J|A|C|S
COMMUNICATIONS

Published on Web 06/07/2008

Highly Chemoselective and Stereoselective Synthesis of *Z*-Enol Silanes

Ananda Herath and John Montgomery*
Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055
Received April 17, 2008; E-mail: jmontg@umich.edu

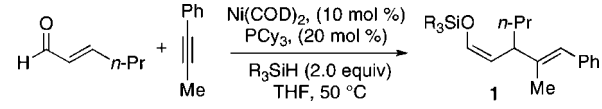
Enol silanes are broadly useful in a range of synthetic transformations including Mukaiyama aldol reactions, Mannich reactions, and metalation to more reactive enolates for subsequent alkylation.[1] The ability to selectively prepare a single alkene stereoisomer renders enol silanes especially valuable in stereospecific transformations. Whereas enolization/silylation sequences of ketones, esters, and amides are well-developed, the corresponding transformations involving aldehydes are limited due to the well-recognized problem of self-condensation competing with enolization. However, powerful strategies for aldol reactions of aldehyde-derived enol silanes have recently emerged,[1] thus suggesting that novel preparative entries to the requisite starting materials could greatly expand the range of possible applications.

The direct enolization of aldehydes is typically accomplished by the combination of silyl triflates with amine bases.[1] Whereas at least modestly *Z*-selective reactions are typically observed, obtaining high selectivity is often challenging. Enone conjugate additions are well-known to be accelerated by silyl chlorides.[2] Similarly, enal conjugate addition/electrophilic silylation sequences are sometimes successful, and these procedures uniformly generate *E*-enol silanes.[3] A feature of each of the above-mentioned strategies for enol silane generation is that electrophilic silylation is involved, and site-selective enol silane installation following these methods is unknown in the presence of reactive groups that would undergo silylation or silyl-mediated chemical transformations. The alkylation of allyloxy carbanions provides an alternate strategy for *Z*-enol silane synthesis;[4] however, strongly basic conditions are required that would also render poor compatibility with reactive functional groups. The Ru-catalyzed coupling of alkynes with allyloxysilanes does provide excellent functional group compatibility, and *E*-enol silanes are selectively produced by this method.[5] Herein, we describe a new method for enol silane installation via the nickel-catalyzed three-component coupling of enals, alkynes, and silanes that is completely *Z*-selective, tolerant of a broad range of reactive functional groups including free alcohols, aldehydes, ketones, and secondary amines, and efficient with a good range of synthetically versatile silane structures. Additional, the exceptional *Z*-selectivity of enol silane installation provides compelling evidence for the involvement of nickel η^1 *O*-enolates in catalytic reactions of α,β-unsaturated carbonyls.

Previous work in our laboratory has demonstrated that a variety of reaction manifolds are accessible in nickel-catalyzed additions of enones or enals with alkynes, including reductive coupling, reductive cycloaddition, and coupling via redox isomerization.[6] Silane reducing agents have not been utilized in any of these classes of reactions; however, we recognized that participation of silanes would potentially allow production of highly functionalized enol silanes that would be useful in the broad classes of reactions described above. Additionally, the functional group tolerance of other silane-based reductive couplings developed in our laboratory and elsewhere suggests that the generation of enol silanes by a nickel-catalyzed reductive process involving silanes would allow installation of a broad array of functionality.[6a]

Considering the potential impact of such a procedure based on the above considerations, we screened a variety of substrates, ligands, silanes, and reaction conditions and found that the three-component coupling of enals (1.0 equiv), alkynes (1.5 equiv), and silanes (2.0 equiv) is broadly efficient with a catalyst derived from $Ni(COD)_2$ (10 mol %) and PCy_3 (20 mol %) in THF. Under these conditions, *Z*-enol silanes are exclusively produced with >98:2 stereoselectivity, and the trisubstituted alkene is installed with similarly exceptional stereoselectivity. Our initial studies focused on evaluating the scope of silanes that efficiently participate in couplings of *E*-hex-2-enal with phenyl propyne (Table 1). Indeed, most silanes examined were efficient participants with this combination of substrates. Couplings with triethylsilane, *tert*-butyldimethylsilane, and triphenylsilane proceeded smoothly to afford the *Z*-enol silanes in high chemical yield and >98:2 *Z*-selectivity (Table 1, entries 1−3). Whereas these products were completely stable in standard silica gel chromatographic separations, the product of coupling with dimethylphenylsilane was unstable to purification, and the corresponding aldehyde was directly obtained via chromatographic purification (Table 1, entry 4). This particular silane is therefore most convenient when the aldehyde is directly desired. Unfortunately, couplings with trichlorosilane and tris(trimethylsilyl-)silane, which are particularly useful in Mukaiyama aldol reactions,[1] were unsuccessful due to catalyst decomposition with the former and sluggish reactivity with the latter.

Table 1. Range of Silanes Tolerated in Enol Silane Generation



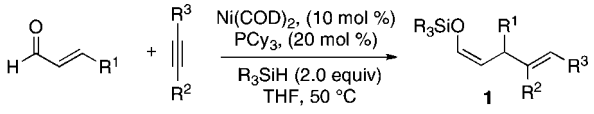
entry	R_3SiH	yield (ratio)[a]
1	Et_3SiH	91% (>98:2)
2	*t*-$BuMe_2SiH$	85% (>98:2)
3	Ph_3SiH	88% (>98:2)
4	$PhMe_2SiH$	81% (>98:2)[b]

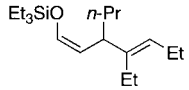
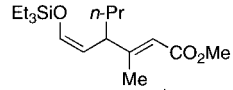
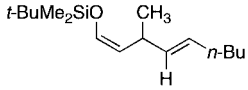
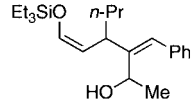
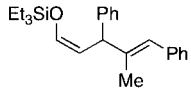
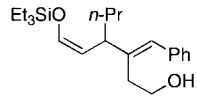
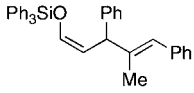
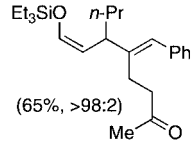
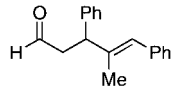
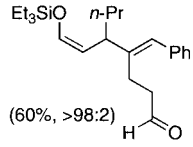
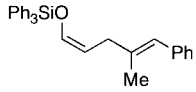
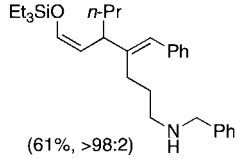
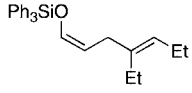
[a] A ratio of >98:2 indicates that no other stereo- or regioisomer was detected at a level greater than 2%. [b] The aldehyde derived from enol silane hydrolysis was obtained as the product of this reaction.

Upon establishing the range of silanes that efficiently participates in this process, we next examined the scope of enal and alkyne structures that may be utilized (Table 2). In addition to the aromatic alkyne depicted (Table 1), a nonaromatic internal alkyne and a terminal alkyne also effectively participated (Table 2, entries 1 and 2). Crotonaldehyde and cinnamaldehyde were efficient participants with a range of silanes (Table 2, entries 2−5), whereas acrolein underwent efficient couplings only with triphenylsilane (Table 2, entries 6 and 7). As noted above, coupling with dimethylphenylsilane led to enol silane hydrolysis upon purification (Table 2, entry 5). With the aim of illustrating chemoselectivity that would not be possible with most other methods for enol silane generation (Scheme 1), we examined a number of functionalized alkynes in couplings with *E*-hex-2-enal, and exceptional functional group tolerance was observed. For example, the reaction cleanly tolerates the ester functionality of ynoates (Table 2, entry 8), free hydroxyls (Table 2, entries 9 and 10), isolated ketones (Table 2, entry 11), isolated aldehydes (Table 2, entry 12), and basic secondary amines (Table 2, entry 13). This combination of substrates illustrates a range of *Z*-enol silanes that are likely inaccessible by any

10.1021/ja802844v CCC: $40.75

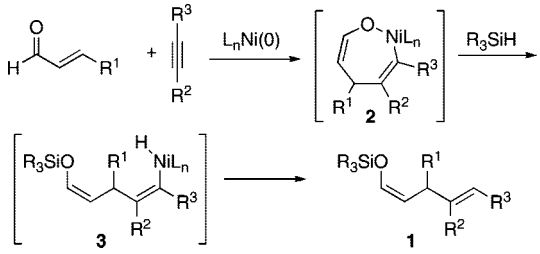
Table 2. Scope and Functional Group Tolerance of Enol Silane Generation[a]



entry	product (yield, ratio)	entry	product (yield, ratio)[a]
1	 (75%, >98:2)	8	 (40%, 92:8)[b]
2	 (50%, 81:19)[b]	9	 (75%, 79:21)[d]
3	 (87%, >98:2)	10	 (91%, >98:2)
4	 (92%, >98:2)	11	 (65%, >98:2)
5	 (86%, >98:2)[c]	12	 (60%, >98:2)
6	 (69%, >98:2)	13	 (61%, >98:2)
7	 (59%, >98:2)		

[a] A ratio of >98:2 indicates that no other stereo- or regioisomer was detected at a level greater than 2%. [b] Isomer ratio refers the regiochemistry of alkyne insertion. [c] Me_2PhSiH was used as reducing agent. [d] Isomer ratio refers to relative stereochemistry of the two stereocenters.

Scheme 1. Mechanism of Enol Silane Generation



other method and complements the powerful Trost procedure that is *E*-selective.[5] The tolerance of simple aldehydes is particularly noteworthy since this suggests that substrates such as that produced in entry 12 would be useful candidates for subsequent Lewis base or Lewis acid promoted intramolecular aldol additions.

In other classes of nickel-catalyzed couplings of enals and alkynes, we proposed that seven-membered oxametallacyclic species were key intermediates, and two examples of such species were fully characterized by X-ray crystallographic and NMR analysis.[7] Those structural studies clearly identified the η^1, *O*-bound nature of the metallacyclic nickel enolates. On this basis, we propose that the transformation described herein proceeds via this precise hapticity and structure of the metallacycle as evidenced by the exclusive *Z*-selectivity of the process. If a C-bound enolate, η^3-enolate, or oxyallyl species were involved,[8] then the *E*-isomer of the enol silane product would be expected. For example, the Mackenzie and Marshall methods involving conjugate additions to enals and the Jamison method involving alkene additions to enals each produce *E*-enol silanes via electrophilic silylation.[3] Therefore, a catalytic cycle for the method disclosed herein can rationally be proposed that involves oxidative cyclization of the enal and alkyne to afford metallacycle **2** with the η^1, *O*-enolate structural motif. The silane may promote the rate of this process,[9] but it does not impede formation of the nickel−oxygen bond as evidenced by the stereochemical considerations noted above. σ-Bond metathesis of the nickel−oxygen bond and the silane would afford intermediate **3**, followed by C−H reductive elimination to afford the observed product **1**. Whereas metallacycle **2** with an η^1 *O*-enolate motif was previously proposed in numerous reactions and rigorously characterized,[7] the acquisition of the *Z*-enol silane products in this study provides the first evidence of its true involvement in a catalytic process rather than simply being a nonproductive catalyst resting state.

In summary, the first method of enol silane synthesis via reductive coupling of enals and alkynes has been demonstrated. Noteworthy features of the process include exceptional *Z*-selectivity and functional group tolerance and applicability to a broad range of silane substitution patterns. The catalytic involvement of metallacyclic intermediates that possess an η^1 *O*-enolate motif provides a clear rationale for the reaction stereoselectivity. We anticipate that this novel entry to functionalized enol silanes will facilitate advances with emerging technologies in Mukaiyama aldol reactions.

Acknowledgment. The authors wish to acknowledge receipt of NSF Grant CHE-0718250 in support of this work.

Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Mukaiyama, T. In *Organic Reactions*; Wiley, New York, 1982; Vol *28*, p 203. (b) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759. (c) Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190. (d) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48. (e) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762. (f) For an organocatalytic strategy that avoids enol silane synthesis, see: Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (g) For an enal reductive aldolization strategy, see: Koech, P. K.; Krische, M. J. *Org. Lett.* **2004**, *6*, 691.
(2) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.
(3) (a) Ho, C.-Y.; Ohmiya, H.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1893. (b) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172. (c) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160. (d) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505. (e) Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (f) Ikeda, S.-i.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015.
(4) Still, W. C.; Macdonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561.
(5) Trost, B. M.; Surivet, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2001**, *123*, 2897.
(6) (a) Review: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (b) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. (c) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (d) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030. (e) Herath, A.; Thompson, B. B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712. (f) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469. (g) Related work: Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032.
(7) (a) Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775. (b) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481. (c) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (d) Hratchian, H.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636.
(8) (a) Cámpora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Gutiérrez, E.; Ruiz, C.; Graiff, C.; Tiripicchio, A. *Chem.—Eur. J.* **2005**, *11*, 6889. (b) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350.
(9) Ogoshi, S.; Oka, M.-a.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802.

JA802844V