryl	product	Pd, mol % ^b	time, h	yield, % ^c
1	4-(MeO)C ₆ H ₄ –	14a	5	1.5	80
2	4-(EtO ₂ C)C ₆ H ₄ –	14b	2.5	0.5	81
3	4-(BnO)C ₆ H ₄ –	14c	5	1.5	74
4	4- <i>t</i> -BuC ₆ H ₄ –	14d	5	4	69
5	4-(NC)C ₆ H ₄ –	14e	2.5	0.5	81
6	3-(O ₂ N)C ₆ H ₄ –	14f	2.5	1	76
7	2-MeOC ₆ H ₄ –	14g	5	14	68
8	1-naphthyl	14h	5	2.5	80

^a 2 mmol scale reaction. ^b 1 equiv of triphenylphosphine oxide per Pd(dba)₂. ^c Yield of isolated product.

4. Investigation into the Silanolate Exchange. The silanolate exchange reaction between DVDS and KOSiMe₃ is crucial for the efficient generation of the active dimethylvinylsilanolate nucleophile. Therefore, further investigation into the exchange was required to aid in further development of the vinylation. In

an earlier study of the exchange process, a reaction temperature of 100 °C in toluene was required for the complete conversion to hexamethyldisiloxane and potassium dimethylvinylsilanolate as observed by ¹⁷O NMR spectroscopy (Scheme 7).⁴⁹

Scheme 7



To compare the results from this study with those described herein, the silanolate exchange was examined in toluene and DMF and was monitored by ¹H NMR spectroscopy. In toluene, no exchange was observed between KOSiMe₃ and DVDS at room temperature (Table 7, entry 1), but partial exchange was observed upon heating to 50 °C (entry 2). However, in DMF, nearly complete exchange occurs within 15 min at room temperature (entry 4). Because the two silanolates possess similar steric environments, the preference for formation of potassium dimethylvinylsilanolate and hexamethyldisiloxane at equilibrium is most likely due to electronic differences. Potassium trimethylsilanolate is more basic than the corresponding dimethylvinylsilanolate because of the presence of three donating alkyl groups, whereas the vinyl group is less donating. That this exchange is under equilibrium control was established by carrying out independent reactions that employed varying amounts of each reagent. In an experiment with a large excess of KOSiMe₃ (entry 4), nearly all of the DVDS was converted to the corresponding silanolate. In contrast, using an excess of DVDS (entry 6) consumes most, but not all, of the limiting

Table 7. Effect of Solvent and Stoichiometry on Silanolate Exchange^a

$ \text{KOSiMe}_3 + \text{DVDS} \rightleftharpoons \text{KOSiMe}_3 + \text{DVDS} $					
entry	solvent	temp, °C	ratio 13/4 (init)	ratio 13/vinyl (init)	ratio 11/4 (obsd)
1	toluene	25	5:1	2.5:1	<5:95
2		50 ^b	5:1	2.5:1	55:45
3		60 ^b	5:1	2.5:1	77:23
4	DMF	25	5:1	2.5:1	96:4
5		25	2.5:1	1.2:1	90:10
6		25	1.2:1	0.6:1	83:17

^a Reactions run in an NMR tube, and analyzed by ¹H NMR analysis.

^b After 1 h of heating. ^c Quantitation of **13** versus **11** was difficult because of overlap of signals.

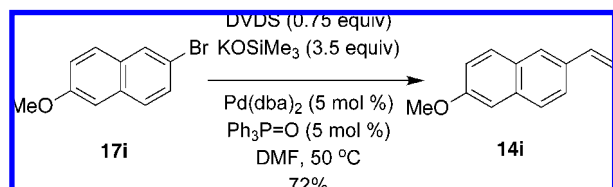
(49) Klapshina, L. G.; Kurskii, Y. A.; Liepins, E.; Terman, L. M.; Shaulova, S. V. *Organomet. Chem. USSR* **1991**, *4*, 16–18.

KOSiMe₃, implying that the basicities of the two silanolates are not very different.⁵⁰ Employing nearly equimolar ratios of DVDS and KOSiMe₃ converts nearly all of the DVDS to potassium dimethylvinylsilanolate. These exchange studies reinforce the results of the third DoE study, which showed that a large excess of potassium trimethylsilanolate and smaller excess of DVDS (0.75 equiv) are required.

5. Vinylation of Aryl Bromides. Although the results of the vinylation of aryl iodides were satisfying, the primary goal of this investigation was to develop a fluoride-free vinylation for aryl bromides. The challenge of engaging aryl bromides in palladium-catalyzed cross-coupling reactions arises from the greater C–Br bond strength relative to that of aryl iodides.⁵¹ This difference is most pronounced in the oxidative addition step of the catalytic cycle of the cross-coupling reactions. The two most common strategies used to overcome this limitation are to raise the reaction temperature or to employ electron-rich, bulky phosphine ligands for palladium that lower the barrier required for oxidative addition.

To this end, a two-pronged strategy was developed that would both capitalize upon the results of the current study and exploit the wide range of ligands currently available for modulating the palladium center. Initially, the conditions developed for iodides were applied in a test case for the vinylation of 2-bromo-6-methoxynaphthalene, **17i** (Scheme 8). By executing the reaction at 50 °C, **17i** was smoothly converted to the corresponding styrene within 3 h, to afford a 72% yield of **14i**.

Scheme 8



Unfortunately, these conditions were not applicable to other aryl bromides. Incomplete reactions and irreproducible results were obtained in DMF at a range of temperatures. A significant amount of palladium black was observed in these reactions, most likely arising from insufficient stabilization of the catalyst. Moreover, dimethylamine was qualitatively noted upon completion of these reactions, likely due to the decomposition of DMF caused by KOSiMe₃ at elevated temperatures. Therefore, the solvent was changed to THF to examine the vinylation of 4-bromoanisole, **17a**, as it was comparable to DMF in the reaction with aryl iodides. Complete consumption of the bromide was observed in 6 h (at reflux), along with a 70% yield (GC) of 4-vinyanisole.⁵² Varying the DVDS stoichiometry did not improve the yield, although a slight increase in the amount of DVDS provided a faster reaction. These conditions were applicable on a preparative scale and were applied to a brief survey of aryl bromides (Table 8).

A variety of aryl bromides were tested in the coupling reaction, and the corresponding styrenes were obtained in modest to excellent yield. Substrates bearing electron-withdrawing

groups in the *para*- (entries 2, 3, and 6) and *ortho*-positions (entry 7) provided reasonable to good yields of the corresponding styrenes. The reaction is compatible with some carbonyl groups, for example, a ketone (entry 3), although an amide was less well tolerated (entry 6), and esters did not survive the coupling conditions, likely due to cleavage by KOSiMe₃. It is worth emphasizing the successful coupling of 4-bromobenzophenone, as it demonstrated the mild reaction conditions associated with this protocol, whereas this substrate failed in the reactions in DMF. Some heterocycles are also well tolerated in the reaction, as evidenced by the high-yielding vinylation of 3-bromoquinoline (entry 4). Moreover, the applicability of this reaction to larger scale was demonstrated by the isolation of 3-vinylquinoline (entry 4) in 91% yield on a 20 mmol scale.

Table 8. Preparative Vinylation of Aryl Bromides Using DVDS

entry	aryl	product	time, h	yield, % ^b
1	4-(MeO)C ₆ H ₄ –	14a	1	71
2	4-ClC ₆ H ₄ –	14j	3	55
3	4-(PhC(O))–C ₆ H ₄	14k	3	93
4	3-quinolyl–	14l	3	91 ^c
5	6-MeO-2-naphthyl–	14i	3	70
6	4-(NMe ₂ C(O))C ₆ H ₄ –	14m	3	34
7	2-CF ₃ C ₆ H ₄ –	14n	3	52

^a 2 mmol scale reactions. ^b Isolated yield. ^c 20 mmol scale.

This protocol was successful for a range of moderately activated aryl bromides. Although 4-bromoanisole and 6-methoxynaphthyl bromide reacted smoothly, other electron-rich bromides were less suitable. In addition, sterically hindered substrates bearing electron-donating groups generally were recovered unreacted. These failures presumably stem from the inability to engage the aryl bromides in the oxidative addition step under these conditions. Increasing the reaction temperature afforded up to a 30% yield of styrenes in selected cases, indicating that oxidative addition was occurring. Unfortunately, the reactions never reached completion, most likely due to catalyst death, even in the presence of stabilizing ligands such as triphenylphosphine.

To address these shortcomings, new conditions that allowed the vinylation to occur at lower temperatures were needed. Under the assumption that the barrier to oxidative addition needed to be lowered, ligands that facilitate this key step at lower temperatures were tested. The study began by examining the vinylation of 4-bromoanisole (**17a**) using a series of dialkyl-2-biphenylphosphine ligands developed by Buchwald and co-

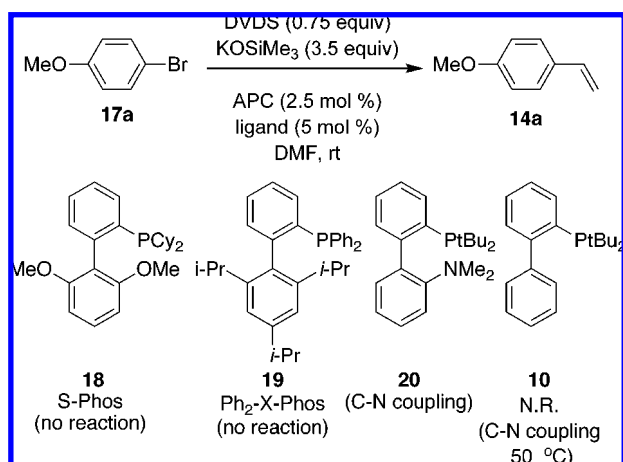
(50) For comparison, allylic alcohol has a pK_a of 15.5, whereas ethanol has a pK_a of 15.9: Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795–798.

(51) Relative bond dissociation energies: C₆H₅–I, 65 kcal/mol; C₆H₅–Br, 81 kcal/mol. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.

(52) The distribution of products was strikingly dependent on the source of the KOSiMe₃. In reactions using KOSiMe₃ purchased from Gelest (two distinct lots), the reduction of the aryl bromide to the corresponding arene was observed at elevated temperature both in the presence and in the absence of a ligand. Moreover, from a number of deuterium labeling experiments, it was determined the hydride was coming from the KOSiMe₃ obtained from Gelest. In reactions using KOSiMe₃ obtained from Aldrich (two distinct lots), no such reduction was observed. To resolve this discrepancy, KOSiMe₃ was prepared by the Gelest method and was found to be indistinguishable from the material obtained from Aldrich. Therefore, the use of KOSiMe₃ from Aldrich for the vinylation of aryl bromides is recommended. The contaminant in the Gelest KOSiMe₃ that is responsible for the reduction was never identified.

workers (Scheme 9).⁵³ No reaction was observed using S-Phos or Ph₂X-Phos, although using ligand **20**, a significant amount of aryl bromide was consumed at room temperature. In this case, 4-methoxydimethylaniline was formed from C–N coupling of **17a** with dimethylamine liberated by the decomposition of DMF, promoted by KOSiMe₃. In the presence of BPTBP (**10**), no reaction was observed at room temperature. However, at 50 °C the aryl bromide was completely consumed and **14a** was observed, although C–N coupling was again observed and was now the major product. At this point, it became clear that the small, nucleophilic KOSiMe₃ was responsible for the unwanted C–N coupling byproducts (indirectly via promoting the decomposition of DMF), thereby stimulating the search for a different activator.⁵⁴

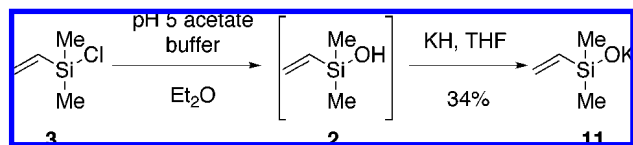
Scheme 9



6. Potassium Dimethylvinylsilanolate as the Vinyl Donor.

The most straightforward solution to replace KOSiMe₃ was to eliminate the requirement for activation by employing the preformed potassium dimethylvinylsilanolate (**11**). Although only traces of product were seen using commercially available **11**, no C–N coupling was observed. To avoid the possibility that these results were caused by impurities in the commercial material, **11** was prepared by the one-pot conversion of chlorodimethylvinylsilane to the silanol and subsequent deprotonation to afford a 34% yield on a 5 g scale (Scheme 10).⁵⁵

Scheme 10



Using prepared **11**, productive vinylation of **17a** was observed at room temperature without C–N coupling (Table 9, entry 1). Increasing the number of equivalents of silanolate had little effect on the yield, whereas increasing the temperature improved the conversion (entries 2 and 3). Concomitant increases in temperature and stoichiometry provided a 63% yield of **14a** in

Table 9. Optimization of the Cross-Coupling with **11**

entry	11, equiv	temp, °C	time, h	yield, % ^a	17a, % ^a
1	1.3	25	2	25	60
2	2.0	25	2	28	67
3	1.3	50	0.5	43	31
4	2.0	50	2	63	18

^a Yield determined by GC analysis (vs an internal standard).

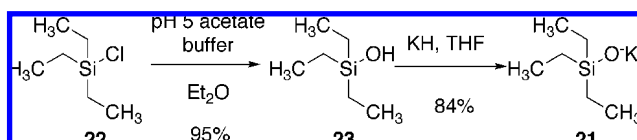
2 h, but no further conversion was observed (entry 4). The remainder of the mass balance was unreacted **17a**.

Incomplete reaction can result from a number of factors including disiloxane formation (observed), which would consume **11**. Although the conversion could be increased by employing 4.0 equiv of the silanolate, complete conversion of the aryl bromide was never observed. To suppress the disiloxane formation, the sodium dimethylvinylsilanolate and the potassium diisopropylvinylsilanolate were prepared to alter the nucleophilicity and steric environment of the vinylsilanolate, respectively. With sodium dimethylvinylsilanolate, no reaction was observed under a variety of conditions, whereas the use of potassium diisopropylvinylsilanolate at 60 °C in THF with **10** provided only small amounts of **14a**. Thus, use of a preformed vinylsilanolate was not the answer.

7. Potassium Triethylsilanolate as the Activator. At this point, the successful vinylation of electron-rich or sterically hindered aryl bromides was stymied by two different problems. The successful coupling of these substrates with **11** in the presence of **10** demonstrated that a judicious choice of ligands was crucial, but also that disiloxane formation must be avoided. On the other hand, disiloxane formation was not a problem with KOSiMe₃/DVDS, but undesired C–N coupling predominated in the presence of ligand **10**. Thus, the silanolate exchange process was revisited with the objective of identifying a new activator for DVDS that was capable of facilitating the silanolate exchange (thus generating **11** in situ) while avoiding the preferential C–N coupling associated with KOSiMe₃.

A suitable activator should exhibit the following features: (1) it should contain no transferable groups, (2) it should exhibit electronic properties similar to those of KOSiMe₃ and facilitate silanolate exchange, but (3) it should be bulkier than KOSiMe₃ to prevent loading on the ArylPdL_nX intermediate, and (4) it should not decompose DMF at temperatures required for vinylation. With these criteria in mind, potassium triethylsilanolate (KOSiEt₃, **21**) was selected for testing. The preparation of KOSiEt₃ began with the buffered hydrolysis of commercially available chlorotriethylsilane (**22**), to afford triethylsilanol (**23**) (Scheme 11). Unlike trimethyl- and dimethylvinylsilanol, which

Scheme 11



(53) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

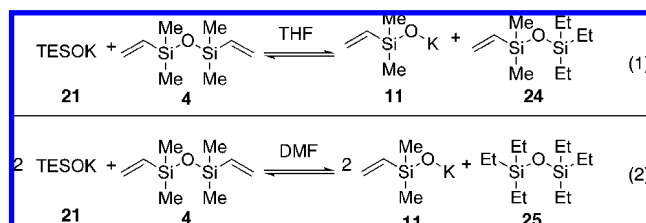
(54) Indeed, even in the absence of DVDS, 4-bromoanisole was converted to the aniline by C–N coupling when combined at 50 °C with KOSiMe₃ and ligand **10**.

(55) The low yield of **11** is attributable to the dimerization of **2**.

were not isolable because of their rapid dimerization, triethylsilanol was obtained in 95% yield upon distillation. The silanol was then treated with potassium hydride in THF to afford an 84% yield of KOSiEt_3 (**21**) as a white powder.

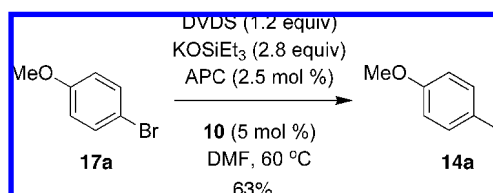
As alluded to above, for KOSiEt_3 to be an effective activator it must exchange with DVDS. In THF, the exchange was complete within 15 min by ^1H NMR analysis.⁵⁶ Interestingly, only one exchange was observed, in which the mixed disiloxane and 1.0 equiv of the dimethylvinylsilanolate were formed (Scheme 12, eq 1). However, in DMF, the exchange was rapid and complete as was observed for KOSiMe_3 (eq 2).

Scheme 12



The first cross-coupling experiment employed KOSiEt_3 (2.8 equiv), DVDS (1.2 equiv), and **17a** with 2.5 mol % of APC and 5 mol % of **10** at 60 °C in DMF.⁵⁷ This reaction provided a 63% yield (GC) of the corresponding styrene within 30 min with no bromide remaining (Scheme 13). More gratifying was the observation that the reaction proceeded at room temperature (54% in 24 h). Other ligands did not improve the reaction; the use of X-Phos provided a 53% yield in 2 h, and S-Phos was completely ineffective. Interestingly, under no conditions was the product of C–N coupling detected, further supporting the hypothesis that KOSiMe_3 was responsible for these side products.

Scheme 13



To improve the amount of productive coupling, different stoichiometries of KOSiEt_3 and DVDS were examined at 50 °C (Table 10). Increasing the amounts of DVDS or KOSiEt_3 alone had no overall effect (entries 1 vs 4, 2 vs 5), whereas increasing the ratio of KOSiEt_3 to DVDS markedly increased the initial reaction rate but not the overall yield (entries 1 vs 2). In contrast, the reaction temperature did influence the yield of the coupling. Decreasing the temperature from 50 to 23 °C afforded a 77% yield of the corresponding styrene after 12 h, although 15% of the starting material remained. A slight increase to 35 °C with a concomitant increase in KOSiEt_3 (4.0 equiv)

(56) See Supporting Information for experimental details.

(57) The ratio of KOSiEt_3 to DVDS was chosen to keep the ratio of activator to available vinyl group consistent with the aryl iodide vinylation reactions. In the case of the iodides, 3.5 equiv of KOSiMe_3 and 0.75 equiv of DVDS were empirically identified from the DoE optimization. Because both vinyl groups of DVDS are available, the ratio of activator to vinyl group is 3.5 to 1.5 (2.3 to 1). Under an original (but later disproven) assumption that only one dimethylvinylsilanolate was available under KOSiEt_3 activation, we began with a 2.3 to 1 ratio of KOSiEt_3 to DVDS (in practice 2.8 to 1.2).

Table 10. Effect of Stoichiometry on Vinylation with KOSiEt_3

entry	KOSiEt_3 , equiv	DVDS, equiv	time, h	14a , % ^a	17a , % ^a
1	3	3	0.5	14	87
			1	21	71
			3	41	42
			6	53	20
2	3	2	0.5	48	31
			1	51	21
			3	57	10
			6	58	4
3	3	1	0.5	54	10
			1	58	4
4	4	3	0.5	34	54
			1	41	40
			3	49	31
5	4	2	0.5	49	25
			1	56	12
			3	58	8

^a Determined by GC analysis (vs internal standard).

provided an 85% yield (GC) with complete consumption of starting material after 4 h. Under these conditions, **14a** was isolated in 74% yield on a 2.0 mmol scale.

8. Preparative Vinylation of Aryl Bromides. A series of aryl bromides was surveyed to test the generality of these vinylation conditions (Table 11). The substrates examined represented a range of electronic and steric influences and contained a number of sensitive functional groups. Aryl bromides with substituents in the 4-position worked well, affording the corresponding styrenes in 50–74% yield (entries 1–5). Electron-rich aryl bromides including those bearing methoxy- or dimethylamino- substituents worked well (72–74% yields, entries 1, 2, and 7). Similarly, electronically neutral substrates such as 1-bromonaphthalene or 3-bromoquinoline also

Table 11. Styrenes from Aryl Bromides^a

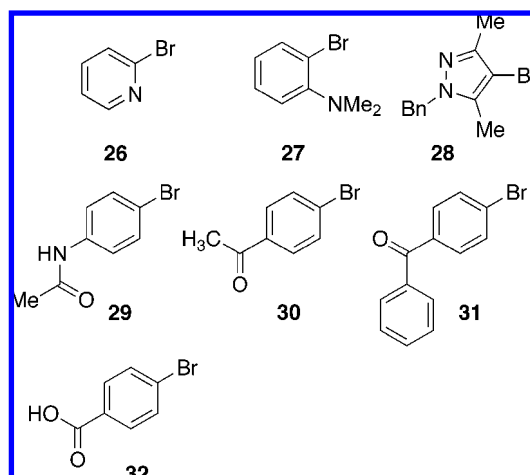
entry	aryl	product	temp, °C	time	yield, % ^b
1	4-(MeO)C ₆ H ₄ –	14a	35	4	74 ^c
2	4-(Me ₂ N)C ₆ H ₄ –	14o	40	24	70 ^{c,d}
3	4-ClC ₆ H ₄ –	14j	40	3	50
4	4-(Me ₂ NCO)C ₆ H ₄ –	14m	40	2	69
5	4-(<i>t</i> -BuO ₂ C)C ₆ H ₄ –	14p	40	2	60
6	3-(TBSOCH ₂)C ₆ H ₄ –	14q	40	24	64 ^{c,e}
7	2-(MeO)C ₆ H ₄ –	14g	40	24	72 ^{c,f}
8	2,4,6-Me ₃ C ₆ H ₂ –	14r	40	24	99 ^c
9	1-naphthyl–	14h	25	12	80 ^g
10	6-(MeO)-2-naphthyl–	14i	25	4	82
11	3-quinolyl–	14l	25	2	79
12	4-BrC ₆ H ₄	14s	40	2	48 ^h

^a 2 mmol scale reactions. ^b Isolated yield. ^c 4.0 equiv of KOSiEt_3 , 2 equiv of DVDS used. ^d Contains 15% bis(4,4'-dimethylamino)stilbene. ^e THF used as solvent. ^f Contains 15% 2-bromoanisole. ^g Contains 5% 1-vinylnaphthalene. ^h 6.0 equiv of KOSiEt_3 , 2.6 equiv of DVDS used.

provided good yields of the corresponding styrenes (entries 9 and 11). Electron-deficient substrates provided diminished yields likely due to competitive anionic polymerization of the corresponding styrene (entries 3–5). Steric hindrance does not interfere with the reaction, as evidenced by the preparation of 2-vinylmesitylene and 2-vinylanisole (entries 7, 8). A variety of functional groups are well tolerated, including amides, amines, ethers, esters, and chlorides. Although these reaction conditions caused the cleavage of a TBS ether, replacing DMF with THF allows the styrene to be formed in good yield without deprotection (entry 6).

Despite the successful vinylation of a variety of bromides, the reaction is not without limitations. The substrates in Chart 2 did not afford the corresponding styrenes using the developed reaction conditions. First, substrates bearing acidic hydrogens are not tolerated in the reaction. Second, styrenes bearing strongly electron-withdrawing groups, such as ketones, polymerized under the reaction conditions, whereas they were tolerated in the reactions in THF. Moreover, hindered substrates containing a Lewis basic site failed in the reaction including the *N*-benzylpyrazole and 2-(dimethylamino)bromobenzene.

Chart 2



Discussion

The primary goal of this project, the development of a non-fluoride-based vinylation of aryl halides, required a method for the generation of a dimethylvinylsilanolate salt in situ. Unlike the coupling of alkenyldimethylsilanols, which are stable, storable substances, the parent dimethylvinylsilanol is too prone to dimerization to make it a useful reagent.

1. Design of Experiment Protocols. Because the parameters for a successful reaction were unknown, the DoE process was initiated with a wide array of variables, including those that had not worked in any previous cases. The first iteration of the DoE plan was designed to refine the selection of variables and eliminate those that showed no promising results. The concept was successful, as KOH, PdCl₂, and toluene were each eliminated given their low success rate, thus allowing fewer variables to be studied with greater frequency in the second design.

The second iteration of DoE was designed with the intent of reagent selection. Whereas DoE protocols are used routinely in the optimization of reaction conditions, there are fewer examples that employ DoE protocols for reactions development, that is,

reagent selection. In this regard, the success of the design was mixed, as the superior activator (KOSiMe₃), solvent (DMF), ligand (dppbO₂), and vinyl donor stoichiometry (2.0 equiv) were clearly identified. However, the identification of optimal vinyl donor, palladium source, and ratio of ligand to palladium was not achieved. Although it was satisfying that three of the four vinyl donors afforded high yields, further investigation was required to distinguish the three. Similarly, there was no distinction provided between APC and Pd(dba)₂. A further shortcoming of the design involved establishing the ligand/palladium ratio. In part, this failure could be attributed to the nature of the optimal bisphosphine bisoxide ligands, known in related systems to prevent catalyst decomposition pathways.⁴⁶ Despite these inconclusive aspects, the overall benefit of the design was seen in the increase in yield from 43% to 95%.

The third iteration of the DoE involved the more common optimization of reagent stoichiometry. A central composite design was selected because of its ability to rapidly accomplish this optimization with good statistical relevance. Because of the high yields (>90%) already observed, center points could be selected with a reasonable amount of confidence that optimal conditions would be found. This choice assumes that the optimal stoichiometry is not much different from the conditions at hand. This assumption proved valid, as the optimal conditions were easily identified. More importantly, DoE protocols allow for higher-order mathematical analyses. From the quadratic model generated by the DoE software, the yields at each time point can be visualized in three dimensions. These graphs (Figure 2) demonstrate the interaction of the following factors: (1) the ratio of KOSiMe₃ to vinyl group (*x*-axis), (2) equivalents vinyl group (*y*-axis), and (3) yield of **14a** (%), (*z*-axis). Each surface model represents a given time point (1 and 3 h) and is delineated by the palladium source.

Two aspects of the reaction are immediately apparent from the above graphs. The first is the difference in reaction rates between APC and Pd(dba)₂. The reactions that use Pd(dba)₂ are apparently faster than those using APC, but only at higher KOSiMe₃/vinyl ratios. Despite the high initial rates, the APC reaction proceeds to similar yields within 3 h. Most likely, this difference in rate is related to the reduction of palladium(II) to palladium(0).⁵⁸ The second is the difference in the factors that significantly impact the reaction for the different palladium sources. In the reactions that employ APC, the number of vinyl equivalents moderately impacts the yield (Figure 2c), whereas the changing the ratio of KOSiMe₃ to vinyl groups has little effect. In contrast, the yields of the reactions employing Pd(dba)₂ are more greatly influenced by the ratio of KOSiMe₃ to vinyl groups (Figure 2b, ~75% yield with 1.41 equiv of KOSiMe₃/vinyl group vs >90% yield with 2.59 equiv of KOSiMe₃/vinyl group), whereas increasing the number of vinyl equivalents has a minimal effect at the 1 h time point. Moreover, at 3 h, there appears to be a deleterious effect of employing high levels of both KOSiMe₃ and DVDS, as the yield diminished in the top corner in comparison to the 1 h yield.

In contrast to the subtle differences between the palladium sources, the second DoE provided clear distinction among the solvents employed; for example, DMF promoted the reaction to a much greater extent than did ethereal solvents. This difference is likely related to a solvent effect on the rate of

(58) Denmark, S. E.; Smith, R. C. *Synlett* **2006**, 18, 2921–2928.

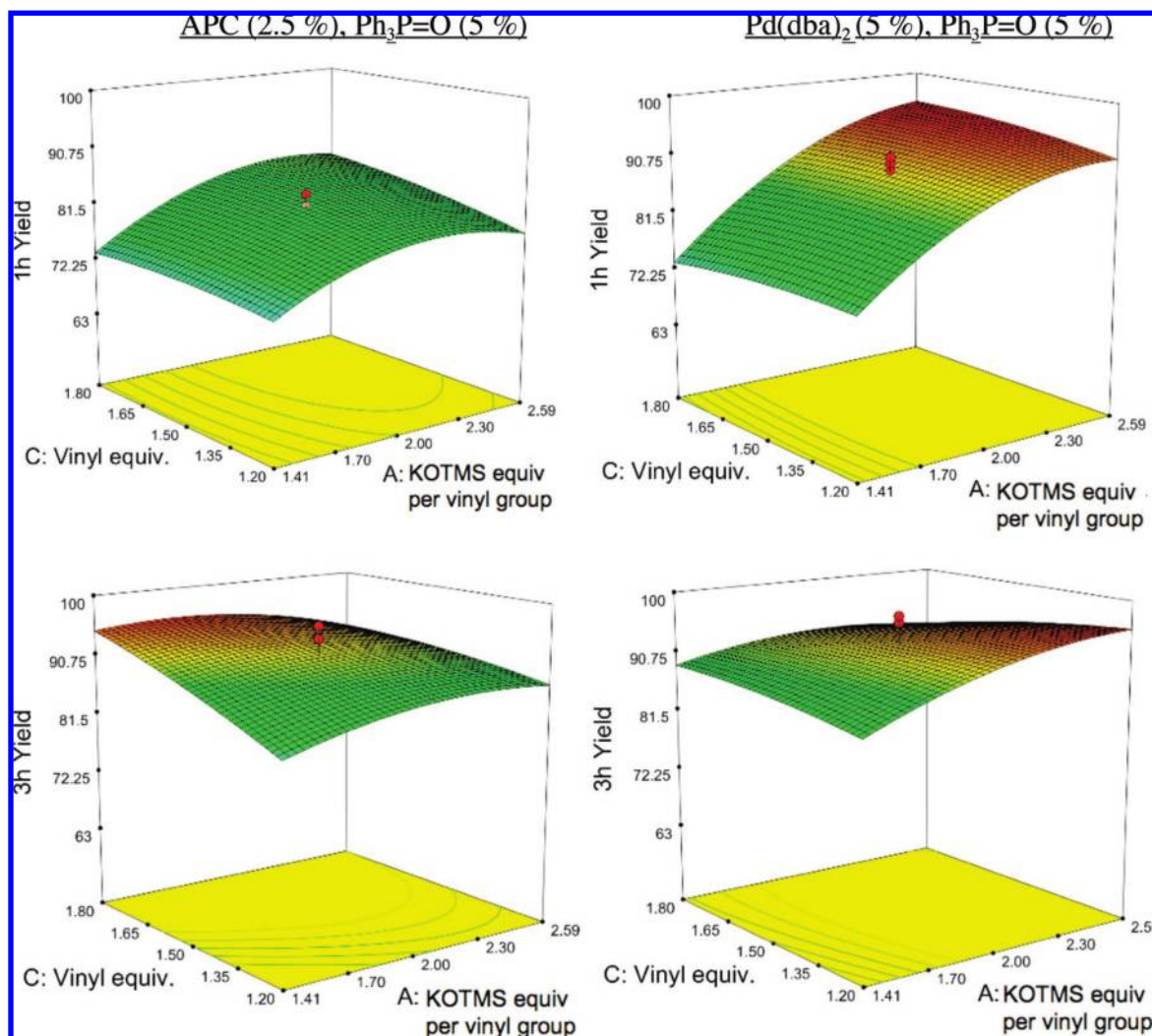


Figure 2. Three-dimensional surface relationships between TMSOK and vinyl equivalents.

silanolate exchange between DVDS and KOSiMe_3 .⁵⁹ Silanolate exchange can take place by either direct displacement or formation of a hypercoordinate siliconate complex. By either mechanism, a change to a more polar solvent is expected to accelerate the rate of displacement and thereby the rate at which the equilibrium is established.

2. Preparative Vinylation of Aryl Iodides. Application of the optimized conditions (KOSiMe_3 (3.5 equiv), DVDS (0.75 equiv), $\text{Pd}(\text{dba})_2$ (5 mol %), $\text{Ph}_3\text{P}=\text{O}$ (5 mol %), DMF, room temperature) to a range of aryl iodides provided good to excellent yields of the corresponding styrenes. Although the reaction had been optimized for 4-iodoanisole, electron-deficient aryl iodides also worked well. It is notable that the vinylation of ethyl 4-iodobenzoate is not complicated by ester cleavage with KOSiMe_3 .⁶⁰ Unfortunately, the reaction of the corresponding methyl 2-iodobenzoate does suffer ester cleavage, as 2-iodobenzoic acid is produced. Also notable is the high yield of the electron-deficient 4-cyano- and 3-nitrostyrenes despite their propensity for anionic polymerization.⁶¹ Although the yields may be somewhat lower than those obtained by other

methods, they are still above 68% without optimization. Moreover, the goal of identifying inexpensive reagents for the vinylation was accomplished, as the palladium catalyst is now the most expensive component in the reaction. Additionally, the reagents require no special handling or preparation, and are nontoxic, which makes them suitable for large-scale applications.

3. Vinylation of Aryl Bromides. Adapting the conditions developed for aryl iodides to the vinylation of aryl bromides was initially envisioned to involve two different strategies. The slower oxidative addition to bromides as compared to iodides was to be overcome by increasing the reaction temperature or by the use of bulky, electron-rich phosphine ligands. Higher temperatures did induce the vinylation of both electron-deficient and sterically unencumbered aryl bromides. Unfortunately, these conditions failed to engage electron-rich or sterically congested aryl bromides. The use of bulky phosphine ligands such as **10** provided either no reaction (at room temperature) or the products of C–N coupling at elevated temperatures.

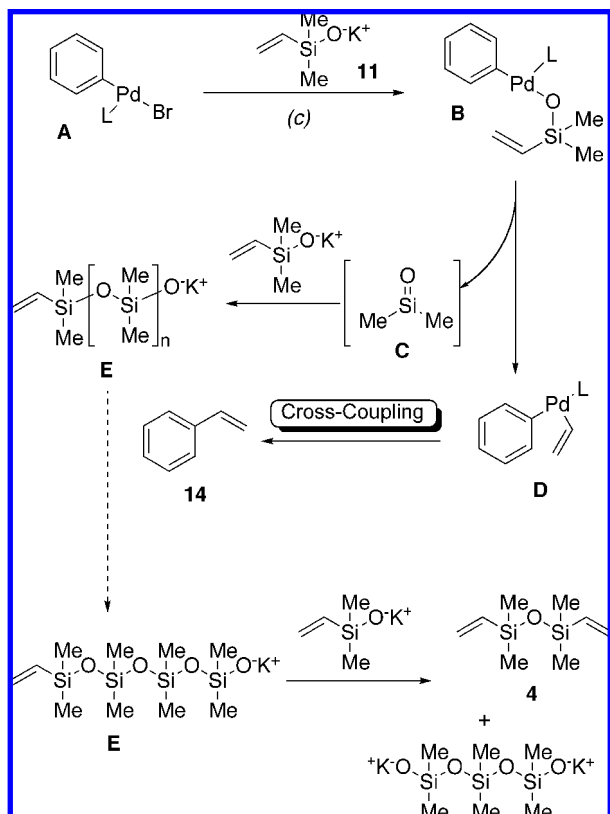
These failures were difficult to reconcile. The vinylation of aryl iodides using $\text{KOSiMe}_3/\text{DVDS}$ demonstrated that the silanolate exchange occurred rapidly at room temperature and therefore could not be responsible for the failure of the reactions with aryl bromides. Moreover, the alkenylation of aryl chlorides in the presence of ligands **18** or **19**³³ suggested that once **11**

(59) Based upon this assumption, it is unclear why NMP performs so poorly in these reactions.

(60) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, 25, 5831–5834.

(61) Hirao, A.; Loykulnant, S.; Ishizone, T. *Prog. Polym. Sci.* **2002**, 27, 1399–1471.

Scheme 14



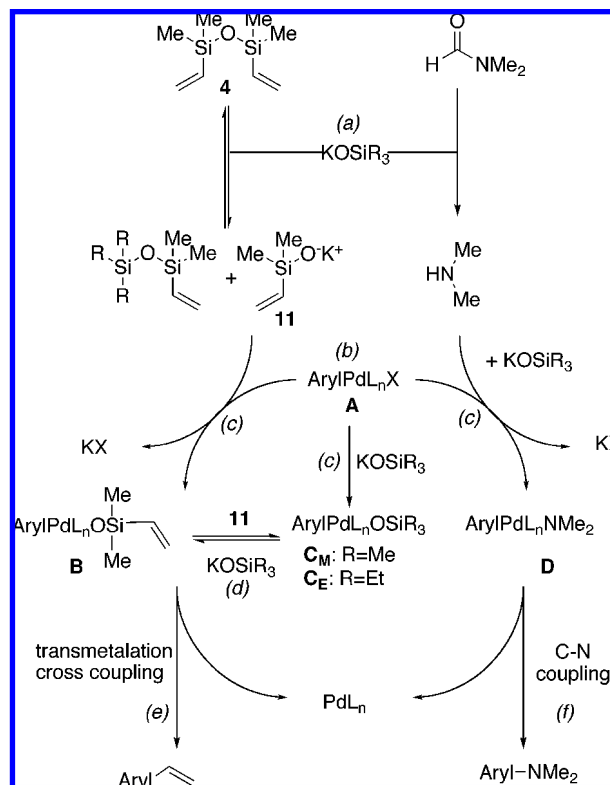
was bound to the palladium center, a pathway should be available for transmetalation. The vinylation of 4-bromoanisole with preformed **11** (in the presence of **10** at room temperature) confirmed the viability of the vinylation pathway. However, no conditions could be found in which the bromide was completely consumed, because of competitive formation of DVDS from **11**. Despite the lack of a proton source, disiloxane formation can occur by disproportionation of **11** with the polysiloxane generated throughout the reaction, providing an alternative pathway for silanolate consumption (Scheme 14, **E** → **4**).

Apparently, KOSiMe_3 is competitively binding to the palladium center, and the exchange of silanolates at palladium must not be possible at room temperature in the presence of **10**. If this exchange were feasible, intermediates bearing **11** would form the product. The successful vinylation promoted by KOSiEt_3 with DVDS supported this hypothesis. A bulkier activator was expected to enable silanolate exchange, but not compete with **11** for binding to the arylpalladium halide, thus resulting in the desired cross-coupling.

Optimization of the reactions with KOSiEt_3 as the activator revealed a few interesting features. The significant rate change observed when KOSiEt_3 or DVDS is independently varied is likely related to the silanolate exchange process, where reversible inhibition of the coupling (initially observed with the aryl iodides) arises from the $\text{Pd}(0)$ -ligating ability of DVDS. Thus, when insufficient amounts of KOSiEt_3 are present to convert all of the DVDS to the silanolate, the remaining DVDS interferes by sequestering the palladium(0).

The application of the optimal reaction conditions proved to be general for a range of electron-rich, electron-neutral, and moderately electron-deficient aryl bromides. Broad functional compatibility was observed due to the relatively mild reaction

Scheme 15



conditions. Aryl bromides bearing strongly electron-withdrawing substituents including carbonyl and nitro groups fail in the reaction, likely due to anionic polymerization of the styrene facilitated by KOSiEt_3 at elevated temperatures.

4. Unified Mechanistic Picture. From the analysis above, a mechanism for the entire process can now be formulated (Scheme 15). This scheme, shown previously as Scheme 12, can now be analyzed in detail for the consequences of activator structure, aryl halide, temperature, and ligands. Each step will be discussed below in the context of the entire body of results.

(a) Silanolate Exchange. Silanolate **11** can be generated in situ by equilibrium redistribution of DVDS with a trialkylsilanolate. Both KOSiMe_3 and KOSiEt_3 can establish this equilibrium, albeit at different rates and with different stoichiometries; however, both are rapid under the conditions of the coupling.

(b) Oxidative Addition. Insertion of palladium(0) into a carbon–iodine bond occurred at room temperature with the aid of a phosphine oxide to stabilize the palladium catalyst. However, for aryl bromides, bulky phosphine ligands were needed to facilitate oxidative addition to provide palladium(II) intermediate **A**.

(c) Partitioning of Intermediate A. Intermediate **A** is formed in a rapid, irreversible step and can then react with either silanolates KOSiR_3 or **11** generated by the equilibrium established in step a. Combination of **A** with **11** would produce the complex **B**, whereas combination with either activator KOSiMe_3 and KOSiEt_3 would produce intermediate **C**, which is believed to be unproductive under the reaction conditions. Alternatively, intermediate **A** can also combine with dimethylamine in reactions using KOSiMe_3 in DMF at elevated temperature.⁶² From the results of room-temperature couplings, we conclude that with KOSiEt_3 , intermediate **B** predominates, whereas with

KOSiMe₃, intermediate **C_M** predominates. Although these assertions seem reasonable on the basis of the differences in steric bulk, to better understand the basis for these conclusions, we must look for evidence further in the catalytic cycle below.

(d) Exchange between B and C. This critical equilibrium is highly dependent on the nature of the activator, the temperature, and the presence or absence of bulky phosphine ligands. For KOSiMe₃ the equilibrium is believed to be rapid at room temperature in the absence of phosphine ligands as evidenced by the successful vinylation of aryl iodides. However, this exchange does not occur readily at room temperature when bulky ligands are present because no reaction is observed with aryl bromides in the presence of **10** (thereby substantiating the overwhelming population of **C_M**).⁶³ Exchange likely takes place at elevated temperatures as cross-coupling (from **B**) is observed. For KOSiEt₃, this equilibrium is not believed to occur because at all temperatures studied productive vinylation was observed. Because vinylation occurs at room temperature, it is believed that either (1) KOSiEt₃ cannot effectively compete with **11** for binding to the palladium center, or (2) if KOSiEt₃ does bind, exchange with **11** is available.

(e) Cross-Coupling. This process can take place at room temperature from aryl iodides and aryl bromides with preformed **11** or with a suitable method for its in-situ generation.

(f) C–N Coupling. The C–N coupling process is observed in DMF with KOSiMe₃ at elevated temperatures from the decomposition of DMF. Because the productive vinylation can take place at lower temperatures (35–40 °C) with KOSiEt₃, competitive C–N coupling is not observed with this activator.

The formulation of this unified mechanistic scheme allows for a clear illustration of the challenges associated with developing a clean, general, and reproducible vinylation with organosilicon reagents. The disparate behavior of the different activators, halides, and ligand sets can now be more clearly understood and nearly all of the data interpreted in the context of this framework. Thus, the superiority of KOSiEt₃ as compared to KOSiMe₃ as an activator for the vinylation can be ascribed to a number of different factors. First, it is capable of generating **11** at room temperature from DVDS in reasonable concentration. Second, because of its bulk, it does not effectively compete with **11** for occupancy on the arylpalladium center, thus allowing the productive coupling to occur at lower temperature. Finally, because coupling can take place at a lower temperature, the decomposition of DMF does not interfere.

Conclusion

Mild, fluoride-free reaction conditions for the vinylation of aryl iodides have been developed via a silanolate exchange reaction. The utilization of Design of Experiment protocols allowed for the examination of multiple variables simultaneously and facilitated rapid formulation reaction conditions for aryl iodides. The adaptation of these conditions to aryl bromides, based on mechanistic experiments, has provided a new, mild alternative for the preparation of substituted styrenes.

Experimental Section

Preparation of 4-Ethenylanisole from 4-Iodoanisole Using KOSiMe₃ (14a**).** In a dry box, KOSiMe₃ (Aldrich,⁵² 896 mg, 7.0 mmol, 3.5 equiv) was added to an oven-dried, two-necked, 10-mL, round-bottomed flask. The flask was removed from the dry box, and Pd-(dba)₂ (57 mg, 0.1 mmol, 0.5 equiv), triphenylphosphine oxide (29 mg, 0.1 mmol, 0.05 equiv), and 4-iodoanisole (468 mg, 2 mmol) were added. The flask was equipped with an argon inlet adapter capped with a septum and evacuated. The flask was then refilled with argon, and this evacuation/refill process was repeated two additional times. The septum was then pierced, and a thermocouple was inserted into the flask. DMF (2.0 mL) and DVDS (344 μL, 1.5 mmol, 0.75 equiv) were then added sequentially via syringe, followed by the remaining DMF (2.0 mL). The reaction mixture was then stirred at room temperature, and the internal temperature was observed to rise from 25 to 52 °C over 10 min. The mixture was allowed to stir for 1.5 h, and then was partitioned between pentane (50 mL) and water (100 mL). The aqueous layer was extracted with pentane (2 × 50 mL), and the organic layers were sequentially washed with water (30 mL). The organic layers were combined and dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by column chromatography (silica gel; 30 mm × 110 mm; pentane/Et₂O, 100/1) afforded 215 mg (80%) of **14a** as a clear, colorless oil. Data for **14a**:⁶⁴ ¹H NMR (500 MHz, CDCl₃) 7.37 (dd, *J* = 6.9 and 1.9, 2H), 6.88 (dd, *J* = 6.8 and 1.9, 2H), 6.68 (dd, *J* = 17.6 and 10.7, 1H), 5.63 (d, *J* = 17.8, 1H), 5.14 (d, *J* = 11.0, 1H), 3.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 159.3, 136.2, 130.4, 127.3, 113.9, 111.5, 55.2; IR 3087, 3004, 2956, 2935, 2908, 2836, 1628, 1608, 1575, 1511, 1461, 1443, 1408, 1320, 1302, 1250, 1175, 1114, 1040, 1024, 991, 901, 835, 815, 709; MS (EI, 70 eV) 134, 119, 91, 65; *R_f* 0.36 (pentane/Et₂O, 50:1).

Preparation of 4-Ethenylbenzophenone from 4-Bromobenzophenone Using KOSiMe₃ (14k**).** To an oven-dried, one-necked, 10-mL, round-bottomed flask equipped with magnetic stir bar and a sidearm gas adapter fitted with a septum were added KOSiMe₃ (Aldrich,⁵² 896 mg, 7 mmol, 3.5 equiv), Pd₂(dba)₃ (58 mg, 0.1 mmol, 0.05 equiv), and triphenylphosphine oxide (28 mg, 0.1 mmol, 0.05 equiv). The gas adapter was attached to an argon manifold, and the flask was evacuated and refilled with argon. This evacuation/refill process was repeated two additional times, and then the flask was charged with THF (4 mL) via syringe. The gas adapter was quickly removed, 4-bromobenzophenone (522 mg, 2 mmol) was added as a solid, and the adapter was replaced. DVDS (500 μL, 2.2 mmol, 1.1 equiv) was then added neat, via syringe, and the mixture was placed in a preheated oil bath and was heated to reflux for 3 h. After the reaction was determined to be complete by GC analysis, the flask was cooled to room temperature, then was filtered through a small pad of silica gel (5 g). The silica plug was rinsed with 50 mL of Et₂O, and the filtrate was concentrated in vacuo. Purification of the crude product by column chromatography (silica gel; 30 mm × 120 mm pentane/Et₂O; 20:1) afforded 386 mg (93%) of **14k** as a white solid. Data for **14k**:^{27b} ¹H NMR (500 MHz, CDCl₃) 7.81–7.78 (m, 4H), 7.59 (t, *J* = 7.6, 1H), 7.49 (d, *J* = 8.3, 2H), 7.48 (t, 2H, *J* = 7.6), 6.78 (dd, *J* = 17.6 and 10.8, 1H), 5.90 (d, *J* = 17.6, 1H), 5.41 (d, *J* = 10.8, 1H); ¹³C NMR (125 MHz, CDCl₃) 195.9, 141.3, 137.5, 136.4, 135.7, 132.0, 130.3, 129.7, 128.0, 125.8, 116.3; IR 3082, 3060, 1927, 1830, 1657, 1577, 1604, 1555, 1447, 1403, 1317, 1278, 1177, 1148, 1116, 1073, 1027, 1000, 990, 938, 924, 857, 797, 789, 755, 703, 681; MS (EI, 70 eV) 209, 208, 132, 131, 105, 103, 77; *R_f* 0.37 (hexane/EtOAc, 20:1).

Preparation of 2-Ethenyl-6-methoxynaphthalene from 2-Bromo-6-methoxynaphthalene Using KOSiEt₃ (14i**).** To an oven-dried, two-necked, 10-mL, round-bottomed flask equipped with magnetic stir bar, septum, and gas adapter were added allylpalladium chloride dimer (18 mg, 0.05 mmol, 0.025 equiv) and 2-(di-*t*-butylphosphino)biphenyl (29 mg, 0.1 mmol, 0.05 equiv). The gas adapter was attached to an argon

(62) Because the formation of dimethylamine was avoided by using KOSiEt₃, there was no need to speculate on the rate of formation of **D** or its relevant equilibria.

(63) From the knowledge that independently prepared **11** couples with bromides at room temperature in the presence of **10**, and the knowledge that **11** is generated rapidly at room temperature from DVDS and KOSiMe₃, we can conclude that in-situ generated **11** cannot compete with KOSiMe₃ and that exchange cannot take place.

(64) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.

manifold, and the flask was evacuated and refilled with argon. This evacuation/refill process was repeated two additional times, and the flask was then charged with DMF (2 mL) via syringe. The argon adapter was removed, 2-bromo-6-methoxynaphthalene (474 mg, 2 mmol) was quickly added as a solid, and the gas adapter was replaced. To the mixture was added DVDS (597 μ L, 2.6 mmol, 1.3 equiv) neat, via syringe. The argon adapter was again removed, KOSiEt₃ (1.0 g, 6.0 mmol, 3.0 equiv) was quickly added, and the argon adapter was replaced. An additional 2 mL of DMF was then added via syringe, and the reaction was stirred for 4 h. After the reaction was determined to be complete by GC analysis, the mixture was cooled to room temperature, then was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL), and the organic layers were washed with water (50 mL). The organic phases were combined, dried over Na₂SO₄ sulfate, and then were filtered and concentrated in vacuo (25 °C, 50 mmHg). Purification of the crude product by column chromatography (silica gel; 30 mm \times 120 mm; pentane/EtOAc; 20/1) afforded 303 mg (82%) of **14i** as a white solid. Data for **14i**:^{27b} mp 85–86 °C; ¹H NMR (500 MHz, CDCl₃) 7.72–7.69 (m, 3H), 7.61 (dd, *J* = 8.6 and 1.5, 1H), 7.14–7.11 (m, 2H), 6.85 (dd, *J* = 17.6 and 10.9, 1H), 5.82 (d, *J* = 17.6, 1H), 5.28 (d, *J* = 10.9, 1H), 3.92 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 158.0, 137.2, 134.6,

133.2, 129.8, 129.2, 127.2, 126.4, 124.0, 119.2, 113.3; IR 3088, 3066, 2960, 2939, 2908, 2839, 1626, 1597, 1507, 1480, 1452, 1404, 1389, 1339, 1267, 1239, 1197, 1178, 1164, 1032, 994, 964, 896, 858, 826, 738; MS (EI, 70 eV) 184, 169, 141, 139, 115; *R*_f 0.32 (pentane/Et₂O, 20:1).

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Note Added after ASAP Publication. Spectra were missing from the Supporting Information initially published on February 28, 2008. The complete PDF file is now available.

Supporting Information Available: Detailed experimental procedures, and full characterization of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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