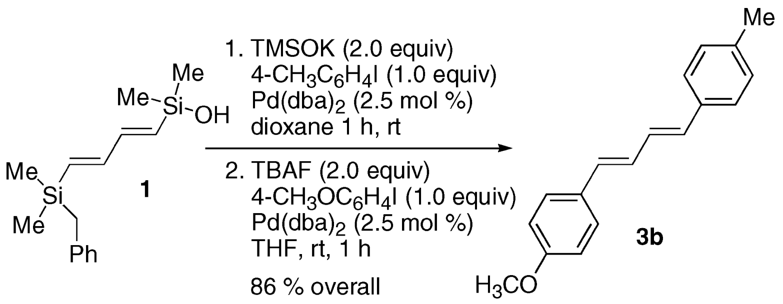
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Sequential Cross-Coupling of 1,4-Bissilylbutadienes: Synthesis of Unsymmetrical 1,4-Disubstituted 1,3-Butadienes

Scott E. Denmark, and Steven A. Tymonko

J. Am. Chem. Soc., **2005**, 127 (22), 8004-8005• DOI: 10.1021/ja0518373 • Publication Date (Web): 14 May 2005



ACS Publications
High quality. High impact.

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Published on Web 05/14/2005

Sequential Cross-Coupling of 1,4-Bissilylbutadienes: Synthesis of Unsymmetrical 1,4-Disubstituted 1,3-Butadienes

Scott E. Denmark* and Steven A. Tymonko

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received March 22, 2005; E-mail: denmark@scs.uiuc.edu

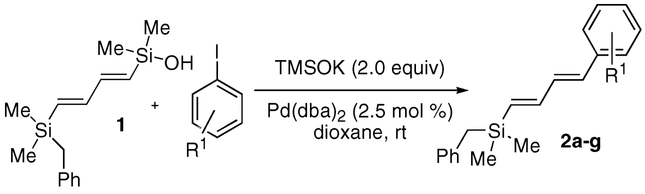
Highly conjugated systems, such as polyenes and aryl polyenes, are a common structural motif in natural products[1] and are also featured prominently in nonlinear optical materials.[2] Traditionally, the synthesis of polyenes relies heavily on stepwise construction of carbon−carbon double bonds independently.[3] However, this approach is tedious and often suffers from poor stereocontrol in setting the alkene geometry. More recently, cross-coupling methods have been employed for the synthesis of a number of polyene natural products in which the key carbon−carbon bond forming step creates the C−C single bond.[4] Highly conjugated systems can be rapidly accessed through double coupling of symmetrical bisstannanes[5] and bisboranes[6] to form symmetrical products. Unsymmetrical products can be prepared through stepwise cross-coupling of 1,2-bis(tributylstannyl)ethylene[7] or reagents bearing two different metals.[8]

Recent reports from these laboratories[9] have demonstrated that many structurally diverse organosilanols are viable precursors in cross-coupling reactions and that these silanols can couple by two mechanistically distinct processes.[10] One pathway is operative under basic conditions and requires only that the silanolate be formed, no additional activation is needed. The second pathway involves the use of fluoride sources that can form the active fluorosiliconate in situ from the silanol or from other precursors. In addition to heteroatom functionalized precursors, a number of phantom or "safety catch" silanes have been developed recently that bear a fluoride cleavable carbon-based residue such as silacylcobutyl,[9f] phenyldimethyl-,[11] 2-pyridyldimethyl-,[12] benzyldimethyl-,[13] and 2-thienyldimethylsilanes.[14]

The availability of these masked silanols presents the intriguing possibility of devising a bissilyl reagent bearing one silyl substituent which readily couples under basic activation while the other silyl substituent is inert. Subsequent fluoride-promoted coupling of the second silyl substituent would allow for sequential coupling in unsymmetrical substrates with an otherwise symmetrical backbone. In this manner, the different mechanistic pathways of base- and fluoride-activated cross-coupling can be used to distinguish between silicon substituents. We describe herein the preparation and sequential cross-coupling of two such differentiable 1,4-bissilylbutadienes.

The viability of this approach was first tested with the bissilyl reagent (*E*,*E*)-[(4-benzyldimethylsilyl)-1,3-butadienyl]dimethylsilanol (**1**).[15] Under activation by KOTMS, bissilyldiene **1** displayed reactivity comparable to that of simple vinyl silanols and reacted uniquely at the silanol moiety, leaving the benzyldimethyl unit intact.[9d] To explore the scope of the KOTMS-promoted reaction, the coupling of **1** was performed with a variety of aryl iodides with $Pd(dba)_2$ as the catalyst (Table 1). The reaction was found to display little dependence upon the electronic nature of the iodide as electron-poor aryl iodides required 0.5 h to reach completion (entries 2 and 5) while electron-rich iodides required only 1 h (entries 1 and 3). The introduction of ortho substituents was found to have a significant rate-retarding effect. Thus, 1-iodonaphthylene and 2-iodotoluene (entries 6, 7) required respectively 4 and 6 h to reach completion. Surprisingly, 4-iodoacetophenone reacted extremely slowly (18 h) under the reaction conditions (entry 4). This sluggish coupling has been previously observed[9d] and could be attributed to the presence of moderately acidic protons on the aryl iodide.

Table 1. TMSOK-Promoted Cross-Coupling of **1** with Aryl Iodides[a]

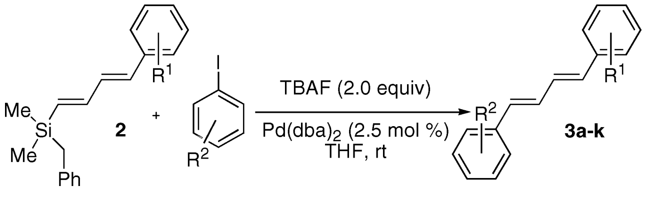


entry	R^1	product	time (h)	yield (%)[b]
1	4-Me	**2a**	1	85
2	4-CN	**2b**	0.5	93
3	4-OMe	**2c**	1	88
4	4-COMe	**2d**	18	76
5	4-NO_2	**2e**	0.5	96
6	*c*	**2f**	4	91
7	2-Me	**2g**	6	96

[a] All reactions employed 1.0 equiv of halide. [b] Yields of analytically pure material. [c] 1-Iodonaphthalene was used.

The successful and selective cross-coupling of the silanol moiety in **1** allowed for the fluoride-based activation of the benzyldimethylsilyl unit for the second cross-coupling event. In the presence of TBAF (2.0 equiv), the benzylsilane reacted cleanly with a wide range of aryl iodides in excellent yield (Table 2). The reaction

Table 2. Fluoride-Promoted Cross-Coupling of **2** with Aryl Iodides[a]



entry	R^1	substrate	R^2	product	time (h)	yield (%)[b]
1	4-OMe	**2c**	4-CO_2Et	**3a**	15 min	88
2	4-OMe	**2c**	4-Me	**3b**	15 min	86
3	4-OMe	**2c**	4-OMe	**3c**	15 min	91
4	4-Me	**2a**	4-CO_2Et	**3d**	1 h	85
5	4-Me	**2a**	4-$COCH_3$	**3e**	1 h	90
6	4-Me	**2a**	4-OMe	**3b**	1 h	91
7	4-Me	**2a**	3-CO_2Et	**3f**	1 h	90
8	4-Me	**2a**	2-CO_2Me	**3g**	1 h	74
9	4-Me	**2a**	*c*	**3h**	1 h	92
10	4-Me	**2a**	*d*	**3i**	4 h	72
11	4-Me	**2a**	2-Me	**3j**	1 h	90
12	4-Me	**2a**	2-CH_2OH	**3k**	12 h	89

[a] All reactions employed 1.0 equiv of halide. [b] Yields of analytically pure material. [c] 1-Iodonaphthalene was used. [d] Ethyl (*E*)-3-iodoacrylate was used.

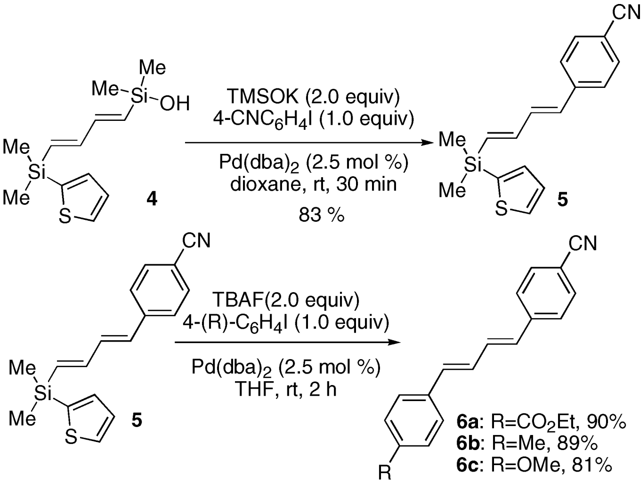
10.1021/ja0518373 CCC: $30.25

displays little dependence upon the electronic and steric nature of the aryl iodide. Electron-poor and electron-rich substrates (entries 4 and 6) as well as ortho-, meta-, and para-substituted iodides (entries 8, 7, and 4) all reacted completely in under 1 h. Notably, (unprotected) 2-iodobenzyl alcohol was a viable substrate for the cross-coupling, affording an 89% yield after 12 h (entry 12). Vinyl iodides could also be engaged in the fluoride-promoted coupling to prepare conjugated trienes. Reaction of **2a** with ethyl (*E*)-3-iodoacrylate, albeit slower than that of aryl substrates, provided triene **3i** in 72% yield after 4 h (entry 10). The overall yield of the two-step coupling process could be improved by subjecting the crude products obtained from the KOTMS-activated coupling to the TBAF-promoted coupling conditions. In this manner, 1,4-diaryl-1,3-butadienes **3b** and **3d** were prepared in enhanced yield relative to the two-step procedure (86 vs 77% and 84 vs 72%, respectively) without any loss in reaction rate or selectivity.

Whereas the electronic character of the iodide coupling partner did not influence the reaction rate, the electronic nature of the benzylsilanes has a significant effect on the fluoride-promoted coupling. Cross-coupling with electron-rich substrate **2c** (derived from an initial coupling with 4-iodoanisole) was significantly faster than the corresponding reactions with silane **2a** (derived from an initial coupling with 4-iodotoluene) (entries 1 and 4). Although the increased reactivity of **2c** is consistent with a turnover limiting transmetalation to an electrophilic arylpalladium(II) intermediate,[10a] the distance over which the electronic perturbation influences the reaction is surprising. Unfortunately, this electronic influence extends to benzylsilanes bearing electron-withdrawing substituents, making then poor substrates for the fluoride-promoted coupling. Under fluoride activation, migration of the benzyl group to the diene, as recently demonstrated by Trost,[16] is competitive with cross-coupling. Attempts to unmask the latent silanol under acidic conditions resulted in desilylation of the diene.

To overcome the problematic benzyl migration, bissilane **4**, in which a 2-thienyl group replaces the benzyl group, was prepared.[15] It was expected that the 2-thienylsilane would survive the initial cross-coupling and provide the desired silanol upon treatment with fluoride without migration.[12] Gratifyingly, KOTMS cleanly and efficiently promoted the cross-coupling of **4** with 4-iodoacetonitrile to afford **5** in 83% yield (Scheme 1). Most importantly, though, the 2-thienyl group was dispatched without incident, and the fluoride-promoted cross-coupling of **5** with ethyl 4-iodobenzoate provided the 1,4-diaryl-1,3-butadiene **6a** bearing two electron-withdrawing substituents.

Scheme 1



In conclusion, we have demonstrated the ability to differentiate the termini of a 1,4-bissilyl-1,3-diene by taking advantage of the mechanistic duality in silicon-based cross-coupling reactions. Through the use of substrates bearing two distinct silyl subunits and complementary reaction promoters KOTMS and TBAF, this approach allows for the construction of unsymmetrical disubstituted 1,4-butadienes. Extension of this method to the preparation of substituted butadienes, geometric isomers of the butadienes, and tetraenes is in progress.

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support. (GM 63167).

Supporting Information Available: Preparation of **1** and **4**, detailed experimental procedures, and full characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999−1023.
(2) For applications of polyenes in nonlinear optics, see the special issue: *Chem. Phys.* **1999**, *245*.
(3) (a) Mori, Y.; Asai, M.; Kawade, J.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315−5330. (b) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685−4696. (c) Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1941−1946.
(4) Representative examples: (a) Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703−706. (b) Dominguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071−15098. (c) Lipshutz, B. H.; Ullman, B.; Lindsley, C.; Pecci, S.; Buzard, D. J.; Dickson, D. *J. Org. Chem.* **1998**, *63*, 6092−6093. (d) Torrado, A.; Iglesias, B.; Lopez, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435−2454.
(5) Representative examples: (a) Zimmermann, E. K.; Stille, J. K. *Macromolecules* **1985**, *18*, 321−327. (b) Thibonnet, J.; Abarbri, M.; Parrain, J.; Duchene, A. *Synlett* **1997**, 771−772. (c) Andersen, D. L.; Back, T. G.; Janzen, L.; Michalak, K.; Pharis, R. P.; Sung, G. C. Y. *J. Org. Chem.* **2001**, *66*, 7129−7141.
(6) (a) Todd, M. H.; Balasubramanian, S.; Abell, C. *Tetrahedron Lett.* **1997**, *38*, 6781−6784. (b) Chaumeil, H.; Le Drian, C.; Defoin, A. *Synthesis* **2002**, 757−760. (c) Li, C.; Shien, S.; Lin, S.; Liu, R. *Org. Lett.* **2003**, *5*, 1131−1134. (d) Perret-Aebi, L.; von Zelewsky, A. *Synlett* **2002**, 773−774.
(7) Representative examples: (a) Waterson, A. G.; Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305−4308. (b) Anderson, O. P.; Barrett, A. G. M.; Edmunds, J. J.; Hachiya, S.; Hendrix, J. A.; Horita, K.; Malecha, J. W.; Parkinson, C. J.; VanSickle, A. *Can. J. Chem.* **2001**, *79*, 1562−1592. (c) In addition, an approach to differentiating 1,6-bisstannanes has been reported: Sorg, A.; Bruckner, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523−4526.
(8) (a) Murakami, M.; Matsuda, T.; Itami, K.; Ashida, S.; Terayama, M. *Synthesis* **2004**, *9*, 1522−1526. (b) Babudri, F.; Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron* **1998**, *54*, 1085−1094. (c) Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966−1968.
(9) (a) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapter 4. (b) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75−85. (c) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. (d) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439−6440. (e) Denmark, S. E.; Wang, Z. *Org Lett.* **2001**, *3*, 1073−1076. (f) Denmark, S. E.; Choi, J.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821−5822.
(10) (a) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865−4875. (b) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876−4882.
(11) Anderson, J. C.; Munday, R. H. *J. Org. Chem.* **2004**, *69*, 8971−8974.
(12) Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 5600−5601.
(13) Trost, B. M.; Machacek, M. R.; Ball, Z. *Org. Lett.* **2003**, *5*, 1895−1898.
(14) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, *31*, 138−139.
(15) See Supporting Information for the preparation of reagents **1** and **4**.
(16) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942−13944.

JA0518373