

Cross-Coupling of Alkynylsilanols with Aryl Halides Promoted by Potassium Trimethylsilanolate

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Abstract: The palladium-catalyzed cross-coupling of aliphatic alkynylsilanols with aryl iodides has been demonstrated with potassium trimethylsilanolate as the coupling promoter and copper(I) iodide as a cocatalyst. The cross-coupling proceeds at room temperature in good to excellent yield with a range of aryl iodides. A comparison of the reactivity of alkynylsilanols, trimethylsilylalkynes, and terminal alkynes under fluoride and fluoride-free conditions was performed to elucidate the role of silicon in the Sonogashira reaction.

Conjugated acetylenes play a major role in synthetic, pharmaceutical, and polymer chemistry.¹ One of the most widely used methods for the construction of conjugated acetylenes is the Sonogashira reaction.² Typically, this reaction involves the coupling of a terminal alkyne with an aryl or vinyl halide in the presence of catalytic amounts of both palladium and copper as well as an excess of an amine base. In the 30 years since the introduction of the Sonogashira reaction, a wide variety of alkynyl organometallic reagents have been examined as cross-coupling substrates such as alkynyltin,³ -boron,⁴ and -zinc reagents.^{5,6} These systems allow for the coupling with aryl and vinyl halides to proceed with high yield under mild conditions but frequently involve the production of toxic side products or the use of sensitive or reactive starting materials. Much less well-studied, but nonetheless viable, alkynylsilicon reagents (both silanes⁷ and silanols⁸) can function as cross-coupling precursors for the Sonogashira reaction under a wide range of reaction conditions. Activation of silicon-based cross-couplings often involves the use of fluoride ion and/or silver salts,⁹ occasionally without the need for a copper cocatalyst.¹⁰ Fluoride-free cross-coupling of trimethylsilylalkynes can be carried out in polar solvents with

copper(I) salts, albeit at elevated temperatures.¹¹ Despite the diversity of experimental protocols, the actual role of the silicon group in the Sonogashira cross-coupling is not well understood. Mechanistic proposals frequently depict transmetalation of an activated alkynylsilicon compound to palladium. However, the coupling of simple, terminal alkynes proceeds readily in the presence of either fluoride ion or silver salts.¹² Given the ready C–Si bond cleavage of alkynylsilanes,¹³ it is reasonable to suspect that fluoride-activated couplings simply involve the in-situ generation of a terminal alkyne.

Recent reports from these and other laboratories have described methods for the palladium-catalyzed cross-coupling of silanols under fluoride-free conditions.¹⁴ The development of alternative methods for activation is desirable because fluoride reagents carry the dual disadvantages of high reagent cost¹⁵ and poor compatibility with silicon-based protecting groups. These studies have shown that potassium trimethylsilanolate (KOTMS)^{15b} can promote cross-coupling of alkenylsilanols (at rates comparable to TBAF) under conditions that are compatible with silicon-based protecting groups. On the basis of these results, we suspected that KOTMS could serve as a suitable activator for the coupling of alkynylsilicon compounds with aryl halides. To demonstrate the viability of KOTMS as a promoter and to better understand the role of the silicon substituent in the Sonogashira reaction, we have undertaken a side-by-side comparison of the reactivity of alkynylsilicon derivatives and terminal alkynes under activation by both TBAF and KOTMS.

The test substrate for these studies, alkynylsilanol **2**, was prepared by a simple two-step sequence (Scheme 1). Reaction of 1-lithio-1-heptyne with chlorodimethylsilane provided the alkynylsilane in 94% yield. Oxidative hydrolysis of this silane with water in the presence of di- μ -chlorobis[(*p*-cymene)chlororuthenium(II)] provided the desired silanol **2** in 87% yield.¹⁶ The two-step synthesis

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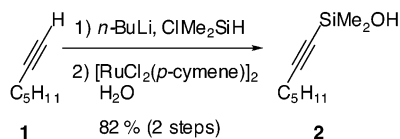
(15) (a) Tetrabutylammonium fluoride (TBAF) (Fluka) \$624/mol.

(b) Potassium trimethylsilanolate (KOTMS) (Aldrich) \$63/mol.

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was necessary as direct conversion of the lithiated alkyne to the silanol with hexamethylcyclotrisiloxane, a method used in aryl and alkenyl silanol synthesis,¹⁷ resulted in low isolated yields and disiloxane formation. However, by use of this two-step method, the purified silanol was found to be quite stable; no disiloxane formation was observed when stored at $-20\text{ }^{\circ}\text{C}$ for several months.

SCHEME 1



With the requisite alkynylsilanol in hand, the palladium-catalyzed cross-coupling of **2** to aryl halides was explored to identify suitable reaction conditions for the competition study. Because the coupling of alkynylsilanols and terminal alkynes under TBAF activation without copper(I) has been demonstrated,¹² experiments were run in the absence of copper(I). Initial optimization experiments identified $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ in DME as the best catalyst and solvent, respectively, for KOTMS-activated cross-coupling at room temperature. Unfortunately, the yield of the isolated product **3a** was poor in all cases. This result was surprising as analysis of the crude reaction mixture by GC revealed only a single product corresponding to the target arylalkyne. Closer investigation into the cause of the low mass balance led to the isolation of two side products formed during the course of the reaction (Scheme 2). The unexpected side products were identified as the cumulene **4** and enyne **5** which were not observed by gas chromatography due to their low volatility. In addition, the cross-coupling of 1-heptyne under similar reaction conditions produced an identical ratio of desired product **3a** to side products **4** and **5**. This observation suggested that the undesired process ensues from an intermediate common to both the terminal alkyne and alkynylsilanol couplings.

These types of side products have not been previously observed in a myriad TBAF-promoted cross-couplings of silanol precursors in these laboratories.¹⁸ Thus, a reinvestigation of the reaction conditions was warranted. Fortunately, the formation of the undesired byproducts **4** and **5** could be completely suppressed by the addition of a catalytic amount of copper(I) iodide to the reaction mixture. The role of copper(I) is clearly not to promote a Castro–Stephens-type coupling,¹⁹ because no reaction was observed in the absence of palladium. Similarly, no reaction occurred in the absence of KOTMS. Apparently, successful coupling at room temperature requires both activation of the silanol and copper(I) as a cocatalyst.²⁰

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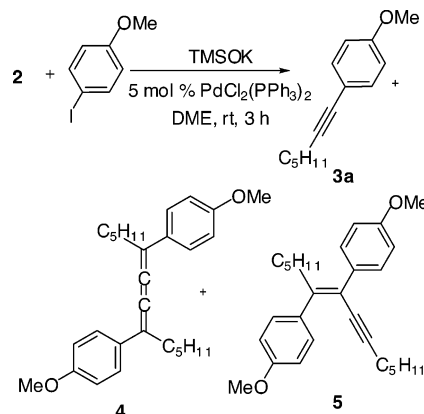
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The role of copper in promoting cross-coupling while suppressing undesired pathways is not well understood.²¹

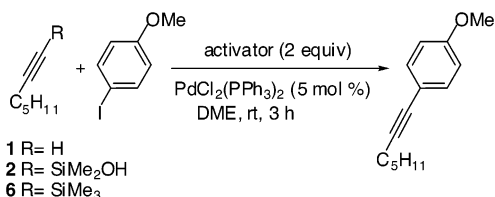
SCHEME 2



Now with appropriately optimized reaction conditions, a direct comparison of the reactivity of 1-heptyne (**1**), dimethyl(1-heptynyl)silanol (**2**), and (1-heptynyl)trimethylsilane (**6**) was undertaken. Both TBAF and KOTMS (with and without CuI) were employed as activators. First, comparison of the reactivity of these three substrates under KOTMS activation was assayed (Table 1, entries 1–3). GC analysis of each reaction mixture after 3 h revealed that silanol **2** underwent cross-coupling significantly faster than heptyne **1**. On the other hand, **6** was completely unreactive. With the addition of a catalytic amount of copper(I), the rates of coupling of all three substrates were enhanced; however, the silanol again reacted significantly faster than the other two. Indeed, under these conditions (even with only 2.5 mol % of the palladium catalyst), **2** was completely consumed in under 3 h at room temperature. The significant disparity in rate between silanol **2** and 1-heptyne **1** under KOTMS activation suggests that the silanol unit plays a key role in the transmetalation of the alkyne to palladium (or to copper thence palladium). This observation is consistent with our previous findings in related systems.¹⁸ The silanol must be activated by the KOTMS without cleavage of the Si–C bond because in-situ deprotection would give identical reaction rates for alkynes **1** and **2**.

A similar comparison of the three alkynyl substrates was performed under TBAF activation. Although all three substrates reacted, once again the silanol **2** coupled faster than both **1** and **6**. However, the differences in the observed coupling rates were not as pronounced as were seen under KOTMS activation. As a result, the role of silicon in the TBAF couplings is not as clear. The similar rates of reaction for 1-heptyne **1** and trimethylsilyl alkyne **6** could correspond to an in situ deprotection followed by fluoride-promoted cross-coupling but direct reaction of an activated silane cannot be ruled out. The somewhat increased rate of reaction for **2** does suggest that a cross-coupling pathway exists that does not go through the terminal alkyne. From a preparative standpoint, it is readily apparent that the use of KOTMS in combination

(21) We have recently speculated on the possibility of silicon to copper transmetalation in the cross-coupling of electron-deficient alkenes. Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, 68, 5153.

TABLE 1. Comparison of Coupling of Alkyne Derivatives

entry	alkyne	activator	additive	3a , ^{a,b} %	iodide, ^a %
1	1	KOTMS		<2	90
2	6	KOTMS		0	99
3	2	KOTMS		25	24 ^c
4	1	KOTMS	5 mol % CuI	14	90
5	6	KOTMS	5 mol % CuI	16	90
6	2	KOTMS	5 mol % CuI	>99	0
7	1	TBAF		17	82
8	6	TBAF		22	83
9	2	TBAF		47	42

^a Yield based on GC analysis relative to an internal standard.

^b 2.5 mol % PdCl₂(PPh₃)₂ was employed in TBAF couplings. ^c Mass balance poor due to formation of **4** and **5**.

with copper(I) iodide as a cocatalyst gives rise to an effective and high yielding cross-coupling unmatched by conditions employing TBAF alone (entries 6 and 9).²²

Next, the scope of the aryl iodides that can be used in the cross-coupling under KOTMS activation with alkynylsilanol **2** was investigated (Table 2). These cross-couplings proceeded smoothly for both electron-rich and electron-poor aryl iodides providing the desired aryl-alkyne products in high yields. Notably, both 4-iodoacetophenone and 3-iodobenzyl alcohol which could potentially be deprotonated under the basic reaction conditions gave the coupling products **3g** and **3h** in 92% and 84% yield, respectively (entries 7 and 8). The reaction with sterically hindered ortho-substituted iodides provided both **3i** and **3j** in 93% isolated yield, but required 24 h to reach completion (entries 9 and 10).

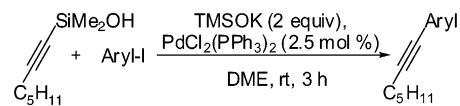
4-Bromotoluene was also tested as a representative aromatic bromide electrophile. Under the standard reaction conditions, only 25% conversion was observed after 24 h. An extensive survey of phosphine ligands²³ did not identify an additive that could effect complete conversion in this time period. However, at 60 °C, in the presence of *t*-Bu₃P, the reaction went to completion in 18 h. Unfortunately, the parent alkyne **1** behaved almost identically. Given the ability to carry out Sonogashira couplings at room temperature with this ligand and aryl bromides,²⁴ there is clearly no advantage to the silanol approach for this set of substrates.

Moreover, attempts to extend the reaction to other functionalized alkynylsilanols were unsuccessful. Alkynylsilanols derived from phenylacetylene and (triisopropylsilyl)acetylene were prepared and subjected to the reaction protocol. Coupling was observed to proceed extremely slowly with these substrates. The sluggish

(22) It should be noted that the TBAF-promoted couplings of alkynylsilanols (ref 8) and terminal alkynes (ref 12a) were performed at 60 °C.

(23) Ph₃P, (*o*-tolyl)₃P, (C₆F₅)₃P, Cy₂(2-biphenyl)P, *t*-Bu₂(2-biphenyl)P, (2-furyl)₃P, Cy₃P, (*t*-Bu₃P)₂Pd, dppb, Ph₃As.

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TABLE 2. Cross-Coupling with Various Aryl Iodides

entry	aryl	product	yield, ^a %
1	4-MeOC ₆ H ₄	3a	95
2	C ₆ H ₅	3b	93
3	1-naphthyl	3c	93
4	4-NCC ₆ H ₄	3d	75
5	4-CH ₃ C ₆ H ₄	3e	87
6	4-O ₂ N C ₆ H ₄	3f	83
7	4-CH ₃ COC ₆ H ₄	3g	92
8	3-HOCH ₂ C ₆ H ₄	3h	84
9	2-CH ₃ C ₆ H ₄	3i	93 ^b
10	2-MeOC ₆ H ₄	3j	93 ^b

^a Isolated yield of analytically pure material. ^b Reaction stirred for 24 h.

reaction can be explained through a rapid protodesilylation of the silanol under the reaction conditions to give the parent terminal alkyne. As was demonstrated in comparing heptynylsilanol **2** with 1-heptyne, the terminal alkyne formed in situ would be expected to be much less competent in the cross-coupling reaction (cf. Table 1, entries 4 and 6). The in-situ formation of the parent alkyne was confirmed through GC monitoring of the reaction mixture in which the parent alkyne was observed to form rapidly. We chose not to optimize the conditions for the coupling of these other substrates as this was deemed outside the scope of our studies on the utility of alkynylsilanols in Sonogashira coupling reactions.

In summary, the cross-coupling of aliphatic alkynylsilanols with aryl iodides has been demonstrated under fluoride-free conditions. Through comparison reactions, the alkynylsilicon groups were found to play a key role in KOTMS-promoted reactions. The KOTMS-activated cross-couplings of alkynylsilanols were superior to couplings activated by TBAF and proceeded in high yields with a variety of aryl iodides. The addition of copper(I) iodide was crucial to achieve clean reactions with reasonable rates. The mild conditions employed also make this approach a viable alternative to the traditional Sonogashira reaction.

Further investigation on the potential to transform organosilanols to organocopper reagents and subsequent manipulation is underway.

Experimental Section

General Experimental Procedures. See the Supporting Information

1-(1-Heptynyl)-4-methoxybenzene (3a). To an oven-dried, 10-mL round-bottom flask equipped with a magnetic stir bar was added 256.0 mg (2.0 mmol, 2.0 equiv) of potassium trimethylsilanolate under a dry argon atmosphere. To this was added sequentially copper(I) iodide (9.6 mg, 0.05 mmol, 0.05 equiv), 2 mL of DME, dimethyl(1-heptynyl)silanol (187.0 mg, 1.1 mmol, 1.1 equiv), 4-iodoanisole (234.0 mg, 1.0 mmol, 1.0 equiv), and PdCl₂(PPh₃)₂ (17.2 mg, 0.025 mmol, 0.025 equiv). The resulting solution was stirred at room temperature for 3 h under a dry argon atmosphere. The reaction mixture was then filtered through a silica plug (3 g) with 75 mL of anhydrous ether. The volatile solvents were removed in vacuo to afford a yellow oil. The oil was taken up in 3 mL of ether and then was purified by

silica gel column chromatography (30 mm × 30 cm) using pentane/ether, 19/1 to afford a pale yellow oil. Bulb-to-bulb distillation (ABT 150 °C, 1.0 mmHg) afforded 191 mg of **3a** (82%) as a colorless oil. Data for **3a**: bp 150 °C (1.0 mmHg ABT); ¹H NMR (500 MHz, CHCl₃) δ 7.26 (dd, *J* = 2, 7, 2 H, 2 × HC(3')), 6.75 (dd, *J* = 2, 7, 2 H, 2 × HC(2')), 3.74 (s, 3 H, -OCH₃), 2.32 (t, *J* = 7.5, 2 H, H₂C(3)), 1.52 (pent, *J* = 7.5, 2 H, H₂C(4)), 1.27–1.35 (m, 4 H, H₂C(5 and 6)), 0.86 (t, *J* = 7.5, 3 H, H₃C(7)); ¹³C NMR (126 MHz, CHCl₃) δ 159.21 (C(4')), 133.10 (C(2')), 116.49 (C(3')), 114.03 (C(1')), 89.07 (C(1)), 80.42 (C(2)), 55.48 (-OCH₃), 31.36 (C(5)), 28.80 (C(4)), 22.47 (C(6)), 19.60 (C(3)), 14.24 (C(7));

GC *t_R* 9.35 min (HP-5, 15 psi, 175 °C for 7 min, 25 °C/min to 225 °C).

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Supporting Information Available: Detailed procedures for the preparation and characterization of alkynylsilanols and arylalkynes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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