Fluoride-Free Cross-Coupling of Organosilanols

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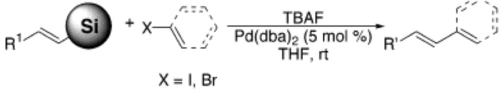
The palladium-catalyzed, cross-coupling reactions of organosilicon compounds to organic halides has, over the past decade, emerged as a viable alternative to the well-established and versatile Stille−Migita−Kosugi coupling of organostannanes[1] and Suzuki−Miyaura coupling of organoboranes.[2] Pioneering studies by Kumada and Hiyama[3] have shown that activation of organofunctional silicon compounds is possible by addition of a fluoride source to promote the palladium-catalyzed, cross-coupling reactions to various organic halides. Since this discovery, chloro- and fluoroorganosilanes and orthosiliconates[4] have been successfully employed in cross-coupling reactions.

Recent disclosures from these laboratories (Scheme 1) have demonstrated the synthetic potential of silacyclobutanes,[5a−c] silanols,[5d,e] silyl hydrides,[5e] and cyclic silyl ethers[5f] for extremely mild cross-coupling reactions which employ tetrabutylammonium fluoride (TBAF•3H_2O) as the activator.

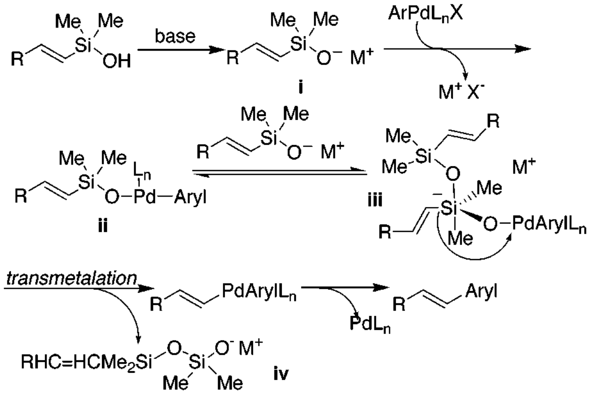
Scheme 1



Although significant progress has been made in advancing the structural versatility of organosilicon cross-coupling, one serious limitation is the use of a fluoride source as the promoter. The need for this agent precludes employment of this reaction in, for example, complex molecule synthesis where either of the coupling substrates contains silyl protective groups. Moreover, TBAF is not inexpensive[6a] and it also makes reaction workup cumbersome on a large scale. Herein we report our successful efforts toward the development of a non-fluoride-activated, organosilicon cross-coupling using inexpensive commercially available reagents.[7]

Our discovery that all of the organofunctional silane precursors converge to a common silanol intermediate in the presence of TBAF•3H_2O illuminated the crucial role played by the hydroxyl group on silicon.[8] An intriguing proposal for the facility of this silicon-based cross-coupling is the formation of a silicon−oxygen−palladium linkage (**ii**, Scheme 2) as a preassociation step prior to transmetalation, thus rendering the rate-determining step intramolecular.[9] If the prerequisite for transmetalation is to generate a pentacoordinate silicon, we hypothesized that a suitably activated species (**iii**) might be accessible by attachment of a second molecule of the silyloxide **i** with the arylpalladium silyloxide **ii** as shown in Scheme 2. In this species the transferable alkenyl group is on an "activated" silicon (central in **iii**) which can then collapse to products though an accelerated transmetalation step.[10]

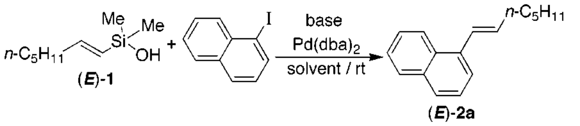
Scheme 2



To test this hypothesis would simply involve the formation of a soluble silyloxide salt in the presence of an appropriate palladium catalyst. The results from our survey of bases and solvents using (1-heptenyl)dimethylsilanol (*E*)-**1** and 1-iodonaphthalene are collected in Table 1. Whereas the lithium silyloxide was unreactive, the sodium salt, generated with NaH in THF clearly manifested the feasibility of this new process (entries 1−4). We found that 2.0 equiv of base was needed for complete conversion, which was then used throughout.[11] The reaction is considerably faster in DMF and DME. Other sodium bases (i.e., NaO*t*-Bu) were less effective promoters. The use of potassium hydride had a dramatic effect on the rate, giving complete conversion within 15 min in DME. Finally, potassium *tert*-butoxide was also able to promote the reaction and gave the highest yield despite having the lowest rate of coupling. Weaker bases, such as K_2CO_3 and K_3PO_4, were ineffective. In all cases examined, the reaction was shown to highly stereospecific.

Application of the optimal reaction conditions to the coupling of (*Z*)-**1** with 1-iodonaphthalene gave rapid cross-coupling but

Table 1. Palladium-Catalyzed Coupling of (*E*)-**1** with 1-Iodonaphthalene[a]



entry	base	solvent	time, min	yield, %[b]	*E*/*Z*-**2a**
1	MeLi	THF	1440	—[c,d]	
2	NaH	THF	480	85	99.7/0.3
3	NaH	DMF	90	78	99.5/0.5
4	NaH	DME	60	81	99.5/0.5
5	KH	THF	120	85	99.7/0.3
6	KH	DME	15	82	99.6/0.4
7	KO*t*-Bu	DME	180	90	99.4/0.6

[a] All reactions performed with 2.0 equiv of base and 5 mol % $Pd(dba)_2$. [b] Yields of chromatographically homogeneous material. [c] 47% recovery of 1-iodonaphthalene. [d] 40% yield of 1-methylnaphthalene.

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

[2] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

[3] For a recent review of the field, see: Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10.

[4] (a) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (c) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137. (d) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053.

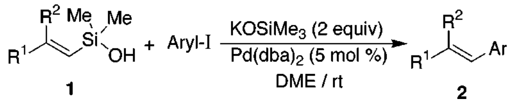
[5] (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495. (c) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999. (d) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (e) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221. (f) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61.

[6] (a) Tetrabutylammonium fluoride trihydrate (Fluka): $624/mol. (b) Potassium trimethylsilanolate (Aldrich): $63/mol.

[7] Hiyama and Mori have reported the use of stoichiometric amounts of Ag_2O as a coupling activator: (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. Hiyama has also reported the use of 6 equiv of NaOH to activate chlorosilanes in cross-coupling reactions: (c) Hagiwara, E.; Gouda, K.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439.

10.1021/ja016021q CCC: $20.00

Table 3. Palladium-Catalyzed Coupling of (*E*)- and (*Z*)-**1** with Aryl Iodides[a]

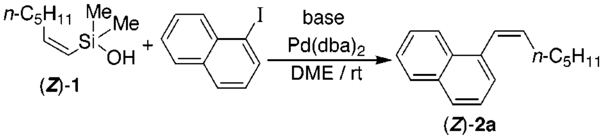


entry	silane	R^1	R^2	aryl	time, h	product	yield, %	ratio, *E*/*Z*[b]
1	(*E*)-**1**	*n*-C_5H_{11}	H	1-naphthyl	2	(*E*)-**2a**	93[c]	97.9/2.1
2	(*Z*)-**1**	H	*n*-C_5H_{11}	1-naphthyl	9	(*Z*)-**2a**	88[c]	2.8/97.2
3	(*E*)-**1**	*n*-C_5H_{11}	H	phenyl	0.5	(*E*)-**2b**	91[c]	99.3/0.7
4	(*Z*)-**1**	H	*n*-C_5H_{11}	phenyl	7.5	(*Z*)-**2b**	86[c]	1.8/98.2
5	(*E*)-**1**	*n*-C_5H_{11}	H	4-$(CH_3CO)C_6H_4$	9	(*E*)-**2c**	82[c]	98.8/1.2
6	(*Z*)-**1**	H	*n*-C_5H_{11}	4-$(CH_3CO)C_6H_4$	13	(*Z*)-**2c**	83[c]	2.9/97.1
7	(*E*)-**1**	*n*-C_5H_{11}	H	4-$(CH_3O)C_6H_4$	1	(*E*)-**2d**	88[c]	99.3/0.7[d]
8	(*Z*)-**1**	H	*n*-C_5H_{11}	4-$(CH_3O)C_6H_4$	9.5	(*Z*)-**2d**	91[c]	1.1/98.9[e]
9	(*E*)-**1**	*n*-C_5H_{11}	H	4-$(NO_2)C_6H_4$	0.25	(*E*)-**2e**	95[f]	98.5/1.5
10	(*Z*)-**1**	H	*n*-C_5H_{11}	4-$(NO_2)C_6H_4$	0.25	(*Z*)-**2e**	85[f]	3.8/96.2
11	(*E*)-**1**	*n*-C_5H_{11}	H	4-$(EtO_2C)C_6H_4$	0.25	(*E*)-**2f**	85[f]	99.8/0.2
12	(*Z*)-**1**	H	*n*-C_5H_{11}	4-$(EtO_2C)C_6H_4$	0.25	(*Z*)-**2f**	83[f]	0.7/99.3
13	(*E*)-**1**	*n*-C_5H_{11}	H	2-$(TBSOCH_2)C_6H_4$	9	(*E*)-**2g**	80[f]	99.5/0.5
14	(*Z*)-**1**	H	*n*-C_5H_{11}	2-$(TBSOCH_2)C_6H_4$	14.5	(*Z*)-**2g**	76[f]	2.0/98.0[g]

[a] Reactions employed 1.1 equiv of **1**. [b] Determined by GC analysis. [c] Yield of chromatographed, distilled products. [d] Accompanied by 3.8% cine-rearranged product. [e] Accompanied by 6.2% cine-rearranged product. [f] Yield of analytically pure material. [g] at 50 °C.

in markedly lower yields, Table 2, entry 1. The remainder of the mass balance was identified as naphthalene, presumably arising from the formation of a palladium hydride species from the excess KH. Although the formation of naphthalene could be suppressed by the use of KO*t*-Bu, the reaction rate with this base was far too low to be synthetically viable. Apparently, KO*t*-Bu is able to compete with the silyloxide for the palladium center, thus serving as a competitive inhibitor. From this observation, we reasoned that the ideal base need only be strong enough to produce a measurable equilibrium concentration of the silyloxide, be capable of associating with and activating species such as **ii**, and not be a competitive inhibitor. Logically, the first choice would be another silyloxide such as the inexpensive[6b] and soluble agent $KOSiMe_3$.[12] We were delighted to find that 2.0 equiv of this mild base could effect the cross-coupling at room temperature, in excellent yield, with stereospecificity and without reduction byproducts (albeit more slowly than KH).[13] Neither increasing nor decreasing the amount of $KOSiMe_3$improved the rate of the coupling.

Table 2. Palladium-Catalyzed Coupling of (*Z*)-1 with 1-Iodonaphthalene[a]



entry	base	equiv	time, h	yield, %	*Z*/*E*-**2a**
1	KH	2.0	0.25	48[b]	98.3/1.7
2	KO*t*-Bu	2.0	24	53[c]	85.5/14.5
3	$KOSiMe_3$	2.0	8	88	98.0/2.0
4	$KOSiMe_3$	3.0	8	73[d]	–
5	$KOSiMe_3$	1.0	18	74[d]	–
6	$KOSiMe_3$	2.0[e]	8	85[d]	–

[a] All reactions employed 5 mol % $Pd(dba)_2$. [b] 30% of naphthalene isolated. [c] 65% conversion of 1-iodonaphthalene. [d] Conversion, %. [e] 0.25 equiv of $(Me_3Si)_2O$ added.

The scope of this new, fluoride-free coupling process was examined under the optimal conditions of 2.0 equiv of $KOSiMe_3$ in DME at room temperature. The results in Table 3 illustrate that cross-coupling products were obtained in excellent yields with reasonable rates. High stereospecificities and good yields were obtained in the coupling of (*E*)- and (*Z*)-**1** to 1-iodonaphthalene and iodobenzene. In addition, both electron-rich (entries 7 and 8) and electron-deficient (entries 5−6 and 9−12) arenes couple quite well, although with varying rates. In general, electron-deficient electrophiles couple most rapidly, except 4-iodoacetophenone. Apparently, the presence of a moderately acidic proton in the substrate has a detrimental effect on the rate of coupling, although the yields were still high and no other byproducts were observed. In contrast to the fluoride-activated couplings of silanols, the rates of coupling with (*Z*)-**1** were significantly lower than those with (*E*)-**1**. The synthetic potential of this new method was clearly demonstrated by the compatibility of a silyl protective group as shown in entries 13−14. *The coupling reaction occurs cleanly in the presence of a TBS-protected alcohol on the aryl iodide,* **9g**, *without any observable deprotection.*[14]

In conclusion, we have developed a synthetically useful non-fluoride-activated, silicon-based, cross-coupling reaction that employs inexpensive, commercially available reagents. The success of in situ generated silyloxide also demonstrates the mechanistically fascinating duality of the silanol moiety as a prosthetic group for controlled carbon−carbon bond formation and as an activator for the coupling. Current efforts to expand the scope of coupling partners with this method as well as to elucidate the kinetic behavior and detailed mechanism of the reaction are in progress.

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Supporting Information Available: Representative procedures for the coupling reactions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000,** *2*, 2491. (b) Wehrli, D. Unpublished studies in these laboratories.

(9) Such an interaction has been proposed for the Suzuki coupling recently: (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461. (b) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458.

(10) For a discussion of the how oxygen substituents on palladium accelerate transmetalation, see: Miyaura. N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

(11) We surmise that the need for 2.0 equiv of base is due to the competitive formation of symmetrical disiloxane (observed by ^{1}H NMR) with lesser amounts of base.

(12) Potassium trimethylsilanolate has found use for dealkylative cleavage of esters, and hydrolysis of nitriles. (a) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831. (b) Merchant, K. J. *Tetrahedron Lett.* **2000**, *41*, 3747.

(13) We were concerned that the in situ formation of $(Me_3Si)_2O$ might in some way influence the reaction. Thus, we added this reagent to the reaction with $KOSiMe_3$ (Table 2 entry 6) and observed only negligible effects.

(14) The compatibility of a TES group to $KOSiMe_3$ (10 equiv) has been documented as well. Barrett, A. G. M.; Peña, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.