Palladium-Catalyzed Cross-Coupling Reactions of Substituted Aryl(dimethyl)silanols

Scott E. Denmark,* Michael H. Ober

245 Roger Adams Laboratory, Box 18, Department of Chemistry, University of Illinois, 600 S. Mathews Avenue, Urbana, IL 61801, USA
Fax: (+1)-217-333-3984, e-mail: denmark@scs.uiuc.edu

Received: June 28, 2004; Accepted: August 30, 2004

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Cesium carbonate and cesium hydroxide monohydrate are effective activators for the palladium-catalyzed cross-coupling of aryl(dimethyl)silanols with substituted aryl halides. Extensive optimization studies led to the identification of key variables (solvent, catalyst, additive, and hydration level) that influence the rate and selectivity of the process. Manipulation of these factors provides an effective coupling method of wide scope and generality. Electron-rich aryl(dimethyl)silanols undergo cross-coupling with aryl iodides and aryl bromides in high yields and high selectivity for the desired cross-coupling products. Alternatively, high yields of cross-coupling products could be obtained with electron-poor or *ortho*-substituted aryl(dimethyl)silanols when activated with cesium hydroxide monohydrate.

Keywords: biaryls; C–C bond formation; cesium carbonate; cesium hydroxide; fluoride-free, hydration effect

Introduction and Background

The discovery and continuing evolution of palladium-catalyzed cross-coupling reactions have greatly facilitated the synthesis of complex molecules by providing an efficient means for carbon-carbon bond formation. Organostannanes,[1] organoboranes[2] and organozincs[3] are the most commonly employed nucleophilic components for cross-coupling reactions with a wide range of halides and pseudo halides. Despite the well-documented success of these methods they still suffer from a number of drawbacks due, in part, to the nature of the organometallic reagents employed as precursors. For example, even though organostannanes are found to react with a number of electrophilic partners, forcing conditions are often required. More importantly, the alkylstannane precursors and by-products are toxic[1b,4] and the tributylstannyl group represents a significant molecular mass. Organozincs and organoboranes must also be handled appropriately due to their moisture and oxygen sensitivity (zinc) and difficulty of purification (boron).[5]

In view of these and other substrate specific drawbacks, the development of viable substitutes for organostannanes and organoboranes remains an important objective. Among the newly developed alternatives, organosilanes have emerged as premier agents for effecting carbon-carbon bond formation of sp–sp^2 and sp^2–sp^2 centers.[6] Since the pioneering studies of Hiyama, Hatanaka and coworkers with alkenyl(fluoro)silanes,[6a] much work has been dedicated to expanding the generality of this process.[7] In particular, the discovery that tetrabutylammonium fluoride (TBAF) could activate these silicon-based precursors was crucial for the exploration of the substrate scope. Subsequent studies have revealed that this cross-coupling method is not limited to alkenyl(fluoro)silanes but is also applicable to the corresponding alkynyl(halo)silanes and aryl(halo)silanes.[8]

Although organo(halo)silanes can perform a wide range of cross-coupling reactions, these compounds are not ideal, as they are difficult to prepare and hydrolyze easily. To avoid these problems yet still maintain the inherent reactivity of organosilanes, a number of alternative cross-coupling precursors have been developed including silacyclobutanes, alkoxysilanes, silanols, and polysiloxanes.[7] These precursors preserve the reactivity and broad scope required for a general cross-coupling process, provide enhanced stability prior to activation under the reaction conditions, and are for the most part easily accessible.[7a]

In general, fluoride sources are highly effective for promoting the palladium-catalyzed cross-coupling of organosilanes. However, the widespread use of silicon protecting groups in complex molecule synthesis precludes the application of a fluoride-activated coupling because

 DOI: 10.1002/adsc.200404204

it jeopardizes the integrity of these protecting groups.[9] Thus, the need for a non-fluoride-based promoter that could facilitate the couplings with equal vigor led to the discovery that simple bases could activate alkenyl(dimethyl)silanols. The first such promoter, silver oxide (Ag_2O), effects the cross-coupling of alkenylsilanols, silanediols, and -triols with aryl and alkenyl halides.[10] As an inexpensive alternative, potassium trimethylsilanolate (TMSOK) can also be employed for the activation of alkenyl(dimethyl)silanols to provide cross-coupling products in high yield.[11]

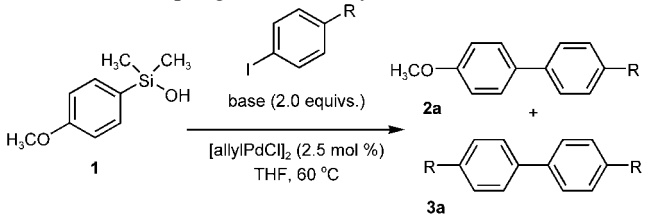
In addition to the alkenylsilanes mentioned above, arylsilanes have been conscripted into useful service for cross-coupling reactions to prepare biaryls.[12] Aryl(fluoro)silanes,[8a, b] aryl(chloro)silanes,[8c–e] aryl(halo)silacylobutanes,[13] aryl(triallyl)silanes[14] and aryl(trialkoxy)silanes,[15] have all shown promise as competent precursors when activated by a fluoride source. Unfortunately, these *aryl*silanes are less reactive than the *alkenyl*silanes and require more forcing conditions to undergo productive coupling.[13,16] Moreover, under these conditions a number of undesirable side-process (primarily homo-coupling[8e,13,15a–c]) have been reported that represent significant obstacles in the development of an efficient process. Herein we describe studies that address the limitations of fluoride activation and homo-coupling in silicon-based cross-coupling reactions. The objective of these studies is the identification of an appropriate non-fluoride activator for the efficient and selective cross-coupling of readily available aryl(dimethyl)silanols to aryl halides with broad scope and generality.[17]

Results

Identification and Optimization of Key Reaction Conditions

Initial attempts to effect the cross-coupling of aryl(dimethyl)silanols employed the conditions previously reported for the cross-coupling of arylsilacyclobutanes[13] and alkenyl(dimethyl)silanols.[11] Thus, a solution of (4-methoxyphenyl)dimethylsilanol (**1**) and ethyl 4-iodobenzoate in THF, was treated with 2.0 equivs. of TBAF and a catalytic amount (2.5 mol %) of allylpalladium chloride dimer ([allylPdCl]$_2$) at room temperature. No products of cross-coupling were observed by gas chromatographic analysis of the reaction mixture. Warming of this mixture to 60 °C stimulated the formation of both the cross-coupling product, as well as the homo-coupling side-product from the dimerization of the aryl iodide (entry 1, Table 1). Even though complete consumption of the aryl iodide was observed after 6 h, this protocol was undesirable because of the amount of the homo-coupling product formed and the inherent drawback of a fluoride-based activation method. With these results as a benchmark for the reaction of aryl(dimethyl)silanols, the more recently developed fluoride-free conditions were investigated. Once again, the combination of **1** with ethyl 4-iodobenzoate was employed using potassium trimethylsilanolate (TMSOK) as the activator. Under these conditions, the iodo ester was cleaved to the corresponding carboxylic acid within 6 h (entry 2). With a more robust partner, 4-iodotoluene, productive cross-coupling was observed but,

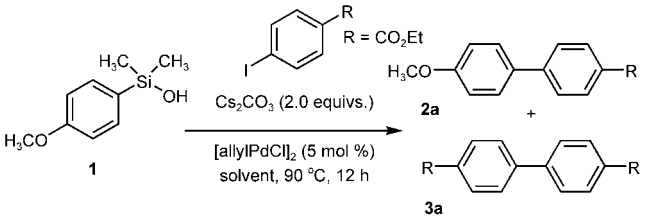
Table 1. Effect of activator on the cross-coupling of **1** with aryl iodides.[a]



Entry	Base	R	Time [h]	Conversion [%][b]	Product ratio (**2a**:**3a**)[c]
1	TBAF	CO_2Et	12	100	75:25
2	TMSOK	CO_2Et	6	0	–
3	TMSOK	CH_3	12	36	78:22[d]
4	Na_2CO_3	CO_2Et	24	0	–
5	K_2CO_3	CO_2Et	24	0	–
6	Rb_2CO_3	CO_2Et	24	8	64:36
7	Cs_2CO_3	CO_2Et	24	45	90:10

[a] Reactions employed 1.2 equivs. of **1**.
[b] Conversion based on consumption of iodide determined by GC analysis.
[c] Determined by GC analysis.
[d] Homo-coupling product is **3b**.

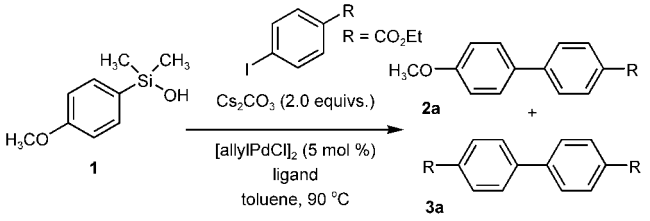
Table 2. Solvent survey for the cross-coupling of **1** with ethyl 4-iodobenzoate.[a]



Entry	Solvent	Conversion [%][b]	Product ratio (**2a**:**3a**)[c]
1	toluene	78	91:9
2	dioxane	88	81:19
3	DME	98	60:40
4	DMF	100	17:83

[a] Reactions employed 1.2 equivs. of **1**.
[b] Conversion based on consumption of iodide determined by GC analysis.
[c] Determined by GC analysis.

Table 3. Effect of additive on the cross-coupling of **1** with ethyl 4-iodobenzoate.[a]



Entry	Ligand[b]	Time [h]	Conversion [%][c]	Product ratio (**2a**:**3a**)[d]
1	Ph_3P	12	100	68:32
2	$(o\text{-tol})_3P$	24	67[e]	84:16
3	$(C_6F_5)_3P$	24	68[e]	54:46
4	$(t\text{-Bu})_3P$	12	99	63:37
5	$(2\text{-furyl})_3P$	3	99	79:21
6	$AsPh_3$	12	100	92:8
7	$AsPh_3$[f]	12	100	92:8
8	dbbp	3	99	12:88
9	dppp[f, g]	3	99	73:27
10	dppb[f, h]	3	99	86:14
11	dppf[f, i]	12	99	73:27

[a] Reactions employed 1.2 equivs. of **1**.
[b] 20 mol % of ligand employed.
[c] Conversion based on consumption of iodide determined by GC analysis.
[d] Determined by GC analysis.
[e] Mass balance is unreacted starting material.
[f] 10 mol % of ligand employed.
[g] 1,3-Bis(diphenylphosphino)propane.
[h] 1,4-Bis(diphenylphosphino)butane.
[i] 1,1′-Bis(diphenylphosphino)ferrocene.

once again, accompanied by an unacceptable amount of the homo-coupling product (entry 3).[18]

To avoid the problems associated with both TBAF and TMSOK, a series of alkaline carbonates was employed in the reaction of **1** with ethyl 4-iodobenzoate. Although sodium and potassium carbonate were ineffective, the reaction was marginally facilitated by rubidium carbonate and, to a slightly greater extent, cesium carbonate (Cs_2CO_3).[19] With 5 mol % of [allylPdCl]$_2$ and 2.0 equivs. of Cs_2CO_3 in toluene at 60 °C, modest conversion (45%) to **2a** was achieved after 24 h (Table 1, entry 7), together with a small amount of the homo-coupling product (**3a**).

Having identified Cs_2CO_3 as a viable activator, an optimization of reaction conditions was undertaken to improve both the rate and selectivity of the reaction. To survey other solvents, the reaction temperature was raised to 90 °C and 5 mol % of [allylPdCl]$_2$ was employed to achieve a reasonable reaction time. Toluene was found to be effective for the reaction, providing a moderate rate and high selectivity for the cross-coupling product (Table 2, entry 1). The use of ethereal solvents such as dioxane (entry 2), dimethoxyethane (DME, bp 85 °C, entry 3) and dimethylformamide (DMF, entry 4) led to an increase in the consumption of the iodide in the 12 h period, but also to an increase in the proportion of the undesired homo-coupling products. All of these reactions remained heterogeneous throughout.

The use of additives in the reaction of **1** with ethyl 4-iodobenzoate was next explored to further accelerate the cross-coupling process and suppress the homo-coupling pathway (Table 3). The addition of 20 mol % of triphenylphosphine (2/1, ligand/palladium) increased the rate of iodide consumption (entry 1). Unfortunately, the selectivity was significantly diminished from the additive free reaction (*cf.* Table 2, entry 1) suggesting that the additive did not effect the cross-coupling, but rather enhanced the homo-coupling pathway. The use of substituted triarylphosphines (entries 2 and 3) slowed the rates of both the cross-coupling and homo-coupling pathways. Tri-*t*-butylphosphine[13] (entry 4) and tri-2-furylphosphine[20] (entry 5), which accelerates the cross-coupling of arylsilacyclobutanes[13] and organostannanes,[20] provided nearly full conversion of the aryl iodide in 12 h and 3 h. Unfortunately, both additives also enhanced the amount of the homo-coupling product.

The use of triphenylarsine[20] led to complete consumption of the aryl iodide in 12 h and maintained the favorable ratio of cross- to homo-coupling products (entry 6). Decreasing the amount of $AsPh_3$ relative to palladium (1/1, ligand/palladium) had no effect on the outcome (entry 7). Surprisingly, 2-(di-*tert*-butylphosphino)biphenyl (dbbp)[21] (entry 8) reversed the reaction selectivity to favor the formation of **3a** over **2a**. The bidentate ligands (1/1, ligand/palladium, entries 9–11) accelerated the consumption of the aryl iodide but, as

with Ph_3As, had little effect on the amount of homo-coupling product observed. Of the bidentate ligands surveyed, only 1,2-bis-diphenylphosphinobutane (dppb) provided a noticeable improvement on the product distribution. Overall, the additives led to an increase in the reaction rate (entries 1, 4, 5, and 8–11) but did not improve the selectivity of the reaction.

Discovery of a Cs_2CO_3 Source Dependence

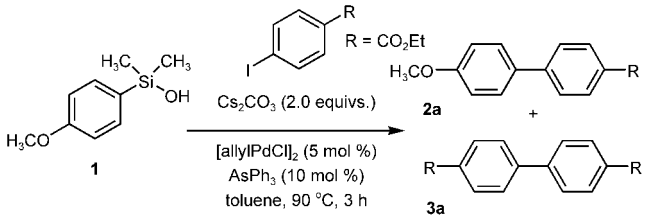
When a different source of Cs_2CO_3 was employed under the optimized conditions, an unexpected and significant effect on the reaction rate was noted. This observation prompted a survey of several different samples of Cs_2CO_3 which provided a wide range of results (Table 4). The outcome of these reactions ranged from essentially complete conversion after 3 h (with the Cs_2CO_3 employed in the studies described above, entry 1), to little conversion after 3 h (with a newly purchased bottle of Cs_2CO_3 stored in the dry box, entry 5). Various samples of Cs_2CO_3 produced moderate conversions including those purchased from different suppliers (entry 3) and those stored in a desiccator for a period time (entry 4). Surprisingly, the reaction was also found to be sensitive to the handling of the salt prior to its use in the reaction. A sample that was removed from the desiccator and intentionally 'aged' on the bench top for 1 h prior to use (entry 2), provided a dramatic enhancement over the same sample which was used directly from the dry environment (entry 4).

From all of the samples tested, it was apparent that the older bottles and those that were not carefully stored under anhydrous conditions provided the best results (entries 1, 3 and 4). Correspondingly, the poorest performance was obtained with newly purchased bottles that were stored in a dry box (entry 5). On the basis of these data and the fact that anhydrous Cs_2CO_3 is known to be a strong desiccant, it was suspected that the samples providing the best results were those that were no longer truly anhydrous. This hypothesis was confirmed by accurately measuring the hydration levels of the samples by thermogravimetric analysis (TGA).[22] The data in Table 4 reveal a striking correlation between hydration level of the Cs_2CO_3 sample and the corresponding conversion in the cross-coupling process. Clearly, water is playing a crucial role in the success of the reaction.[23]

Therefore, to find the optimal hydration level for the reaction and establish a reproducible protocol for the cross-coupling, water was added to the reaction mixture containing newly purchased 'anhydrous' Cs_2CO_3[22b] (Figure 1). As was observed with the 'naturally hydrated' Cs_2CO_3 samples, an increase in the conversion of **1** and ethyl 4-iodobezoate to **2a** was also observed with the addition of 2–5 equivs. of H_2O per Cs_2CO_3. The conversion to **2a** decreased at higher water loadings (6 equivs.). Interestingly, the selectivity of the reaction was not dependent on the level of hydration (5–7% homo-coupling product was observed).

The method by which the Cs_2CO_3 was "hydrated" was also found to influence the results. As previously men-

Table 4. Dependence on Cs_2CO_3 source of the cross-coupling of **1** with ethyl 4-iodobenzoate.[a]



Entry	Cs_2CO_3 source	Conversion [%][b]	TGA [equivs. H_2O]
1	Aldrich (shelf)[c]	85	1.90
2	Aldrich (aged 1 h)[d]	73	0.98
3	AlfaAesar (shelf)[c]	68	0.74
4	Aldrich (desiccator)	41	0.31
5	Aldrich (dry box)	34	0.20

[a] Reactions employed 1.2 equivs. of **1**.
[b] Conversion based on consumption of iodide determined by GC analysis.
[c] Unknown age.
[d] Aldrich (desiccator) aged on bench top open to atmosphere

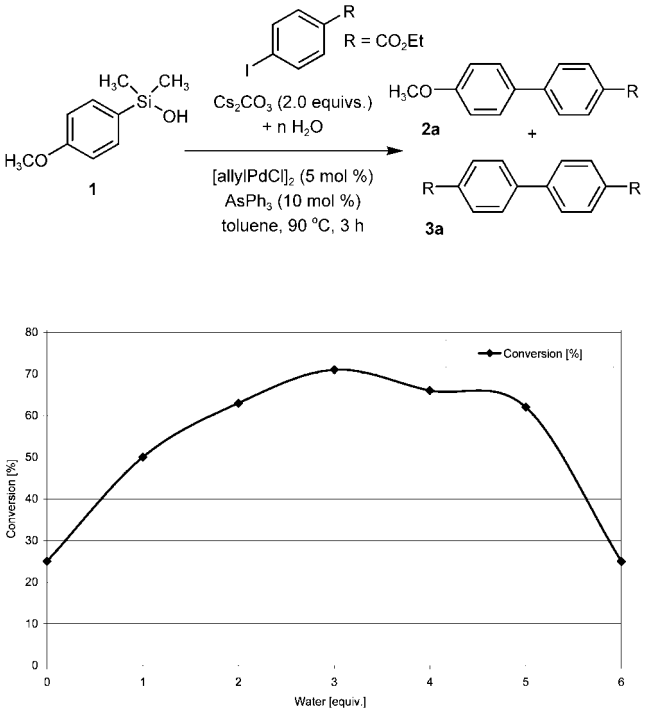


Figure 1. Effect of hydration on the cross-coupling of **1** with ethyl 4-iodobenzoate.[a]

tioned, aging the activator by allowing it to pick up moisture from the atmosphere was effective, but also cumbersome, time-consuming and potentially irreproducible. The most reproducible results (70% conversion after 3 h) were secured by addition of H_2O to the solvent followed then by solid Cs_2CO_3 or the addition of H_2O to a slurry of Cs_2CO_3. The addition of H_2O to solid Cs_2CO_3 followed by suspension of the solid in the reaction solvent provided a poorer conversion (28% after 3 h).

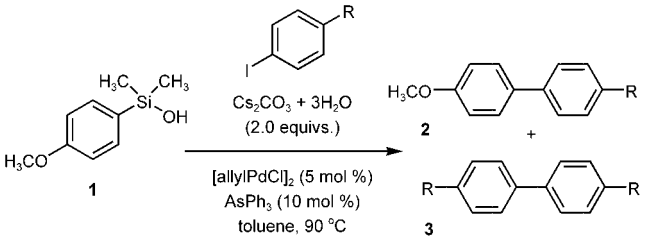
Cs_2CO_3 Activated Cross-Coupling of Arylsilanols with Aryl Halides

Cross-Coupling of (4-Methoxyphenyl)dimethylsilanol with Aryl Iodides

The scope of the Cs_2CO_3-promoted cross-coupling reaction of **1** with a variety of aryl halides could now be investigated (Table 5). Gratifyingly, high yields of biaryl products and similar reaction times were obtained with both electron-rich (entry 2) and electron-poor aryl iodides (entry 1, 3, and 5–7). The reaction was found to be tolerant of a number of functional groups including ester (entry 1), ketone (entry 3), nitrile (entry 4), and nitro groups (entry 7). In most cases, only a small amount (4–7%) of the undesired homo-coupling product was isolated.

Unlike the 4-substituted aryl iodides described above, 2-substituted aryl iodides reacted much more slowly, but were completely selective for the cross-coupling products. To capitalize on the excellent selectivity of these substrates, a change in the solvent from toluene to dioxane (shown previously to increase reaction rates, see Table 2, entry 2) facilitated the coupling of these substrates. A reinvestigation of the ideal hydration level for the Cs_2CO_3 activator revealed that only 2 equivs. of water were necessary when dioxane was employed as the reaction solvent.[24] Under these new conditions, the cross-coupling of a number of the 2-substituted aryl iodides was examined (Table 6). The 2,4′-disubstituted biaryl products were isolated in high yields in all cases with no homo-coupling products observed. As with the 4-substituted aryl iodides, a wide range of substituents was tolerated under the reaction conditions and little effect on rate or selectivity was observed with electron donating and electron-withdrawing substituents.

Table 5. Cross-coupling of **1** with 4-substituted aryl iodides.



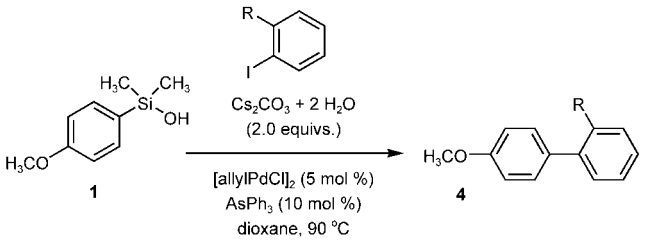
Entry	R	Time [h]	Product	Yield [%][b]	Product ratio (**2**:**3**)[c]
1	CO_2Et	8	**2a**	87	96:4
2	CH_3	6	**2b**	90	94:6
3	$COCH_3$	3	**2c**	91	100:0
4	H	8	**2d**	91	94:6
5	CN	6	**2e**	85	93:7
6	CF_3	3	**2f**	87	95:5
7	NO_2	6	**2g**	88	94:6

[a] Reactions employed 1.2 equivs. of **1**.
[b] Yield of chromatographed, recrystallized products.
[c] Determined by GC analysis.

Cross-Coupling of (4-Methoxyphenyl)dimethylsilanol with Aryl Bromides

The nature of the halide in the electrophilic coupling partner also played an important role; aryl iodides and aryl bromides were competent, but aryl chlorides were not. Reactions of aryl bromides under the conditions prescribed for the reaction of **1** with the corresponding iodides were found to be more selective for the cross-coupling pathway. Additionally, the use of dppb (noted in the original additive survey, Table 3, entry 10) in place of Ph_3As provided a further increase in the selectivity of the reaction (Table 7). Many different substituents on the aryl bromides were tolerated under the reaction conditions and little effect on efficiency was observed between electron-rich and electron-deficient coupling partners.

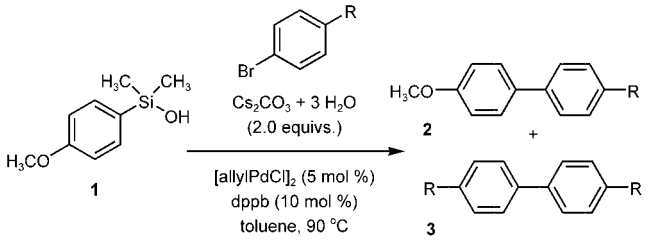
Table 6. Cross-coupling of **1** with 2-substituted aryl iodides.[a]



Entry	R	Time [h]	Product	Yield [%]
1	CH_3	24	**4a**	85[c]
2	CF_3	24	**4b**	81[b, d]
3	OCH_3	24	**4c**	84[b, d]
4	NO_2	24	**4d**	83[c]
5	CO_2CH_3	24	**4e**	88[c]
6	[f]	24	**4f**	86[c]

[a] Reactions employed 1.2 equivs. of **1**.
[b] Yield of chromatographed, recrystallized products.
[c] Yield of chromatographed, distilled products.
[d] Yield of analytically pure material.
[e] Determined by GC analysis.
[f] 1-Iodonaphthalene.

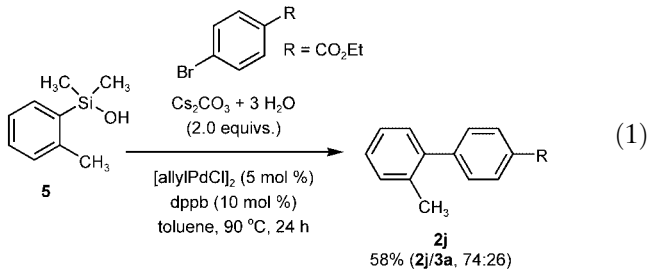
Table 7. Cross-coupling of **1** with 4-substituted aryl bromides.[a]



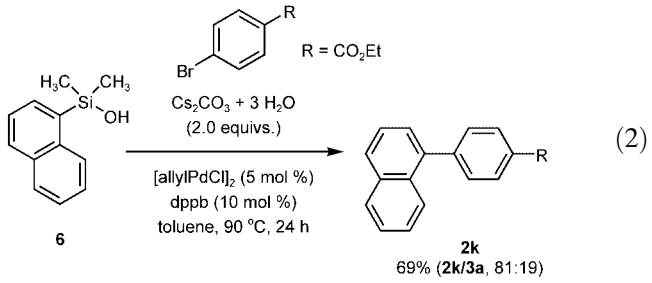
Entry	R	Time [h]	Product	Yield [%][b]	Product ratio (**2**:**3**)[d]
1	CO_2Et	24	**2a**	90	>99:1
2	CH_3	18	**2b**	90	>99:1
3	H	12	**2d**	85	>99:1
4	OCH_3	18	**2 h**	92	–:–[e]
5	*c*-hexyl	18	**2i**	79[c]	–:—:-[f]

[a] Reactions employed 1.2 equivs. of silanol.
[b] Yield of chromatographed, recrystallized products.
[c] Yield of analytically pure material.
[d] Determined by GC analysis.
[e] Not applicable.
[f] Not determined

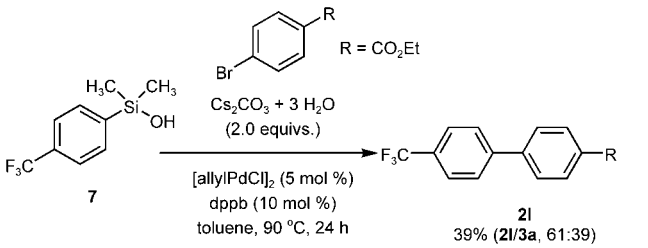
The foregoing examples show clearly that the scope of the aryl halide partner in the Cs_2CO_3-promoted cross-coupling is broad. Unfortunately, a similar range was not observed for variation of the aryl(dimethyl)silanol component. Cesium carbonate-promoted reactions of aryl(dimethyl)silanols such as **5**, **6** and **7** [Equations (1)–(3)] were sluggish and unselective for the formation of the desired cross-coupling products. A re-examination of key reaction conditions including solvent, additives, reaction temperature, and reaction stoichiometries did not provide an acceptable protocol for the cross-coupling of these substrates.



(1)



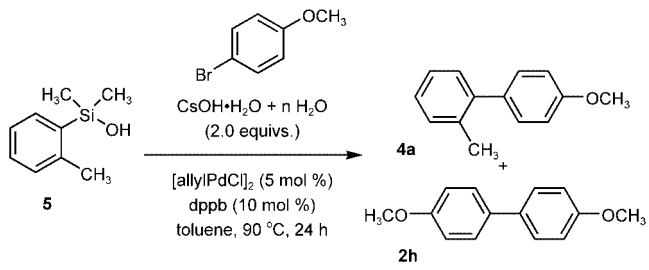
(2)



(3)

Investigation of Other Cesium Salts as Activators

To identify a suitable activator for substrates **5**–**7**, an investigation of other available cesium salts ($CsHCO_3$ and $CsOH \cdot H_2O$) was undertaken. Under the standard conditions with **5** and 4-bromoanisole, no reaction was observed in the presence of $CsHCO_3$ whereas $CsOH \cdot H_2O$ showed activity comparable to that of Cs_2CO_3. Optimization of the reaction conditions required only reexamination of the amount of water added and the solvent. An investigation of the optimal hydration level revealed that the addition of 2 equivs. of water per $CsOH \cdot H_2O$ (providing *in situ* formation of $CsOH \cdot 3\ H_2O$) gave complete conversion of the aryl bromide within 24 h (Figure 2). Once again, the addition of more water to the reaction mixture (3 and 4 equivs.) only decreased the consumption of the bromide.



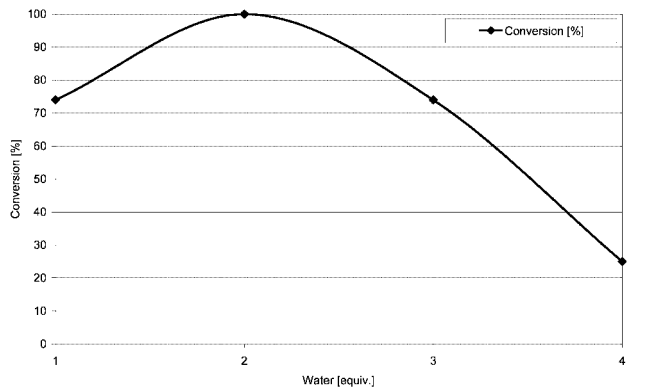
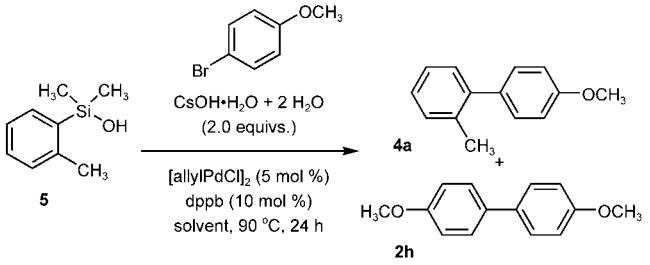


Figure 2. Effect of hydration on the cross-coupling of **5** with 4-bromoanisole.

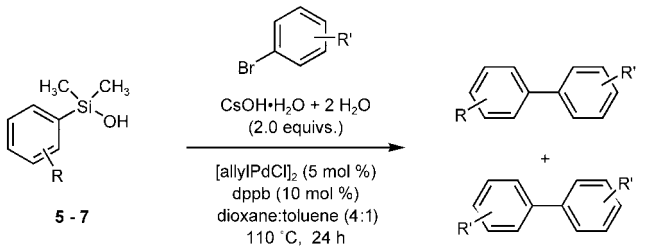
Table 8. Solvent optimization of the cross-coupling of **5** with 4-bromoanisole.[a]



Entry	Dioxane/ Toluene	Conversion [%][b]	Product ratio (**4a** : **2 h**)[c]
1	1/0	100	91 : 9
2	4/1	96	94 : 6
3	3/2	92	94 : 6
4	2/3	86	95 : 5
5	1/4	75	98 : 2
6	0/1	38	> 99 : 1

[a] Reactions employed 1.2 equivs. of **5**.
[b] Conversion based on consumption of bromide determined by GC analysis.
[c] Determined by GC analysis.

Table 9. Cross-coupling reactions of substituted aryl(dimethyl)silanols with substituted aryl bromides.[a]



Entry	R	R′	Product	Yield [%][c]	Product ratio[d]
1	2-CH_3 (**5**)	4-OCH_3	**4a**	83	91 : 9
2	1-naphthyl (**6**)	4-OCH_3	**4f**	82	93 : 7
3	4-CF_3 (**7**)	4-OCH_3	**2f**	54	83 : 17
4	4-CF_3 (**7**)	2-CH_3		26	> 99 : 1
5	1-naphthyl[b] (**6**)	2-CH_3	**4g**	85	> 99 : 1

[a] Reactions employed 1.2 equiv. of silanol.
[b] Reactions employed 2.0 equivs. of silanol.
[c] Yield of chromatographed, recrystallized products.
[d] Ratio of cross- to homo-coupling products determined by GC analysis.

Identifying the optimal solvent for the reactions with $CsOH \cdot H_2O$ was more difficult than for Cs_2CO_3. With the new activator, toluene led to a sluggish (albeit selective) reaction (Table 8, entry 6) whereas dioxane led, in high conversion, to an unacceptable product mixture (Table 8, entry 1). We were intrigued by the possibility of merging the beneficial properties of these two solvents by investigating various blends. Indeed, adding increasing amounts of toluene to the dioxane successfully increased the selectivity of the cross-coupling reaction while only incrementally decreasing the overall conversion. A 4 : 1 ratio of dioxane to toluene provided both an acceptable rate and selectivity for the cross-coupling process (entry 2).

$CsOH \cdot H_2O$ Activated Cross-Coupling of Substituted Arylsilanols with Aryl Bromides

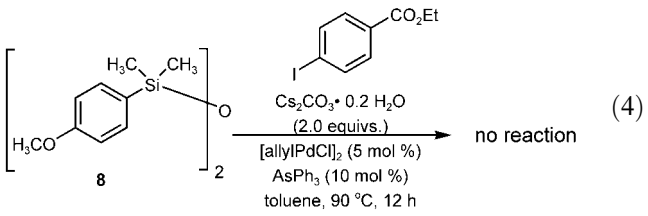
Under the conditions identified above, $CsOH \cdot 3\,H_2O$ (produced *in situ* from the addition of 2 equivs. of H_2O to commercially available $CsOH \cdot H_2O$) was found to effect the cross-coupling of aryl(dimethyl)silanols that were not activated by the Cs_2CO_3 system (Table 9). The use of aryl bromides as coupling partners was required as aryl iodides provided unacceptable amounts of the undesired homo-coupling product. In the cases surveyed, 2-substituted aryl(dimethyl)silanols such as 2-tolyl(dimethyl)silanol, **5**, and 1-naphthyl(dimethyl)silanol, **6**, both provided the desired cross-coupling product (entries 1, 2 and 5), but required heating of the reaction mixture to 110 °C to effect complete conversion of the aryl bromide within a 24 h period. Even selective formation of a 2,2′-*ortho*-substituted coupling product, **4g** was possible under these conditions (entry 5). The electron-poor aryl(dimethyl)silanol, 4-trifluorotolyl(dimethyl)silanol, **7** did provide cross-coupling products, but the reactions were found to be problematic. The reactions with different substrates gave either poor selectivity or unacceptably low conversion (entries 3 and 4).[25]

Even though the overall scope of the cross-coupling reactions of aryl(dimethyl)silanols was improved by the use of $CsOH \cdot H_2O$, it is not necessarily superior to the Cs_2CO_3 as an activator. The enhanced reactivity of $CsOH \cdot H_2O$ over Cs_2CO_3 is advantageous, but at the cost of substrate scope. Aldehydes, esters, and nitriles that were tolerated by Cs_2CO_3 were found to be incompatible with the $CsOH \cdot H_2O$ system. Therefore, the Cs_2CO_3 and $CsOH \cdot H_2O$ protocols are complementary. Overall, these two systems provide a generalized, non-fluoride-based, cross-coupling method with good scope and generality.

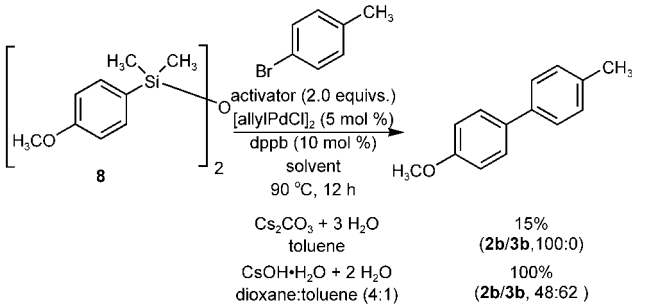
The Importance of the Silanol and its Salts

The crucial role of the silanol function in **1** for a successful cross-coupling was clearly illustrated by the failure to observe any product in the reaction of the derived disiloxane, **8**, under standard reaction conditions with ethyl 4-iodobenzoate [Equation (4)]. On the other hand, the disiloxane did react with 4-bromotoluene when hydrat-

ed Cs_2CO_3 or $CsOH \cdot H_2O$ was used as the activator [Equation (5)].



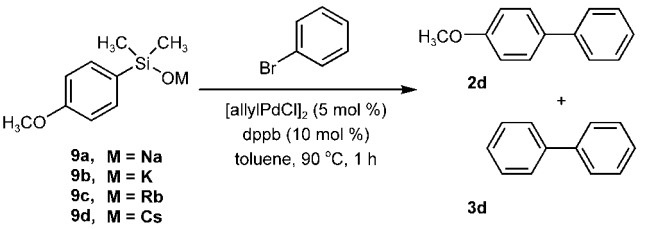
(4)



(5)

To understand the dramatic counterion effect observed among the carbonate bases (Table 1), the Na, K, Rb and Cs salts of **1** were independently prepared and the rates of their coupling reactions determined. The salts, **9**, were easily generated by combining **1** with an excess of the corresponding metal hydrides (for the Na and K silanolates) or with an equimolar amount of the active metal (for the Rb and Cs salts). Each of these salts was combined with bromobenzene in the presence of 5 mol % of $[allylPdCl]_2$ and 10 mol % of dppb (Table 10). All of the silanolates were highly active in the cross-coupling process. Remarkably, the rates of the reactions (judged by the amount of aryl bromide remaining after 1 h at 90 °C) were very similar, but the lower conversion with the sodium salt is ambiguous. Whereas the K, Rb and Cs salts were completely soluble in toluene at room temperature, the Na salt was only partially soluble, therefore precluding any conclusions about relative reactivity. Thus, the small variation in rate of the pure silanolates **9**, compared to the large variation in rate of **1** with the metal carbonates, clearly implicates the solubility of the activators and the ionic character of the silanolates as critical determinants as will be discussed in detail below.

Table 10. Cross-coupling of (4-methoxyphenyl)dimethylsilanolates with bromobenzene.[a]



Entry	M	Conversion [%][b]	Product ratio (**2d** : **3d**)[c]
1	Na	55	89 : 11
2	K	80	89 : 11
3	Rb	81	90 : 10
4	Cs	91	88 : 12

[a] Reactions employed 2.0 equivs. of silanolate.
[b] Conversion based on consumption of bromide averaged over two runs and determined by GC analysis.
[c] Determined by GC analysis.

Discussion

Role of the Activator

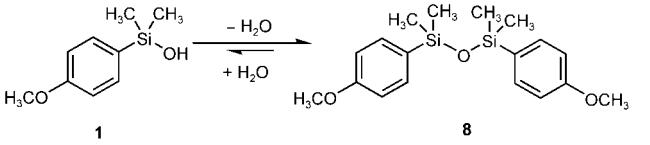
The two most potent activators, TBAF and TMSOK, were *a priori* excluded from consideration on the basis of their limited functional group compatibility.[26] Nevertheless, it is interesting to note (for later discussion of the mechanism) that these two soluble activators also gave high proportions of the homo-coupling product. The simultaneous operation of the homo-coupling pathway with TBAF finds precedent in the work of Albanese[27a] (as well as Lemaire for tetrabutylammonium bromide[28b]) although the actual reducing agent remains obscure. However, the activation of the homo-coupling pathway by TMSOK has not been documented. In an interesting control experiment in which 4-iodoanisole was subjected to the standard reaction conditions (without **1**), no homo-coupling product was observed after 24 h at 90 °C. An identical experiment in which 1.0 equiv. of TMSOK was added showed 76% conversion to 4,4′-dimethoxybiphenyl in the same time period. We suspect that TMSOK is serving both to promote the coupling (*vide infra*) as well as the reducing agent.

The significant difference in the ability of the alkali metal carbonates to promote the coupling led to the identification of Cs_2CO_3 (and subsequently $CsOH \cdot H_2O$) as a viable activator for this process. The sluggish rate of reaction in the presence of these salts (as compared to either TBAF or TMSOK) is easily interpreted in view of their poor solubility in most organic solvents. The importance of solubility is clearly substantiated by the dramatic rate in which the preformed, soluble silanolates **9** reacted under the standard conditions (Table 10). Therefore, designation of Cs_2CO_3 as a successful activator and Na_2CO_3, K_2CO_3, and Rb_2CO_3 as unsuccessful lies not in the ability of these salts to promote the cross-coupling pathway but instead in their lack of solubility under the reaction conditions. Although reliable data are not available, the success of $CsOH \cdot H_2O$ may also relate to solubility. Finally, the productive coupling

of the preformed K, Rb and Cs silanolates at comparable rates has significant mechanistic implications which will be elaborated below.

The Hydration Effect

The serendipitous discovery of the importance of water to the success of the cross-coupling process highlights some of the unique features of this reaction. Unlike reactions promoted by TBAF or TMSOK in which either a silanol or a disiloxane can serve as the donor,[28,29] the reactions promoted by Cs_2CO_3 require the silanol function [Equation (4)]. One of the unavoidable consequences of heating the reactions is the formation of the thermodynamically more stable disiloxanes [Equation (6)]. Indeed, quantitative GC monitoring of a reaction that employed "anhydrous" Cs_2CO_3 showed that the slowing of the reaction over time corresponded to the simultaneous increase in the amount of the disiloxane, **8** (Table 11). Because **8** is not active toward cross-coupling, the addition of H_2O is required to shift the disiloxane/silanol equilibrium to continuously replenish the silanol (and therefore silanolate), increasing the overall efficiency of the reaction.



1 8 (6)

The increase in conversion observed with the addition of water may also be due, in part, to an increase in the solubility of the cesium salt. However, the addition of more than 5 equivs. of water (which visibly increased the solubility of the Cs_2CO_3) eroded the reaction efficiency.[30] On the other hand, the increased reaction rate observed in dioxane compared to toluene, most likely results from the greater solubility of Cs_2CO_3 in the latter.[31] Nevertheless, water was also beneficial for reactions in dioxane (interestingly at a lower hydration level).

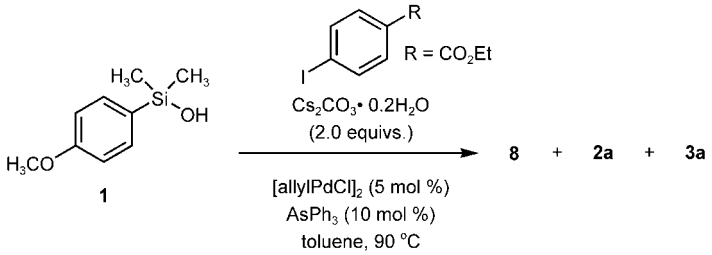
As with any reaction that is dependent upon a preequilibrium to provide the reactive species, temperature will have divergent effects. Obviously, the overall rate of the process should increase with increasing temperature, but the rate at which the silanol is converted to unreactive disiloxane will also increase. Thus, we conclude that water is playing multiple roles in enhancing the efficiency of the reactions, but that more quantitative conclusions are not possible.

Insight into the Mechanistic Aspects of the Reaction

Even though a full mechanistic picture of this cross-coupling cannot be drawn from the investigations provided above, several important insights can be gleaned from the data. Recent investigations on the mechanism of cross-coupling of *alkenyl*(dimethyl)silanols provides a solid foundation on which to analyze the mechanism of reactions with *aryl*(dimethyl)silanols (Figure 1). The initial event involves an oxidative insertion of the palladium(0) catalyst into the aryl halide to form palladium(II) intermediate **I**. Displacement of the halide in **I** by the cesium silanolate would then provide the key intermediate **II** which contains a Pd–O–Si linkage for the crucial transmetalation.[29b] Migration of the anisyl unit directly from this species (or an activated 'ate' complex) would then provide the diorganopalladium(II) intermediate **III** which should undergo rapid, reductive elimination to provide the biaryl product as well as regenerate the palladium(0) catalyst.

Although it is reasonable to adapt the basic outline from the cross-coupling of *alkenyl*(dimethyl)silanols,

Table 11. Disiloxane formation during the cross-coupling of **1** with ethyl 4-iodobenzoate.



Entry	Time [h]	**1** [mol %][a]	Iodide [mol %][a]	**8** [mol %][a]	**2a** [mol %][a]	**3a** [mol %][a]
1	0	120	100	–	–	–
2	3	72	70	7	31	–
4	12	44	45	12	53	2.5
5	24	21	34	18	63	3

[a] Determined by GC analysis relative to an internal standard with ethyl 4-iodobenzoate as the limiting reagent.

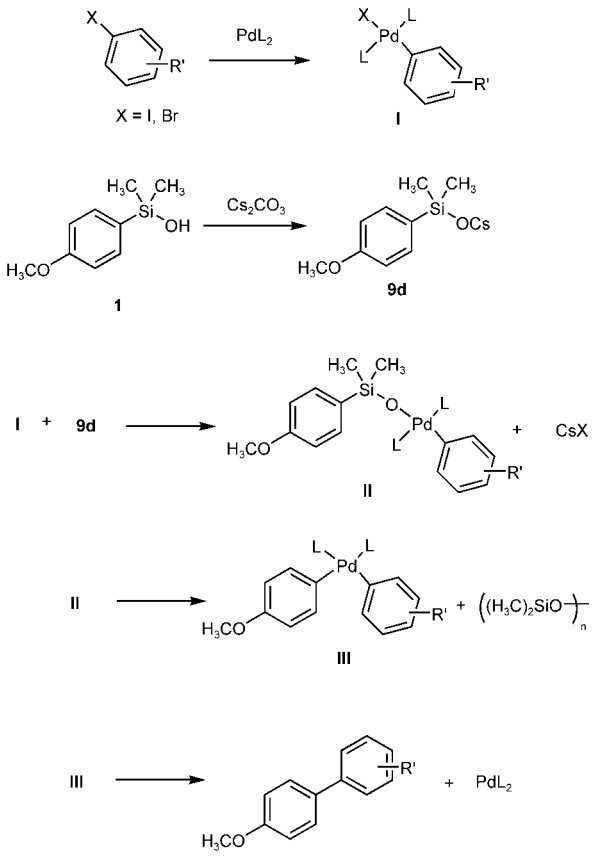


Figure 3. Proposed mechanism for cross-coupling of aryl(dimethyl)silanols.

several observations made during the course of this study imply important differences. Foremost, the rate-determining step for the cross-coupling of *aryl*(dimethyl)silanols is most likely not the displacement of the halide by silanolate at the palladium center as was seen for *alkenyl*(dimethyl)silanols. The absence of a meaningful difference between the rate of cross-coupling of aryl iodides and bromides strongly supports this notion as does the similarity in rate of cross-coupling of the K, Rb and Cs silanolates (**9b–d**) with bromobenzene.[32] The lack of a halide effect also implies that the oxidative insertion of the aryl halide by Pd(0) also precedes the rate-determining step of the reaction and is corroborated by the similar reactivity observed by electron-rich and electron-deficient aryl halides. Finally, the temperatures required for the productive cross-coupling of aryl(dimethyl)silanols are much higher than those required for alkenyl(dimethyl)silanols which is not consistent with the steric difference between an alkenyl and an arylsilane. Which of the remaining steps is turnover-limiting (transmetalation from **II** or activation of **II** followed by transmetalation from the activated 'ate' complex, or reductive elimination) will require thorough kinetic analysis.[33]

Nature of the Homo-Coupling Pathway

The homo-coupling by-product observed in the majority of the reactions represents the most significant problem in this process. Through judicious choice of activator, solvent and especially additive, the formation of this by-product could be suppressed, but not completely eliminated. The pervasive presence of the homo-coupling product suggests the possibility of an intimate link between the cross- and homo-coupling pathways. In some cases, such as those reactions employing TBAF, the link between the two competing pathways has been identified.[29a] More importantly, the ability of TMSOK to initiate formation of the homo-coupling product under the prescribed reaction conditions suggests that the silanolates themselves may be involved in both cross- and homo-coupling processes.

An important insight into the dual role of the silanolates is highlighted by the divergent results from the reactions **1**/Cs_2CO_3 with bromobenzene (Table 7, entry 3) and those of the cesium silanolate **9d** with the same electrophile (Table 10, entry 4). Both of these reactions clearly involve the cesium silanolate **9d**, but differ primarily in the equilibrium concentration of this species. In the presence of Cs_2CO_3 the steady state concentration of **9d** is low and the homo-coupling product is not observed. On the other hand, the preformed silanolate is completely soluble in toluene and therefore the initial concentration of this species is at a maximum. In this case, a significant proportion of the homo-coupling product is observed.

If we now interpret these observations in light of the mechanism proposed above, an interesting hypothesis emerges. At low silanolate concentration, intermediate **II** may suffer direct transmetalation followed by reductive elimination to provide the desired product. However, at higher silanolate concentration, a secondary pathway becomes available which involves a second equivalent of both the silanolate and the aryl halide leading to the homo-coupling product. In this scenario, the role of additives can be understood in terms of their ability to influence the relative rates of direct transmetalation from **II** versus the insertion of **II** into a second aryl halide. More concrete conclusions must await a full elucidation of the mechanism.

Conclusions

A set of reaction conditions have been identified that can promote the cross-coupling of aryl(dimethyl)silanols with aryl halides. For must substrates, hydrated Cs_2CO_3 is recommended (in conjunction with $[allylPdCl]_2$ and an additive), but less reactive substrates can benefit from use of the more aggressive $CsOH \cdot H_2O$. Toluene is the solvent of choice for reactive substrates whereas dioxane is preferred for slower substrates. To enhance the efficiency of the reactions, aryl

iodides require the use of Ph_3As whereas aryl bromides react faster when dppb is employed. The scope and generality of the system is broad, and good yields of the desired cross-coupling products can be obtained.

The higher reaction temperatures and use of heterogeneous bases lead to disiloxane formation which erodes the reaction efficiency. This problem led to the important discovery of the role of water to maintain a steady state concentration of the reactive silanol. Detailed optimization of the reaction variables has provided a better understanding of the behavior of arylsilanols and important insights into the unique mechanism by which they undergo cross-coupling reactions.

Experimental Section

General Remarks

See Supporting Information for general experimental details as well as procedures for the preparation and characterization of all precursors and cross-coupling products.

General Procedure for the Cesium Carbonate Activated Palladium-Catalyzed Cross-Coupling of (4-Methoxyphenyl)dimethylsilanol with 4-Substituted Aryl Iodides

Anhydrous cesium carbonate (651 mg, 2.0 mmol, 2.0 equivs.) was suspended in dry toluene (1.0 mL) at room temperature in a 5-mL, round-bottom flask with a magnetic stir bar and fitted with a reflux condenser and an argon inlet adapter. To this suspension was added dropwise H_2O (108 μL, 6 mmol, 3.0 equivs. per Cs_2CO_3) and the resulting slurry was allowed to stir for 10 min. The aryl iodide (1.0 mmol), and **1** (218 mg, 1.2 mmol, 1.2 equivs.) were then added, followed by $[allylPdCl]_2$ (18.3 mg, 0.05 mmol, 0.05 equivs.), and triphenylarsine (30.6 mg, 0.1 mmol, 1.0 equiv. per Pd). The flask was then purged with argon and placed in a 90 °C oil bath. The reaction progress was monitored by GC analysis at certain intervals until completion. Sampling of the reaction was performed by removing 10 μL aliquots of the mixture *via* syringe. The aliquot was filtered through a small plug of silica gel and eluted with 5 mL of ethyl acetate. The aliquot was then analyzed by GC. Upon completion, the reaction mixture was cooled to room temperature, treated with H_2O (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under vacuum. The crude product was further purified by column chromatography (SiO_2) to afford the biaryl product which was further purified by recrystallization.

General Procedure for the Cesium Hydroxide Monohydrate Activated Palladium-Catalyzed Cross-Coupling of Substituted Aryl(dimethyl)silanols with Substituted Aryl Bromides

Anhydrous cesium hydroxide monohydrate (336 mg, 2.0 mmol, 2.0 equivs.) was suspended in a mixture of dry toluene (0.8 mL) and dry dioxane (0.2 mL) at room temperature in a 5-mL round-bottom flask with a magnetic stir bar and fitted with a reflux condenser and an argon inlet adapter. To this suspension was added drop-wise H_2O (72 μL, 4 mmol, 2.0 equivs. per CsOH) and the resulting slurry was allowed to stir for 10 min. The aryl bromide (1.0 mmol), and **1** (218 mg, 1.2 mmol, 1.2 equivs.) were then added, followed by $[allylPdCl]_2$ (18.3 mg, 0.05 mmol, 0.05 equivs.), and 1,4-bis(diphenylphosphino)-butane (dppb) (42.6 mg, 0.05 mmol, 0.5 equivs. per Pd). The flask was then purged with argon and placed in a heated oil bath. The reaction progress was monitored by GC analysis at certain intervals until completion. Sampling of the reaction was performed by removing 10 μL aliquots of the mixture *via* syringe. The aliquot was filtered through a small plug of silica gel and eluted with 5 mL of ethyl acetate. The aliquot was then analyzed by GC. Upon completion, the reaction mixture was cooled to room temperature, treated with H_2O (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under vacuum. The crude product was further purified by column chromatography (SiO_2) to afford the biaryl product which was further purified by bulb-to-bulb distillation or recrystallization.

Acknowledgements

We are grateful to the National Institutes of Health for generous financial support (R01 GM GM63167-01A1).

References and Notes

[1] a) J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; b) Y. N. Mitchell, in: *Metal-catalyzed, Cross-coupling Reactions*, (Eds.: F Diederich, P. J. Stang), Wiley-VCH: Weinheim, Germany, **1998**, Chapter 4; b) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1.

[2] a) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) A. Suzuki, *Pure Appl. Chem.* **1994**, *66*, 213; d) A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749; e) A. Suzuki, in: *Metal-catalyzed, Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH: Weinheim, Germany, **1998**, Chapter 2.

[3] a) E. Negishi, *Pure Appl. Chem.* **1981**, *53*, 2333; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) P. Knochel, in: *Metal-catalyzed, Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH: Weinheim, Germany, **1998**, Chapter 9.

[4] M. R. Krigman, A. P. Silverman, *Neurotoxicology* **1984**, *5*, 129.

[5] a) K. M. Hossain, T. Kameyama, T. Shibata, K. Takagi, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2415; b) K. A. Smith, E. M. Campi, W. R. Jackson, S. Marcuccio, C. G. M. Naeslund, G. B. Deacon, *Synlett* **1997**, 131; c) M. S. Wong, X. L. Zhang, *Tetrahedron Lett.* **2001**, *42*, 4087; d) H. Yoshida, Y. Yamaryo, J. Ohshita, A. Kunai, *Tetrahedron Lett.* **2003**, *44*, 1541.

[6] a) T. Hiyama, *J. Organomet. Chem.* **2002**, *653*, 58; b) T. Hiyama, Y. Hatanka, *Pure and Appl. Chem.* **1994**, *66*, 1471; c) T. Hiyama, in: *Metal-Catalyzed, Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH: Weinheim, Germany, **1998**, Chapter 10; d) S. E. Denmark, R. F. Sweis, in: *Metal-Catalyzed Cross-Coupling Reactions*. 2nd edn., (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, Vol. 1, **2004**, Chapter 4.

[7] a) S. E. Denmark, M. H. Ober, *Adrichimica Acta* **2003**, *36*, 75; b) S. E. Denmark, R. F. Sweis, *Chem. Pharm. Bull.* **2002**, *50*, 1531; c) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835; d) T. Hiyama, E. Shirakawa, *Topics in Current Chemistry*, **2002**, *219*, 61.

[8] a) Y. Hatanaka, T. Hiyama, *Tetrahedron Lett.* **1990**, *31*, 2719; b) Y. Hatanaka, S. Fukushima, T. Hiyama, *Chem. Lett.* **1989**, 1711; c) F. Homsi, K. Hosoi, K. Nozaki, T. Hiyama, *J. Organomet. Chem.* **2001**, *624*, 208; d) E. Hagiwara, K. Gouda, Y. Hatanaka, T. Hiyama, *Tetrahedron Lett.* **1997**, *38*, 439; e) Y. Hatanaka, K. Goda, Y. Okahara, T. Hiyama, *Tetrahedron*, **1994**, *50*, 8301.

[9] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, **1999**, pp. 113–148.

[10] a) K. Hirabayashi, A. Mori, J. Kawashima, M. Suguro, Y. Nishihara, T. Hiyama, *J. Org. Chem.* **2000**, *65*, 5342; b) K. Hirabayashi, J. Kawashima, Y. Nishihara, A. Mori, T. Hiyama, *Org. Lett*, **1999**, *1*, 299.

[11] S. E. Denmark, R. F. Sweis, *J. Am. Chem. Soc.* **2001**, *123*, 6439.

[12] a) T. D. Nelson, R. D. Crouch, *Org. React.* **2004**, *63*. 264; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; c) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263; d) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977; e) M. Sainsbury, *Tetrahedron* **1980**, *36*, 3327.

[13] S. E. Denmark, Z. Wu, *Org. Lett.* **1999**, *1*, 1495.

[14] a) Y. Nakao, T. Oda, A. K. Sahoo, T. Hiyama, *J. Organomet. Chem.* **2003**, *587*, 570; b) A. K. Sahoo, Y. Nakao, T. Hiyama, *Chem. Lett.* **2004**, *33*, 632.

[15] a) M. E. Mowery, P. DeShong, *Org. Lett*. **1999**, *1*, 2137; b) H. M. Lee, S. P. Nolan, *Org. Lett.* **2000**, *2*, 2053; c) M. E. Mowery, P. DeShong, *J. Org. Chem.* **1999**, *64*, 1684; d) J.-Y. Lee, G. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 5616.

[16] S. E. Denmark, D. Wehrli, J. Y. Choi, *Org. Lett.* **2000**, 2491.

[17] A preliminary account of this work has already appeared: S. E. Denmark, M. H. Ober, *Org. Lett.* **2003**, *5*, 1357.

[18] Under the established reaction conditions without an activator, neither the cross-coupling nor the homo-coupling products are observed within 24 h (using **1** and ethyl 4-iodobenzoate). Furthermore, combination of the catalyst and the aryl iodide in THF at 60 °C does not provide any homo-coupling product **3a** over the same time period, but **3a** was observed in less than 1 h when TMSOK is added to this reaction mixture!

[19] a) D. D. Hennings, T. Iwama, V. H. Rawal, *Org. Lett.* **1999**, *1*, 1205; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **1999**, *38*, 2411; c) M. Haddach, J. R. McCarthy, *Tetrahedron Lett.* **1999**, *40*, 3109.

[20] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.

[21] a) S. E. Denmark, R. F. Sweis, *Org. Lett.* **2002**, *4*, 3771; b) J. P. Wolfe, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1999**, *38*, 2413; c) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550.

[22] a) Hydration level determined by thermogravametric analysis (TGA) in the University of Illinois Microanalytical Service Laboratory; b) commercially available Cs_2CO_3 purchased from Aldrich Chemical Co. was found to contain 0.2 H_2O/Cs_2CO_3.

[23] For a recent review on the accelerating effect of water in organic transformations, see: S. Ribe, P. Wipf, *Chem. Commun.* **2001**, 299.

[24] This observation most likely results from the greater affinity that dioxane has for water than does toluene. To determine the partitioning of H_2O between the solid Cs_2CO_3 and the reaction solvent, samples of Cs_2CO_3 were mixed in either toluene or dioxane containing 3.0 equivs. of H_2O at 90 °C for 3 h. The remaining solid Cs_2CO_3 was removed by filtration and analyzed by TGA to determine the hydration level. The filtrate was analyzed by Karl Fischer titration to determine the amount of water remaining in solution. These studies revealed that a higher percentage of the H_2O was contained in the solution phase of dioxane (0.74 equivs. of H_2O) than in the solution phase of toluene (0.01 equiv. of H_2O).

[25] A number of different potassium bases (K_2CO_3, $KHCO_3$, KOH, KO-*t*-Bu, K_3PO_4, K_2SO_4, at various hydration levels in different combinations of toluene and dioxane failed to promote the coupling of **7** with 4-bromoanisole.

[26] F. Polyak, W. D. Lubell, *J. Org. Chem.* **1998**, *63*, 5937.

[27] a) D. Albanese, D. Landini, M. Penso, S. Petricci, *Synlett* **1999**, 199; b) V. Penalva, J. Hassan, L. Lavenot, C. Gozzi, M. Lemaire, *Tetrahedron Lett.* **1998**, *39*, 2559.

[28] S. E. Denmark, L. Neuville, M. E. L. Christy, S. A. Tymonko, manuscript submitted.

[29] a) S. E. Denmark, D. Wehrli, R. F. Sweis, *J. Am. Chem. Soc.* **2004**, *126*, 4865; b) S. E. Denmark, R. F. Sweis, *J. Am. Chem. Soc.* **2004**, *126*, 4876.

[30] A similar effect was noted in previous studies on the use of water to modulate the reactivity of TBAF on the cross-coupling with triflates, see: S. E. Denmark, R. F. Sweis, *Org. Lett.* **2002**, *4*, 3771.

[31] Qualitative determination of the solubility of Cs_2CO_3: toluene, 0.7 mg/mL; dioxane, 1.9 mg/mL.

[32] The Na silanolate **9a** cannot be considered as its solubility in toluene was not assured.

[33] It is worth noting that the similar rates of cross-coupling of the K, Rb, and Cs silanolates suggests that anionic activation of **II** is not occurring and that transmetalation occurs directly as the tetracoordinate species as in the case of *alkenyl*(dimethyl)silanolates.

