ORGANIC
LETTERS

2003
Vol. 5, No. 11
1895−1898

Ruthenium-Catalyzed Vinylsilane Synthesis and Cross-Coupling as a Selective Approach to Alkenes: Benzyldimethylsilyl as a Robust Vinylmetal Functionality

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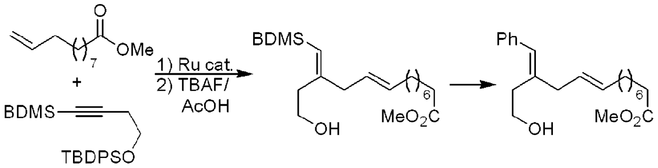
Received March 17, 2003

ABSTRACT



Ruthenium-catalyzed alkyne hydrosilylation or silyl-alkyne Alder ene reactions provide entry into benzyldimethylsilyl (BDMS)-substituted alkenes. The BDMS-vinylsilanes are further elaborated through mild palladium-catalyzed cross coupling and show significant stability to intervening synthetic operations, including silyl ether deprotection.

In the course of several recent studies into the synthesis of variously substituted vinylsilane products by simple addition reactions in the presence of a ruthenium catalyst,[1,2] we are investigating the synthetic elaboration of the vinylsilane products. Palladium-catalyzed cross-coupling reactions of vinylsilanes have been increasingly investigated in recent years and are an important synthetic application of these products.[3−5] Typically, silanes with heteroatom substituents are necessary for efficient reactivity,[6] and hydrosilylation with alkoxysilanes followed by cross-coupling can be an efficient process.[2,7] However, in the context of Alder ene reactions,[1] extension to alkoxy silanes proved to be problematic, as the alkoxy-alkynylsilane reagents are much less stable than their alkoxy-vinylsilane counterparts and are subject to hydrolysis and/or decomposition even under the mild Lewis acid conditions of the ruthenium catalyst.

In addition to these challenges specific to our investigations, alkoxy-vinylsilanes in general suffer from a number of drawbacks. The sterically undemanding silanes that give the best results in cross-coupling reactions are sensitive to acidic or basic hydrolysis. This problem becomes much worse when molecules contain neighboring functionality such as hydroxyl groups, since the vinylsilane then cyclizes to give an even less stable silacycle, necessitating the use of hydroxyl protecting groups. Finally, such alkoxy-vinylsilanes are generally incompatible with silicon-based protecting groups, and in our view the incompatibility with silicon-based protecting groups represents a substantial obstacle to the use of silicon-based cross-coupling reactions in synthesis.[4]

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[1] Trost, B. M.; Machacek, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693−4697. Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. *Org. Lett.* **2000**, *2*, 1761−1764.

[2] Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726−12727.

[3] (a) Denmark, S. E.; Pan, W. *J. Organomet. Chem.* **2002**, *653*, 98−104. (b) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771−3774. (c) Denmark, S. E.; Pan, W. T. *Org. Lett.* **2001**, *3*, 61−64. (d) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299−301.

[4] Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439−6440.

[5] Mowery, M.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137−2140.

[6] Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541.

[7] Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565−568. Denmark, S. E.; Wang, Z. G. *Org. Lett.* **2001**, *3*, 1073−1076.

10.1021/ol034463w CCC: $25.00

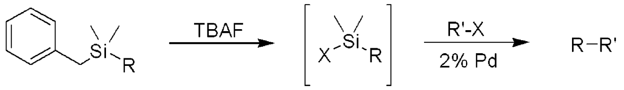


Figure 1.

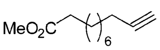
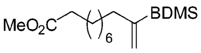
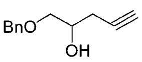
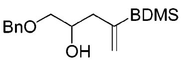
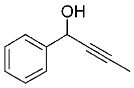
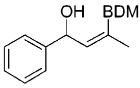
We set out to find a more stable, all-carbon-substituted silicon group that would still function in cross-coupling. Although some groups have utilized all-carbon silicon species in cross-coupling reactions,[8] the previously reported methods have not been demonstrated to possess the desired attributes described above.[9] Phenyldimethylsilyl is an extremely stable cross-coupling precursor but requires harsh activation conditions.[8c,d] Thiophenyl[9] and pyridyl[8e] groups provide efficient coupling; however, their stability has not been well demonstrated. Also, thiophenyl and pyridyl groups are themselves reactive moieties that might interfere with intervening chemistry. Efforts with the benzyldimethylsilyl (BDMS) group in oxidation chemistry led us to consider the use of this group for cross coupling.[10] The BDMS group is surprisingly stable to acid and buffered fluoride conditions, as well as to strong base. However, it undergoes debenzylation virtually instantaneously at 0 °C with TBAF in THF as the first step in the oxidation of such species, presumably to an Si-X intermediate,[8b] which then is oxidized by the addition of peroxide. The ease of this transformation under conditions identical to those commonly employed in cross-coupling reactions led us to postulate that debenzylation in the presence of an appropriate coupling partner, followed by the addition of a palladium catalyst, would lead to cross-coupled products in a simple operation.

Initially, we investigated the ruthenium-catalyzed synthesis of various benzyldimethylvinylsilanes through hydrosilylation (Table 1) and alkyne−alkene coupling reactions (Table 2). Both pathways produce highly functionalized, geometrically defined di- or trisubstituted olefins (Table 1).[11] Whereas the more reactive and labile alkoxy or strained cycloalkyl silanes are not compatible with the alkene−alkyne coupling reaction, the benzyldimethyl silyl group cleanly affords the 1,4-diene products in good yields. Importantly, the BDMS group is stable to chromatography and does not undergo silacycle formation with the pendant free hydroxyl (Table 1, entry 3).

With access to the benzyldimethylvinylsilanes in hand, we turned to the cross-coupling reaction. Treatment of 1,1-disubstituted vinylsilanes and the desired electrophilic partner with TBAF at 0 °C, followed by addition of 2.5% Pd_2dba_3• $CHCl_3$ and stirring at ambient temperature, affords the 1,1-disubstituted products.[12] The mild reaction conditions lead

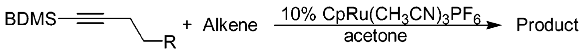
Table 1. Alkyne Hydrosilylation with Benzyldimethylsilane[a]

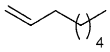
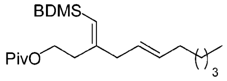
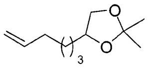
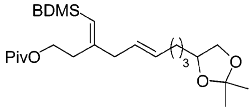
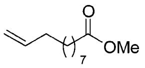
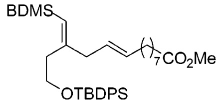
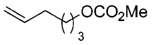
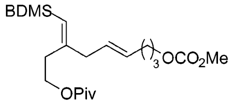
$$\text{Alkyne} \xrightarrow[\text{acetone}]{\text{2\% Cp*Ru(CH}_3\text{CN)}_3\text{PF}_6 \quad \text{1.2 eq. BDMS-H}} \text{Product}$$

	alkyne	product	yield
1			100
2			91[b]
3			91

[a] All reactions employed 1.0 equiv of alkyne and 1.2 equiv of BDMS−H in acetone (*x* M) at room temperature and were complete within 20 min. [b] Isolated as a 14:1 regioisomeric mixture.

Table 2. Alder Ene Reactions of Benzyldimethylsilyl-alkynes[a]



	R	alkene	product	yield[b]
1	OPiv			79
2	OPiv			81
3	O-TBDPS			60 (75)
4	OPiv			62 (77)

[a] All reactions employed 1.0 equiv of alkyne and 5.0 equiv of alkene in acetone (0.2 M) at room temperature and were complete within 4 h. [b] Yields in parentheses represent yield based on recovered starting alkyne.

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[8] (a) Denmark, S.; Choi, J. *J. Am. Chem. Soc.* **1999**, *121*, 5821−5822. (b) Denmark, S.; Wehrli, D.; Choi, J. *Org. Lett.* **2000**, *2*, 2491−2494. (c) Anderson, J.; Anguille, S.; Bailey, R. *Chem. Commun.* **2002**, 2018−2019. (d) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317. (e) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 11577−11585.

[9] During the course of this work, it was reported that alkenyldimethyl-(2-thienyl)silanes offer significant acid and base stability and also function in cross-coupling reactions: Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, 138−139.

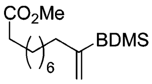
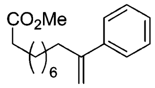
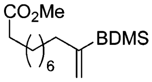
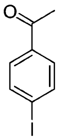
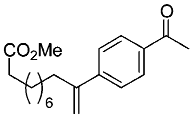
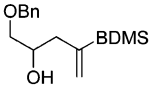
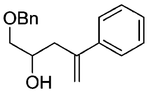
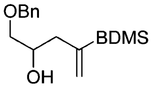
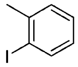
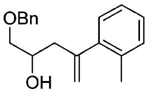
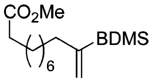
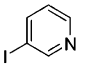
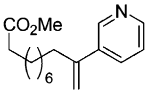
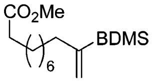
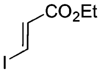
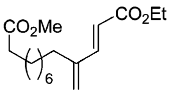
[10] Miura, K.; Hondo, T.; Takahashi, T.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 2129−2132.

[11] Note that the BDMS does slow the rate of the alkene−alkyne coupling reaction in comparison to the TMS group. This lowers the turnover number for very complex coupling partners.

[12] **General Procedure for Cross Coupling.** A solution of vinyl benzyldimethylsilane (1 equiv) and aryl or vinyl halide (1.5 equiv) in THF (0.3 M) under Ar was cooled to 0 °C. Tetrabuylammonium fluoride (2.2 equiv, 1 M in THF) was added dropwise, and the resulting solution was stirred for 10 min. Solid Pd_2dba_3•$CHCl_3$ (2.5 0.025 equiv) was added, and the reaction was allowed to warm to room temperature. Reactions were generally complete within 4 h, whereupon the dark solution was flushed through a plug of silica with ether, concentrated in vacuo, and purified via silica chromatography.

to a general process that is tolerant of many functional groups, including esters and free alcohols. A variety of electrophilic partners (Table 3) can be successfully employed, including sterically hindered *ortho*-iodotoluene and heteroaromatics such as 3-iodopyridine. Furthermore, under the same conditions, *trans*-iodoacrylate is coupled to afford a synthetically useful 1,4-diene.

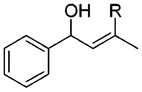
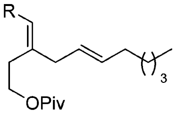
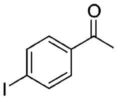
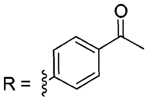
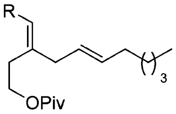
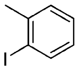
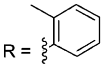
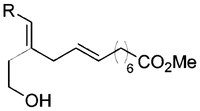
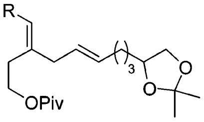
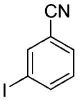
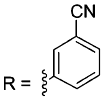
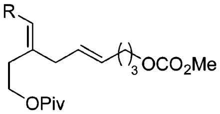
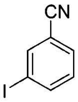
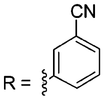
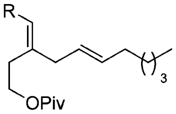
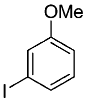
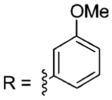
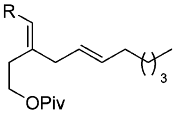
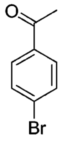
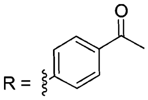
Table 3. Palladium-Catalyzed Cross-Coupling of 1,1-Disubstituted Vinylsilanes[a]

	vinyl silane	R-X	product	% yield
1		PhI		97
2				89
3		PhI		95[b]
4				91[b]
5				78[c]
6				65

[a] All reactions employed 1.0 equiv of vinyl BDMS and 1.5 equiv of R−X in THF (0.3 M) at 0 °C. TBAF (2.2 equiv) was added, and the mixture was stirred for 10 min followed by addition of 2.5% Pd$_2$dba$_3$·CHCl$_3$. The mixture was then stirred at room temperature. Reactions were complete within ca. 4 h. [b] Isolated as a 14:1 regioisomeric mixture from the hydrosilylation step. [c] Reaction was performed at 50 °C.

Sterically encumbered vinylmetal species have consistently been difficult coupling partners in classic cross-coupling reactions such as the Stille reaction.[13] Generally, these substrates require extra additives, heat, and long reaction times. However, the cross coupling of sterically hindered trisubstituted benzyldimethylsilanes proceeds well under the aformentioned conditions (Table 4).[3a,c] Sterically hindered electrophiles (*ortho*-iodotoluene) still afford products in good yield. Electron-rich aryl iodides (3-iodoanisole) also couple in moderate yields. More striking is the coupling of activated aryl bromides at room temperature in good yields. This mild protocol performs better than those previously reported that require higher temperatures and more forcing reaction conditions.[5]

Table 4. Palladium-Catalyzed Cross-Coupling of Trisubstituted Vinylsilanes[a]

	vinyl silane (R=BDMS)	R-X	product	% yield
1		PhI	R=Ph	76
2				91
3				79
4		PhI	R = Ph	88[b]
5				92[c]
6				70[c]
7				60
8				67[c,d]

[a] All reactions employed 1.0 equiv of vinyl BDMS and 1.5 equiv of R−X in THF (0.3 M) at 0 °C. TBAF (2.2 equiv) was added, and the mixture was stirred for 10 min followed by addition of 2.5% Pd$_2$dba$_3$·CHCl$_3$. The mixture was then stirred at room temperature. Reactions were complete within ca. 4h. [b] Isolated as a 14:1 mixture of olefin regioisomers from the hydrosilylation step. [c] Reaction performed at 50 °C.

The ubiquity of silicon-based hydroxyl protecting groups in synthesis puts serious constraints on cross-coupling methodologies that are incompatible with such protecting groups. Unfortunately, most activated vinyl silanes used for cross-coupling are not stable to the mild protocols for removal of silyl ether protecting groups. However, the BDMS group is stable to many conditions typically employed to remove silyl ethers. For example, an alcohol protected with the robust TBDPS group (eq 2) can be cleanly liberated in the presence of buffered fluoride, i.e., TBAF and AcOH, in aqueous DMF without affecting the vinyl BDMS. To our knowledge, this is the first demonstration of a silicon cross-coupling precursor stable to silyl ether deprotection. Furthermore, treatment of vinyl BDMS with mild acid or strong base (3 M NaOH/MeOH) returns the vinyl silane unscathed. We believe that the results presented here offer more

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[13] (a) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605. (b) For a general review of cross coupling: Stang, P. J. *Metal Catalyzed Cross Coupling Reactions*; Diederich, F., Ed.; Wiley-VCH: New York, 1998.

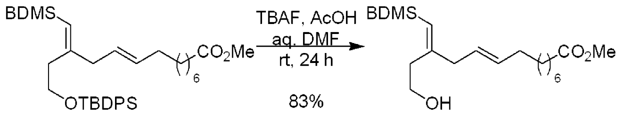

Figure 2.

flexibility in timing the installation of a vinylmetal species, allowing it now to be done at an early stage in chemical synthesis. It is also possible to carry such groups through a wide variety of intervening chemistry rather than being required to install vinylmetal groups immediately prior to their use. The stability of the BDMS group to silyl ether deprotection is an important step toward an orthogonal silicon-based cross-coupling method, though it is important to note that the alternative, cross-coupling in the presence of silyl ethers,[14] likely removes a silyl ether during the TBAF-mediated cross-coupling of the BDMS-substituted olefin.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. Z.T.B. is a Stanford Graduate Fellow. Mass Spectra were provided by the Mass Spectrometry Regional Center of the University of California–San Francisco supported by the NIH division of Research Resources.

Supporting Information Available: Experimental procedures as well as characterization data for all vinylsilanes and coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Fluoride-free coupling of silyl groups bearing an Si–OH have been shown to be compatible with silyl ethers. See ref 4.