ORGANIC
LETTERS

2000
Vol. 2, No. 20
3221−3224

Mild and General Cross-Coupling of (α-Alkoxyvinyl)silanols and -silyl Hydrides

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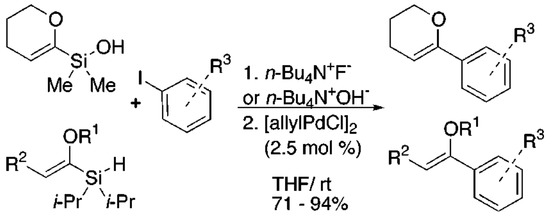
Received August 2, 2000

ABSTRACT



(α-Alkoxyvinyl)silanols and (α-alkoxyvinyl)silyl hydrides are efficiently converted to aryl vinyl ethers by a palladium(0)-catalyzed cross-coupling reaction with aryl halides in the presence of tetrabutylammonium fluoride or hydroxide. Yields are generally high, and the reaction is compatible with a wide range of functional groups.

The advent of transition metal-catalyzed cross-coupling reactions between (primarily) main-group organometallic species and organo(pseudo)halides has revolutionized the construction of linkages between unsaturated carbon centers. Among the most powerful methods are the Stille coupling of organostannanes, the Suzuki coupling of organoboranes, and the Negishi coupling of organozinc reagents.[1]

Following the pioneering work of Sakurai, Corriu, and Hiyama,[2] we have recently demonstrated that simple organosilicon compounds can serve effectively as the nucleophilic partners in cross-couplings, thus providing a viable alternative to the problems associated with toxicity (Sn) and handling (B, Zn) of other reagents.[3,4] Our initial disclosures on the use of silacyclobutanes[3a,b,d] was followed by the discovery that dialkylsilanols[3c] are equally active in cross-coupling. Notable among the features of this process are the following: (1) the mildness of the reaction conditions, (2) the short reaction times, (3) the stereospecificity with respect to both addends, and (4) the compatibility of various functional groups. As part of a rapidly expanding program to define the scope of the silanol-based cross-coupling, we have investigated the ability of various (α-alkoxyvinyl)silicon groups to be transferred to aryl and alkenyl acceptors.[5]

The rapid and high-yielding reactions of silicon electrophiles with organolithium reagents provide ready access to silicon coupling components in a single step. Thus, metalation of 2*H*-3,4-dihydropyran with *t*-BuLi according Soderquist's procedure[6] and subsequent reaction with hexamethylcyclotrisiloxane (D3)[7] resulted in the formation of [2-(5,6-dihydro-4*H*-pyranyl)]dimethylsilanol (**1**) in 68% yield, Scheme 1.

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[1] (a) Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985. (c) Tsuji, I. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 1996.

[2] 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.

[3] (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821−5288. (b) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495−1498. (c) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565−568. (d) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999−1003.

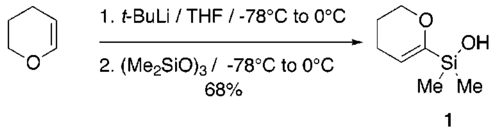
[4] For other examples of silicon-based cross-coupling, see: (a) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266−3270.

[5] To the best of our knowledge, only a single example of cross-coupling of an α-hetero-functionalized organosilane has been reported. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918−920.

[6] Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830−833.

10.1021/ol0064112 CCC: $19.00

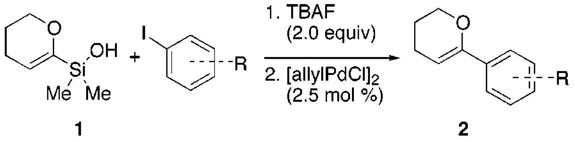
Scheme 1



The optimization of the palladium(0)-catalyzed cross-coupling was guided by our previous studies with alkenylsilanols.[3c] Accordingly, silanol **1** was first combined with a 1.0 M solution of tetrabutylammonium fluoride (TBAF·3H_2O, Fluka) in THF at room temperature, followed by the addition of the aryl iodide and the palladium complex (Pd(dba)$_2$). We were delighted to find that the reactions were clean and generally complete within 10−20 min. However, as had been noted previously, we encountered difficulties in the purification step because (1) the polarity of the products was similar to the dba ligand and to the polysilicone byproducts and (2) the products were found to be particularly labile in air and on chromatographic media. Moreover, reverse-phase (C-18) silica chromatography was either not efficient or led to partial decomposition of the products if long gradient elutions were used. By using rapid silica gel column chromatography, we were able to separate the polysilicone byproducts, but the product was always contaminated with dba. By the simple expedient of replacing the Pd(dba)$_2$ catalyst with [allylPdCl]$_2$, we were able to secure **2** in an analytically pure form.

With a viable protocol in hand, the scope of the reaction was further investigated with aryl iodides bearing electron-withdrawing or -donating groups in para, meta, or ortho positions (Table 1). For all aryl iodides examined, the reaction proved to be fast and high yielding. Several features of the reaction are noteworthy: (1) electron-withdrawing or -donating groups exhibit similar reactivity (entries 4 and 6), (2) the steric effect of ortho substituents is minimal (cf. entries 1 and 4−7) except in the case of the 2-carbomethoxy group (entry 3) were chelation between the carbonyl moiety and the palladium may slow the reductive elimination step, (3) the reaction tolerates diverse functionalities such as ester, nitro, cyano (vide infra), ether, and even hydroxyl.

Table 1. Palladium-Catalyzed Cross-Coupling of **1** with Aryl Iodides[a]



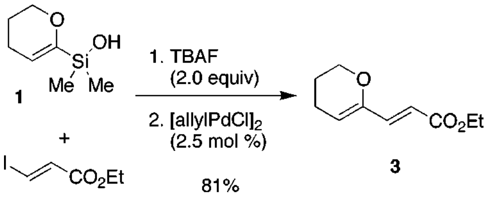
entry	R	time, min	product	yield,[b] %
1	4-CO_2Et	10	**2a**	84
2	3-CO_2Et	10	**2b**	86
3	2-CO_2Me	240	**2c**	92
4	2-NO_2	10	**2d**	85
5[c,d]	2-CH_3	20	**2e**	80
6	2-OCH_3	10	**2f**	74
7[c,d]	2-CH_2OH	20	**2g**	88
8	3-CH_2OAc	20	**2h**	87

[a] All reactions employed 1.2 equiv of **1**. [b] Yield of analytically pure materials. [c] Yield of chromatographically homogeneous materials. [d] 1.2 equiv of **1** and 5 mol % of Pd(dba)$_2$ were used.

The mild reaction conditions and uniformly high yields compare favorably with other methods to produce these compounds. For example, **2e** has been previously prepared using a Stille coupling.[8] The conditions were considerably more vigorous requiring 2 h in refluxing acetonitrile to produce **2e** in 80% yield. The silanol coupling described herein was complete in 10 min at room temperature and gave the same yield of the product. Furthermore, compound **2g** has been obtained in 55% yield from 2-bromobenzyl alcohol by use of an organostannane-based cross-coupling method.[9]

The cross-coupling of **1** with an alkenyl electrophile, ethyl (*E*)-3-iodoacrylate, was also briefly examined (Scheme 2). The reaction rate and yield were comparable to that obtained with aryl iodides, and after 2 h, **3** could be isolated in 81% yield after Al_2O_3 chromatography. The corresponding (*Z*)-3-iodoacrylate suffered decomposition under the reaction conditions and did not lead to coupling.

Scheme 2



Having demonstrated that [2-(5,6-dihydro-4*H*-pyranyl)]dimethylsilanol serves efficiently in the cross-coupling reaction, we next investigated other α-alkoxyvinyl donors such as a dihydrofuran and butoxy vinyl ether. Following on the successful coupling of silanol **1**, we first considered the use of (1-butoxyvinyl)dimethylsilanol and [2-(4,5-dihydrofuranyl)]dimethylsilanol. Unfortunately, the sequence established for the synthesis of **1** (lithiation of the vinyl group and subsequent quenching with D3) did not provide the silanols cleanly.[10] Previous experience with handling silanols suggested that increasing the bulk of the silicon substituent could make the products more tractable.[3c] Since hexaiso-

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(7) (a) Sieburth, S. McN.; Mu, W.*J. Org. Chem.* **1993**, *58*, 6314−6318. (b) Sieburth, S. McN.; Fensterbank, L. *J. Org. Chem.* **1993**, *58*, 7584−7586.

(8) Macleod, D.; Moorcroft, D.; Quayle, P.; Dorrity, M. R. J.; Malone, J. F.; Davies, G. M. *Tetrahedron Lett.* **1990**, *31*, 6077−6080.

(9) Spirocyclization of compound **2g** was observed, when dissolved in "aged" $CDCl_3$: Elsley, D. A.; Macleod, D.; Miller, J. A.; Quayle, P.; Davies, G. M. *Tetrahedron. Lett* **1992**, *33*, 409−412.

(10) Mori has reported the synthesis of [2-(4,5-dihydrofuranyl)]dimethylsilanol using D3, but in our hands the procedure failed to give pure product: Hirabayashi, K.; Takahisa, E.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2409−2417.

propylcyclotrisiloxane is not commercially available,[11] an alternative procedure was considered that involves (1) lithiation of the vinyl ether, (2) addition to chlorodiisopropylsilane (to form the intermediate silyl hydride), (3) oxidation of the hydridosilane with chlorine to form the chlorosilane, and (4) alkaline hydrolysis to produce the silanol.[3c]

However, before carrying out this sequence, it occurred to us that the hydridosilane itself might serve as a competent partner the cross-coupling reaction. Since palladium is known to insert into silicon−hydrogen bonds,[12] an intermediate R−Si−Pd−H species would be formed, which could either lead to the cross-coupled product (after transmetalation and reductive elimination) or to the reduced arene (by a hydride transfer). If indeed successful, the hydridosilane could represent a useful precursor for cross-coupling in those cases wherein the hydroxyl functionality would not be tolerated.

To test this idea, hydridosilanes **4**, **5**, and **6** were synthesized as outlined above, Scheme 3.[13] Subjecting the hydridosilane **4** to the optimized reaction protocol with 2-iodotoluene gave rise to a small amount of coupling product along with 1,5-diphenyl-3-pentanone[14] from reduction of dba. Interestingly, we noted the evolution of a gas when the silane was mixed with TBAF. Since it is well-known that hydrolysis or alcoholysis of silyl hydrides can be catalyzed by fluoride ion at room temperature (thus liberating H_2),[15] we surmised that the coupling product could have arisen from the silanol formed in situ (from the TBAF water of hydration) by hydrolysis of the silyl hydride.

Scheme 3

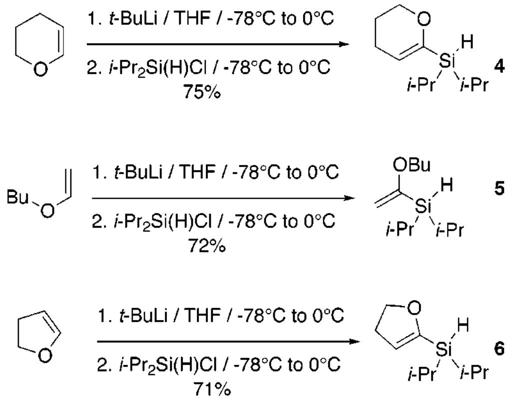
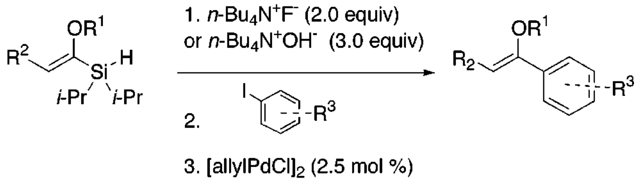
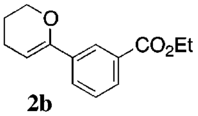
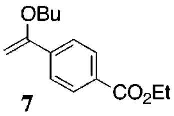
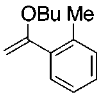
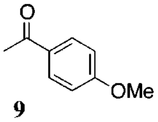
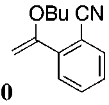
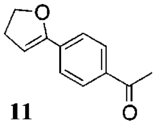


Table 2. Palladium-Catalyzed Cross-Coupling of Silyl Hydrides with Aryl Iodides[a]



entry	silane	R^3	time, min	product	yield %[b]
1[c]	**4**	$3\text{-CO}_2\text{Et}$	10	 **2b**	81
2[c,d]	**5**	$4\text{-CO}_2\text{Et}$	10	 **7**	89
3[d]	**5**	2-Me	30	 **8**	83
4[c,d,e]	**5**	4-OMe	10	 **9**	94
5[d,f]	**5**	2-CN	900	 **10**	76
6[g]	**6**	4-MeCO	10	 **11**	71

[a] 1.2 equiv of silyl hydride, 2.0 equiv of TBAF, and 2.5 mol % of [allylPdCl]$_2$ were used unless otherwise specified. [b] Yield of analytically pure materials. [c] Yield of chromatographically homogeneous materials.[d] 1.4 equiv of **5** and 2.5 mol % of [allylPdCl]$_2$ were used. [e] The intermediate enol ether was hydrolyzed directly (1 N HCl). [f] 2-Bromobenzonitrile was used. [g] 3.0 equiv of TBAOH was used.

A slight modification to the reaction protocol supported this hypothesis. The silane was first combined with TBAF solution for 10−20 min at room temperature until no gas evolution was observed. At that point the organic iodide and the palladium complex were added sequentially. Using this modified procedure,[16] we were able to prepare compounds **2b** and **7**−**11** (Table 2). For comparison, compound **2b**, which was previously prepared from silanol **1**, could be

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(11) Reaction of the lithium reagents with dichlorodiisopropylsilane was unselective and messy.

(12) (a) Kunai, A.; Sakurai, T.; Toyoda, E.; Ishikawa, M.; Yamamoto, Y. *Organometallics* **1994**, *13*, 3233−3236. (b) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569−8571.

(13) 2-(4,5-Dihydrofuranyl)dimethylsilane and [2-(5,6-dihydro-4*H*-pyranyl)]dimethylsilane have been described: (a) Lukevics, E.; Gevorgyan, V.; Golberg, Y.; Popelis, J.; Garvas, M.; Gaukhman, A.; Shimanska, M. *Heterocycles* **1984**, *22*, 987−991. (b) Gevorgyan, V.; Borisova, L.; Lukevics, E. *J. Organomet. Chem.* **1990**, *393*, 57−67. (c) Groh, B. L.; Magrum, G. R.; Barton, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 7568−7569.

(14) Chen, C.-D.; Huang, J.-W.; Leung, M.-K.; Li, H.-h. *Tetrahedron* **1998**, *54*, 9067−9078.

(15) Deneux, M.; Akhrem, I. C.; Avetissian, D. V.; Myssoff, E. I.; Vol'pin, M. E. *Bull. Soc. Chim. Fr.* **1973**, 2638−2642.

(16) This is the same protocol developed for the cross-coupling of silacyclobutanes which also need to be "hydrolyzed" prior to reaction. For a mechanistic investigation, see: Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491−2494.

isolated in 81% yield starting from silyl hydride **4**. Synthesis of aryl butoxy vinyl ethers could also been achieved. As in the case of **1**, electron-withdrawing or -donating groups exhibit nearly the same reactivity (entries 2 and 4), but with **5**, steric effects attenuate the rate of reaction (entry 3). Even the less reactive 2-bromobenzonitrile afforded the corresponding aryl vinyl ether **10** in 76% yield.[17] These coupling products also proved difficult to purify to analytical standards. For example, in the case of 4-iodoanisole, the vinyl ether had to be hydrolyzed to the methyl ketone **9** to facilitate characterization.

Attempted reaction of silyl hydride **6** under these conditions surprisingly failed. Closer inspection of the reaction mixture revealed that, unlike **4** or **5**, **6** suffered rapid protiodesilylation in the presence of TBAF releasing dihydrofuran. Fortunately, replacement of the TBAF solution with tetrabutylammonium hydroxide (3.0 equiv) solution in MeOH allowed the coupling reaction to proceed smoothly and compound **11** was isolated in 71% yield (Table 2, entry 6). The base-promoted hydrolysis of silyl hydrides to silanols is well documented[18] as is our prior demonstration of the ability of hydroxide ion to promote the cross-coupling of silanols.[3c] The disparate behavior of the dihyropyranyl- compared to the dihydrofurylsilane underscores how subtle changes in structure influence the balance between success and failure in these complex, metal-catalyzed processes. Moreover, the mildness of this procedure holds particular promise for the use of the silyl hydride variant in complex molecule synthesis.

In conclusion, we have demonstrated that (α-alkoxyvinyl)-silanol (**1**) is a versatile donor for Pd(0)-catalyzed cross-coupling reactions with aromatic halides. In addition, we have shown that (α-alkoxyvinyl)silyl hydrides **4**, **5**, and **6** serve as viable precursors for the corresponding silanols and, after in situ activation with fluoride or hydroxide ion, undergo rapid and high-yielding cross-coupling with aryl halides. In the case of vinyl ether **5** this process allows for the ready preparation of methyl ketones by simple hydrolysis.

Further studies on the ability of other silafunctional components to participate in the reaction, along with application of these reagents in the synthesis of *C*-arylglycosides are in progress.

Acknowledgment. We are grateful to the National Science Foundation (NSF CHE 9803124) and the Pharmacia and Upjohn Company for generous financial support.

Supporting Information Available: Procedures for the preparation and full characterization of **1**, **4**, **5**, and **6** as well as for **2a−2h**, **3**, **7**, **8**, **10**, and **11** and representative procedures for coupling reactions . This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Typical conditions for the cross-coupling of 1-(ethoxyvinyl)-tributylstannane with aryl halides are considerably more harsh (95−105 °C, 18−96 h). Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114−3118.

[18] Eaborn, C. *Organosilicon Compounds;* Butterworth: London, 1960; p 200.