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Cross-Coupling Reactions of Arylsilanols with Substituted Aryl Halides

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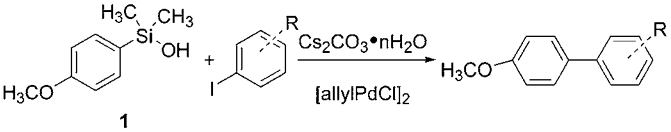
ABSTRACT



The palladium-catalyzed cross-coupling of arylsilanols with aryl iodides and aryl bromides (in the presence of cesium carbonate) furnished various biaryl products in high yield. An extensive series of optimizations led to the identification of key variables, including activator, solvent, catalyst, and hydration level, that influence the rate and selectivity of the process. Manipulation of these features provided an effective coupling method of wide scope and generality.

The transition metal-catalyzed cross-coupling of aryl halides and aryl organometallic nucleophiles has gained considerable attention as an effective method for the formation of the biaryl subunit.[1,2] Organotin[3] and organoboron[4] reagents have found wide use in synthetic organic chemistry as a viable approach toward this structural motif, but due to the toxicity and sensitivity of these reagents, the development of alternative methods is of great interest. Organosilanes are a stable and nontoxic alternative to these methods, allowing for similar or superior reactivity and scope in most cases.[5] The use of organosilanes as aryl organometallic nucleophiles for the formation of biaryls has been limited to a few cases. Aryl(fluoro)silanes[6] and aryl(chloro)silanes,[7] activated by a fluoride source, have been shown to undergo palladium-catalyzed cross-coupling with aryl bromides, iodides, and triflates[6a] to give unsymmetrical biaryl products. This method has also been applied to solid-phase synthesis.[7a] Under milder conditions, aryl(trialkoxy)silanes[8] and arylsilacyclobutanes[9] have also been reported as viable approaches to fluoride-activated aryl−aryl cross-coupling.

A recent report from these laboratories described the palladium-catalyzed cross-coupling of alkenylsilanols under fluoride-free conditions.[10] This modification highlights the inherent reactivity of alkenyldimethylsilanols through activa-

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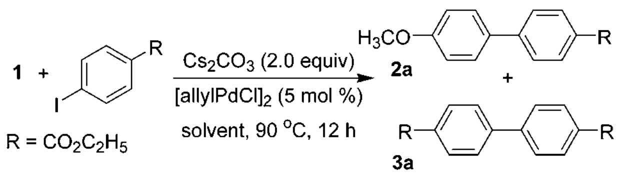
tion with mild inorganic bases and demonstrates the compatibility of this protocol with a wide scope of coupling partners. The intrinsic advantage of organodimethylsilanols is also manifested in the ease of synthesis and stability of the coupling precursors.[11] An important extension is to apply this method to the less reactive arylsilanols for the formation of unsymmetrical biaryl compounds. The use of silver salts for the activation of aryl(dimethyl)silanols, arylsilanediols, and arylsilanetriols toward coupling with aryl bromides and iodides has been previously explored by Hiyama and coworkers.[12] Careful investigation of the palladium-catalyzed cross-coupling of aryl(dimethyl)silanols in these labs has now revealed that cesium carbonate can also be employed as an activator for this reaction.[13]

Initial investigation of the cross-coupling of (4-methoxyphenyl)dimethylsilanol (**1**)[11b] with ethyl 4-iodobenzoate and cesium carbonate under catalysis by allylpalladium chloride dimer ([allylPdCl]$_2$) at 90 °C did provide the desired cross-coupling product (**2a**) but also provided the undesired homocoupling product (**3a**).[14] The low reactivity of **1** and the formation of **3a** in significant quantities focused the optimization on improving the reaction rate and suppressing the homocoupling pathway.

To increase the reaction rate, the nature of the basic activator was surveyed. TBAF, TMSOK, and Rb_2CO_3 were competent activators for the reaction but were not selective for the cross-coupling product. Next, a survey of reaction solvents revealed that toluene (entry 1, Table 1) provided a moderate reaction rate and high selectivity for the cross-coupling product (**2a**) over the homocoupling product (**3a**). The use of ether-based solvents, dioxane (entry 2) and dimethoxyethane (DME) (entry 3), led to an increase in the conversion of the iodide to products but was less selective for the cross-coupling process. Other solvents provided acceptable rates of conversion of the aryl iodide but afforded the undesired cross-coupling product preferentially (entry 4). All of the experiments described in Table 1 were heterogeneous; Cs_2CO_3 was observed throughout the course of the reaction.

Table 1. Solvent Optimization of the Cross-Coupling of **1** with Ethyl 4-Iodobenzoate[a]

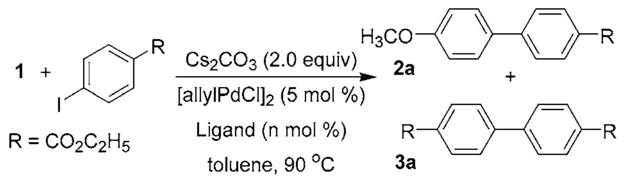


entry	solvent	conversion (%)[b]	product ratio (**2a**/**3a**)[c]
1	toluene	78	91.3/8.7
2	dioxane	88	81.1/18.9
3	DME	98	60.0/40.0
4	DMF	100	16.9/83.1

[a] Reaction employed 1.2 equiv of silanol. [b] Conversion based on the loss of iodide determined by GC analysis. [c] Determined by GC analysis.

To further accelerate the cross-coupling process and suppress the homocoupling pathway, the use of additives in the reaction of **1** with ethyl 4-iodobenzoate was explored (Table 2). The addition of 20 mol % triphenylphosphine (2/1 ligand/palladium) along with **1**, ethyl 4-iodobenzoate, 5 mol % [allylPdCl]$_2$, and 2 equiv of Cs_2CO_3 (entry 1) did increase the rate of iodide consumption. However, the **2a**/**3a** selectivity was significantly diminished compared to the additive-free reaction (Table 1, entry 1) suggesting that the additive did not effect the cross-coupling reaction but did enhance the homocoupling pathway. The addition of substituted triarylphosphines (entries 2 and 3) showed an attenuation of the overall reaction rate. Tri-*tert*-butylphosphine[9] (entry 4) and tri-2-furylphosphine[15] (entry 5), which are known to

Table 2. 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	68.3/31.7
2	$(o\text{-tol})_3P$	24	67[e]	84.4/15.6
3	$(C_6F_5)_3P$	24	68[e]	54.4/45.6
4	$(t\text{-Bu})_3P$	12	99	63.0/37.0
5	$(\text{furyl})_3P$	3	99	79.3/20.7
6	$AsPh_3$	12	100	91.6/8.4
7	2-biphenyl-$(t\text{-Bu})_2P$	3	99	11.9/88.1
8	DPPP[f,g]	3	99	73.1/26.9
9	DPPB[f,h]	3	99	85.9/14.1
10	DPPF[f,i]	12	99	73.0/27.0

[a] All reactions employed 1.2 equiv of silanol. [b] 20 mol % ligand. [c] Conversion based on the loss of iodide determined by GC analysis. [d] Determined by GC analysis. [e] Mass balance is unreacted starting material. [f] 10 mol % ligand. [g] 1,3-Bis(diphenylphosphinopropane). [h] 1,4-Bis(diphenylphosphinobutane). [i] 1,1′-Bis(diphenylphosphinoferrocene).

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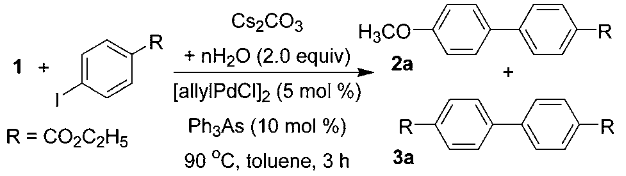
accelerate the cross-coupling of arylsilacyclobutanes and organostannanes, gave essentially full conversion of the aryl iodide in 12 and 3 h respectively, but unfortunately these additives also accelerated the rate of the homocoupling to provide a less favorable product distribution. Triphenylarsine (entry 6), which has also been shown to provide rate acceleration in the cross-coupling of organostannanes,[15] provided full conversion of the aryl iodide in 12 h while also suppressing the homocoupling pathway, thus affording a better product distribution than the additive-free reaction. The use of 2-(di-*tert*-butylphosphino)biphenyl[16] (entry 7) surprisingly provided a switch in the reaction selectivity, favoring the formation of **3a** over **2a**. The bidentate additives (entries 7−9) gave enhanced reactivity for conversion of the aryl iodide but did not afford any improvement in the product distribution of the reaction. Thus, the additives did provide an increase in the reaction rate (entries 1, 4, 5, and 7−9) but did not improve the selectivity of the reaction. *Only triphenylarsine (entry 6) was found to enhance both the rate and selectivity of the reaction.*

With the optimized reaction conditions in hand, the scope and generality of the reaction was investigated. However, during the course of this survey, a reaction rate dependence on the source of Cs_2CO_3 was discovered. Bottles of Cs_2CO_3 from different suppliers and of different vintages gave different results! We suspected that varying levels of hydration was the origin of the problem. Analysis of Cs_2CO_3 samples from commercial sources revealed that each contained different amounts of H_2O.[17] Interestingly, the sample of Cs_2CO_3 employed in the foregoing optimization studies contained the most water (ca. 1.9 equiv of H_2O per Cs_2CO_3) and was found to be the most active in the cross-coupling reaction.

Clearly, “anhydrous” Cs_2CO_3 is not the ideal activator for this process, nor are commercial samples uniform in their level of hydration. Thus, to determine the optimal hydration level, anhydrous cesium carbonate (purchased from Aldrich Chemical Co.[18]) was suspended in toluene and varying amounts of H_2O were added to form the hydrated species in situ. The cross-coupling reaction of **1** with ethyl 4-iodobenzoate under otherwise optimized reaction conditions was carried out, and the results are collected in Table 3. With the anhydrous sample of Cs_2CO_3 (Table 3, entry 1), the rate of consumption of ethyl 4-iodobenzoate was significantly attenuated compared to reactions that employed the hydrated salt (Table 3, entries 2−6). The optimal hydration level was found to be 2−4 equiv of H_2O per Cs_2CO_3; addition of more than 3 equiv of H_2O had a slight adverse effect on the reaction rate.[19,20]

Table 3. Effects of Hydration on the Cross-Coupling of **1** with Ethyl 4-Iodobenzoate[a]

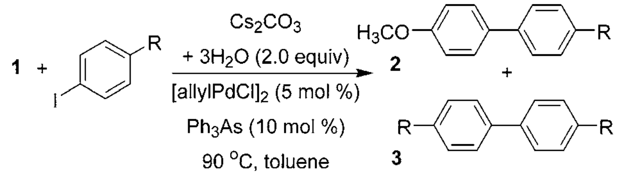


entry	n[b]	conversion (%)[c]	product ratio (**2a**/**3a**)[d]
1	0	50	100/0
2	1	73	94.0/6.0
3	2	87	94.0/6.0
4	3	88	94.4/5.6
5	4	87	93.6/6.4
6	5	80	91.8/8.2

[a] Reactions employed 1.2 equiv of silanol. [b] Equiv of H_2O relative to Cs_2CO_3. [c] Conversion based on loss of iodide determined by GC analysis. [d] Determined by GC analysis.

Now with a reproducible procedure, the scope of the reaction could be investigated with **1** and a series of 4-substituted aryl iodides (Table 4). In all cases, the reaction showed high compatibility as well as acceptable yield for all of the coupling products. 4-Substituted aryl iodides containing electron-withdrawing substituents (entries 1, 3, and 5−7) exhibited reactivity similar to that of iodobenzene (entry 4) and those with electron-donating substituents (entry 2). All substrates showed good levels of selectivity for the cross-coupling product.

Table 4. Cross-Coupling of **1** with 4-Substituted Aryl Iodides[a]



entry	R	time (h)	product	yield (%)[b]	product ratio (**2**/**3**)[c]
1	$CO_2C_2H_5$	8	**2a**	87	95.7/4.3
2	CH_3	6	**2b**	90	94.2/5.8
3	$COCH_3$	3	**2c**	91	100/0
4	H	8	**2d**	91	93.7/6.3
5	CN	6	**2e**	85	93.3/6.7
6	CF_3	3	**2f**	87	95.4/4.6
7	NO_2	6	**2g**	88	94.0/6.0

[a] Reactions employed 1.2 equiv of silanol. [b] Yield of chromatographed, recrystallized products. [c] Determined by GC analysis.

The reaction of aryl bromides with **1** under the conditions determined for 4-substituted aryl iodides was found to be problematic, giving little or no desired product in most cases. Fortunately, replacement of the triphenylarsine with the

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(16) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(17) Hydration level determined by thermal gravimetric analysis (TGA) in the University of Illinois Microanalytical Service Laboratory.

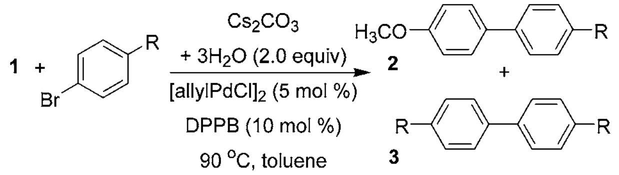
(18) TGA analysis of this sample showed 0.2 equiv of H_2O per Cs_2CO_3.

(19) For a recent review on the accelerating effect of water in organic transformations, see: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

(20) It is interesting to note that the selectivity of the reaction is not effected by the hydration level of the cesium carbonate.

bidentate additive (DPPB)[21] led to satisfactory rates of cross-coupling for these substrates (Table 5). In general, the reactions were slower than those with the aryl iodides (entries 1−3), but no homocoupling product was observed in any of the cases.

Table 5. Cross-Coupling of **1** with 4-Substituted Aryl Bromides[a]

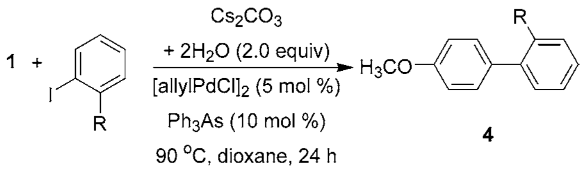


entry	R	time (h)	product	yield (%)[b]	product ratio (**2**/**3**)[c]
1	$CO_2C_2H_5$	24	**2a**	90	100/0
2	CH_3	18	**2b**	90	100/0
3	H	12	**2d**	85	100/0
4	OCH_3	18	**2h**	92	d
5	*c*-hexyl	18	**2i**	79[e]	f

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

The final class of electrophilic substrates, 2-substituted aryl iodides, also coupled slowly with **1** under the conditions previously developed for 4-substituted aryl iodides. Changing the reaction solvent to dioxane did facilitate the cross-coupling and had no detrimental effect on the selectivity of the reaction. Reinvestigation of the effect of hydration in dioxane identified the (in-situ-formed) dihydrate of Cs_2CO_3 as the optimal activator for this system. Even under these optimized conditions, the reaction rates were still attenuated compared to those obtained with 4-substituted aryl iodides in the cross-coupling of **1** (Table 6). Nevertheless, the yields of coupling products from a variety of 2-substituted aryl iodides were still high and no homocoupling products were observed in any of the cases.[22] 2-Substituted aryl iodides containing both electron-withdrawing (entries 2, 4, and 5) and electron-donating substituents (entries 1, 3 and 6) exhibited similar reactivity and yield.

Table 6. Cross-Coupling of **1** with 2-Substituted Aryl Iodides[a]



entry	R	product	yield (%)
1	CH_3	**4a**	85[c]
2	CF_3	**4b**	82[b,d]
3	OCH_3	**4c**	84[b,d]
4	NO_2	**4d**	83[c]
5	CO_2CH_3	**4e**	88[c]
6	1-naphthyl	**4f**	86[c]

[a] Reactions employed 1.2 equiv of silanol. [b] Yield of chromatographed, recrystallized products. [c] Yield of chromatographed, distilled products. [d] Yield of analytically pure material.

In summary, Cs_2CO_3 was found to be an efficient activator for the formation of unsymmetrical biaryls in the palladium-catalyzed cross-coupling reaction of arylsilanols. The importance of water in ensuring reasonable reaction rates has been demonstrated. The reaction solvent and added ligands have also been identified as crucial experimental variables that effect the rate and the selectivity of the coupling process. The success of the reaction with various aryl iodides and aryl bromides was dependent on manipulation of these key features to provide optimal results. This study provides the guidelines for a logical adjustment of reaction parameters to provide efficient, high rates, yields, and selectivities for a wide range of substrates. The expansion of the scope of silanol coupling partners is currently under investigation.

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Supporting Information Available: Detailed procedures for all coupling reactions and full characterization of **2a**−**i** and **4a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Other bidentate ligands (DPPE, DPPP, and DPPF) also facilitated the cross-coupling of **1** with arylbromides.

[22] Determined by GC analysis of the crude reaction mixture.