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Direct Conversion of β-Hydroxyketones to Cyclic Disiloxanes

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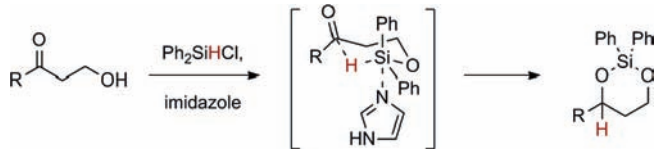
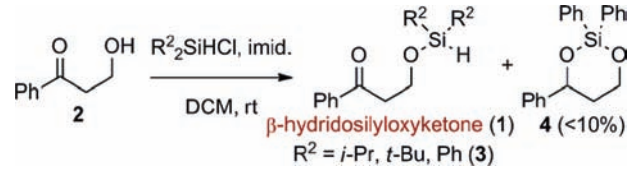
ABSTRACT



***β*-Hydroxyketones can be directly converted to cyclic disiloxanes using diphenylchlorosilane in the presence of imidazole and an amine base. The reaction is proposed to proceed via a nucleophilic activation mechanism through a cyclic chairlike transition state affording hydrosilylated products with high diastereoselectivity.**

Carbonyl hydrosilylation represents a mild and selective alternative to main-group metal hydrides for the introduction of hydroxyl functionality.[1] Ongoing research has produced examples of both Lewis acid-[2] and Lewis base-mediated[3] hydrosilylations along with various transition metal catalysts[4] for this purpose. As part of an ongoing program investigating the intramolecular hydrosilylation of prochiral β-silyloxyketones, we set out to prepare several hydridosilyl ethers of type **1** with differing silicon substitution as it is known that substituents on silicon can have a profound influence on stability and reactivity (Scheme 1).[5] While the diisopropyl- and di-*tert*-butyl derivatives were generated without incident by silylation of **2**[6] with the appropriate dialkylchlorosilane (1.2 equiv) in the presence of imidazole (2.5 equiv), formation of the corresponding diphenylhydridosilyl ether **3** was accompanied by small amounts of cyclic disiloxane **4**.[7]

Scheme 1. Preparation of Hydridosilyl Ethers



(1) For a recent review, see: Larson, G. L.; Fry, J. L. Ionic and Organometallic-Catalyzed Organosilane Reductions. *Organic Reactions*; Denmark, S. E., Ed.; John Wiley & Sons Inc.: New York, 2008; Vol. 71.

(2) For select examples, see: (a) Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, W. R., Jr.; Silverman, S. B. *J. Org. Chem.* **1978**, *43*, 374. (b) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129. (c) Piers, W. E.; Chivers, T. *Chem. Soc. Rev.* **1997**, 345.

(3) For select examples, see: (a) Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *J. Organomet. Chem.* **1978**, *148*, C1. (b) Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *J. Chem. Soc., Chem. Commun.* **1981**, 121. (c) Fry, J. L.; McAdam, M. A. *Tetrahedron Lett.* **1984**, *25*, 5859. (d) Kira, M.; Sato, K.; Sakurai, H. *J. Org. Chem.* **1987**, *52*, 948.

(4) For select examples see: (a) [Re] catalyst: Kennedy-Smith, J. J.; Nolin, K. A.; Gunterman, H. P.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 4056. (b) [Cu] catalyst: Kaur, H.; Kauer Zinn, F.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157. Lipshutz *J. Organomet. Chem.* **2001**, *624*, 367. (c) [Au] catalyst: *J. Organomet. Chem.* **2007**, *692*, 1799. (d) [Ni] catalyst: Tran, B. L.; Pink, M.; Mindiola, D. J. *Organometallics* **2009**, *28*, 2234.

(5) Morkin, T. L.; Leigh, W. J. *Acc. Chem. Res.* **2001**, *34*, 129. (b) Parisa, S. I. M.; Lemke, F. R. *Inorg. Chem. Commun.* **2005**, *8*, 425. (c) Denmark, S. E.; Neuville, L.; Christy, M. E.; Tymonko, S. A. *J. Org. Chem.* **2006**, *71*, 8500. (d) Duczmal, W.; Maciejewska, B.; Sliwinska, E.; Mareiniec, B. *Trans. Met. Chem.* **1995**, *20*, 162.

(6) Khan, A. T.; Parvin, T.; Choudhury, L. H.; Ghosh, S. *Tetrahedron Lett.* **2007**, *48*, 2271.

(7) (a) For a previous example of ketone reductions with diphenylsilane, see: Gilman, H.; Diehl, J. *J. Org. Chem.* **1961**, *26*, 4817−4820. (b) For a recent tandem silylation/hydrosilation, see: Shchepin, R.; Xu, C.; Dussault, P. *Org. Lett.* **2010**, ASAP, DOI: 10.1021/ol1018757.

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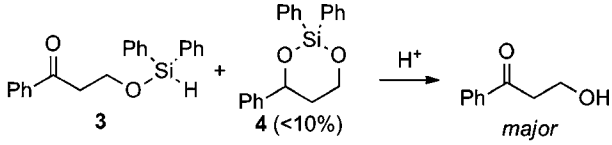
In general, organosilicon hydrides do not undergo spontaneous reactions with organic compounds unless the organic substrate is a reasonably strong electrophile or the silane has been first activated by the interaction of a nucleophilic species with the silicon center. It was thought that, in analogy to other Brønsted acid catalyzed carbonyl hydrosilylation reactions,[8] HCl (presumably as the imidazolium salt) liberated during the course of the reaction might serve to activate the carbonyl oxygen facilitating delivery of hydride from silicon. Attempts to increase the amount of hydrosilylation product by treatment of a mixture of **3** and **4** with various acids including imidazolium hydrochloride, however, met with failure, the reactions affording predominantly desilylated starting material and/or decomposition under more forcing conditions (Scheme 2).

Scheme 2. Attempted Acid-Mediated Hydrosilylation[a]

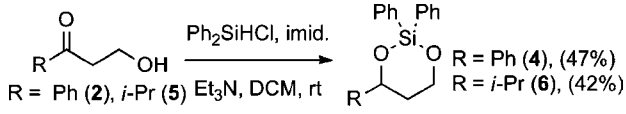


H^+ = PPTS, CSA, $(PhO)_2P(O)OH$, imidazole•HCl.

[a] H^+ = PPTS, CSA, $(PhO)_2P(O)OH$, imidazole•HCl.

Alternatively, in an attempt to make the reaction more basic, various amine additives were evaluated for their ability to promote the formation of **4** (Scheme 3). It was found that

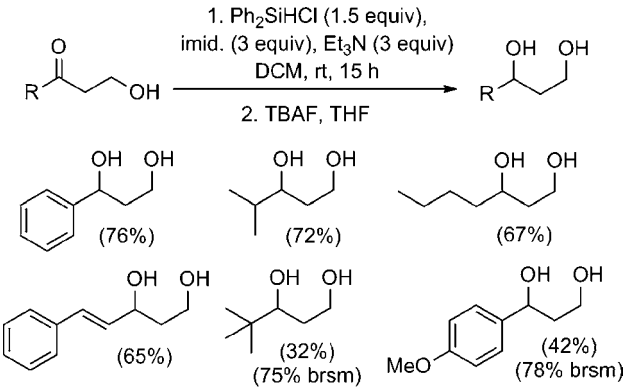
Scheme 3. Base-Promoted Cyclic Siloxane Formation



upon addition of triethylamine or Hünig's base to the reaction mixture containing imidazole, the amount of hydrosilylated product was substantially increased, **2** and **5** directly converted to disiloxanes **4** and **6**, respectively.[9] The products **4** and **6** proved highly susceptible to hydrolysis of one or more Si−X bonds giving a complex mixture of products upon aqueous workup or attempted purification on silica.[10] Pure material could be obtained for analysis, albeit in low yield, by performing the reaction with an excess of β-hydroxyketone substrate relative to diphenylchlorosilane. Ammonium salts generated during the reaction were removed by trituration, and the product was flushed through a plug of Florisil to remove unreacted starting material.

To test the generality of the reaction, several β-hydroxyketones were prepared[11] and subjected to our optimized hydrosilylation conditions (Scheme 4). The sensitive cyclic

Scheme 4. Hydrosilylation/Desilylation 1,3-Diol Synthesis



siloxane products thus obtained were directly converted the corresponding 1,3-diols by treatment with TBAF. As can be seen from the results, both aryl- and alkyl-β-hydroxyketones were reduced in comparable yield. Alkene functionality in the cinnamaldehyde-derived substrate was not hydrosilylated under these reaction conditions.[12] The reaction did however prove somewhat sensitive to steric and electronic deactivation, both the *tert*-butyl and methoxybenzene substrates giving lower conversion under identical reaction conditions.

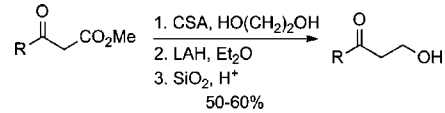
While the overall mechanism for this transformation is still under investigation, several statements can be made concerning the role of certain reagents and intermediates based on the following observations: Imidazole is essential for hydrosilylation to occur. Reactions performed without imidazole and only triethylamine did not afford cyclic siloxane products, giving predominantly noncyclized β-hydridosilyloxyketones of type **3** (Scheme 5, eq 1). However, using a large excess of imidazole did not increase the amount of hydrosilylated product obtained. Moreover, substituting imidazole for DMAP or *N*-methylimidazole (NMI) failed to produce any of the hydrosilylation product as detectable by ^{1}H NMR. β-Hydroxy functionality is necessary for carbonyl hydrosilylation under these reaction conditions. Treatment of propiophenone with diphenylchlorosilane, imidazole, and

(8) (a) Anwar, S.; Davis, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 831. (b) Davis, A. P.; Anwar, S. *Tetrahedon* **1988**, *44*, 3761.

(9) For a recent example of reductions involving a phenylsilane and triethylamine, see: Frost, C. G.; Hartley, B. C. *J. Org. Chem.* **2009**, *74*, 3599.

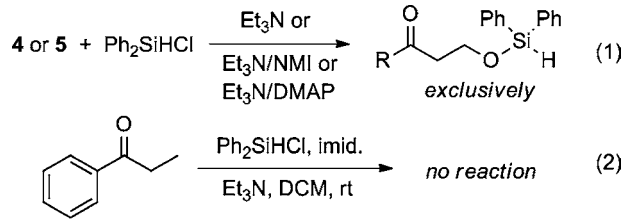
(10) For another report on diphenylsiloxane instability, see: Blackwell, J. E.; Foster, K. L.; Beck, V. H.; Piers, W. E. *J. Org. Chem.* **1999**, *64*, 4887.

(11) β-Hydroxyketone substrates were prepared according to the following general protocol described in :Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y. B.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.



(12) For a review of alkene hydrosilylation, see:Yamamoto, K.; Hayashi, T. Hydrosilylation of olefins. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; 1998; Vol. 2, p 120.

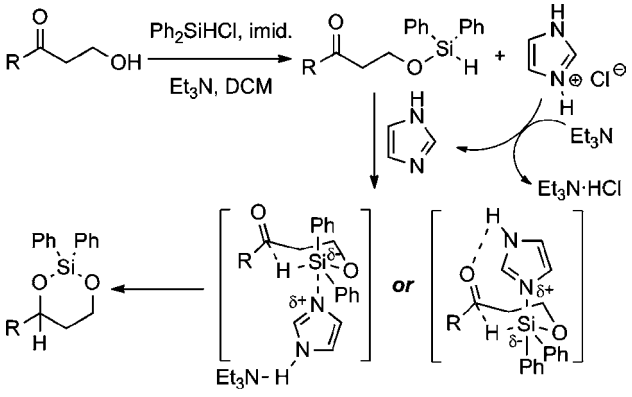
Scheme 5. Hydrosilylation Specificity



triethylamine gave exclusively starting material even after prolonged reaction times as detectable by ^{1}H NMR (Scheme 5, eq 2).

On the basis of these observations, the reaction is proposed to proceed through a nucleophilic activation mechanism.[13] It has been shown that otherwise unreactive organosilicon hydrides will react with carbonyl compounds when certain nucleophilic species are added.[13] This is thought to arise from the formation of an intermediate valence-expanded, pentacoordinate hydrosilanide that is a stronger reducing agent than the tetravalent precursor.[14] Imidazole in this regard occupies a central role, with several imidazolium silicates having been characterized by NMR and X-ray diffraction.[15] It is therefore assumed that the observed cyclic disiloxane product is the result of imidazole activation post hydridosilylether formation (Scheme 6).

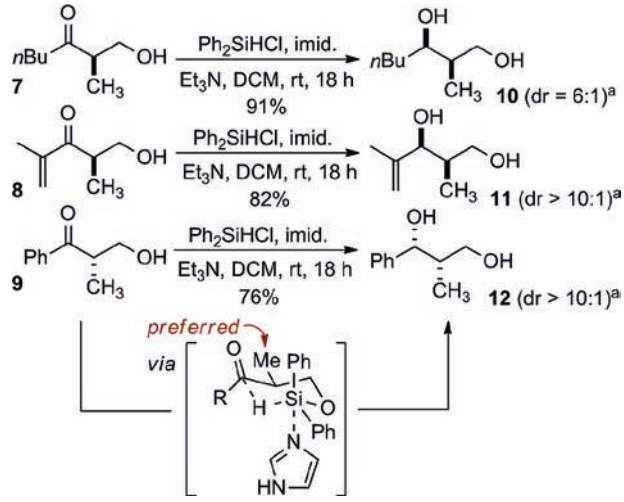
Scheme 6. Proposed Mechanism for Direct Disiloxane Formation



The developing negative charge at silicon can be stabilized by the phenyl substituents explaining the differential reactivity of the diphenylchlorosilane compared to di-*tert*-butyl and diisopropyl derivatives. While the failure of *N*-methylimidazole to promote hydrosilylation could suggest a nucleophilic/electrophilic role for imidazole[16] with activation of the carbonyl through *N*−H hydrogen bonding,[17] the role of triethylamine might also be explained by promoting silicate formation through abstraction of this proton.[18] Attempts to further elucidate the mechanism by in situ ^{1}H and ^{29}Si NMR analysis failed to produce evidence of an intermediate pentacoordinate silicate;[19] however, stepwise hydridosilyloxyketone and subsequent cyclic disiloxane formation were clearly observed.

If the hydride is indeed delivered intramolecularly proceeding through a rigid chairlike transition state, it was anticipated that the reaction might occur with high levels of diastereoselectivity. To test this, ketoalcohols **7**−**9**[20] were prepared and subjected to hydrosilylation conditions followed by desilylation with TBAF (Scheme 7). In all cases, the

Scheme 7. Diastereoselective Intramolecular Hydrosilylation[a]



[a] Determined by ^{1}H NMR.

corresponding 1,3-diol products (**10**−**12**) were obtained in good yield and with high diastereoselectivity. A comparison of spectral data to that reported in the literature[20,21] and/or

(13) For select examples of Lewis basic activation of silanes as reducing agents, see: (a) Gan, L.; Brook, M. *Can. J. Chem.* **2006**, *84*, 1416. (b) Riduan, S. N.; Zhang, Y. G.; Ying, J. Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 3322. (c) Malkov, A. V.; Liddon, A. J. S.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432. (d) Tan, M.; Zhang, Y.; Ying, J. Y. *Adv. Synth. Catal.* **2009**, *351*, 1390.

(14) Gronert, S.; Glaser, R.; Streitwieser, A. *J. Am. Chem. Soc.* **1989**, *111*, 3111.

(15) (a) Boyer, J.; Corriu, R. J. P.; Kopton, A.; Mazhar, M.; Poirier, M.; Royo, G. *J. Organomet. Chem.* **1986**, *301*, 131. (b) Brelière, C.; Carrè, F.; Corriu, R. J. P.; Poirier, M.; Royo, G. *Organometallics* **1986**, *5*, 388. (c) Boyer, J.; Brelière, C.; Corriu, R. J. P.; Kopton, A.; Poirier, M.; Royo, G. *J. Organomet. Chem.* **1986**, *311*, C39–C43.

(16) (a) Chopra, S. K.; Martin, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 5342. (b) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090.

(17) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761.

(18) For an example of coordinated imidazole stabilization by amines, see: Balch, A. L.; Watkins, J. J.; Doonan, D. J. *Inorg. Chem.* **1979**, *18*, 1228.

(19) Wang, Z.; Wroblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 8021.

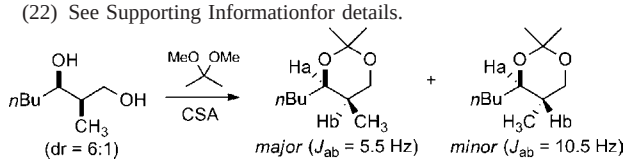
(20) Yakura, T.; Yoshimoto, Y.; Ishida, C.; Mabuchi, S. *Tetrahedron* **2007**, *63*, 4429–4438.

(21) For a previous synthesis of **10**, see: Marimganti, S.; Wieneke, R.; Geyer, A.; Maier, M. E. *Eur. J. Org. Chem.* **2007**, *17*, 2779.

detailed NMR analysis after conversion to the cyclic acetal[22] revealed that each of the reactions occurred with the same sense of diastereoselection. The formation of *syn*-propionate products can be rationalized as a preference for the methyl group to assume an equatorial position at the transition state.

In summary, β-hydroxyketones can be directly converted to cyclic disiloxanes under mild conditions using diphenylchlorosilane promoted by imidazole in the presence of triethylamine. The reaction is thought to proceed by cooperative Lewis base activation of silicon affording a transient hydridosilicate, that then delivers hydride to the carbonyl carbon intramolecularly via a chairlike transition state. This proposed mechanism is consistent with the diastereoselectivity observed for the reduction of compounds **7**−**9**. Current efforts are aimed at elucidating the complete mechanism for this transformation, further examining the substrate scope, and highlighting the utility of this protocol in the context of complex natural product synthesis.

(22) See Supporting Informationfor details.



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Supporting Information Available: Experimental procedures and spectral data for compounds **4**, **6**, **7**, **8**, **10**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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