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# A Constellation of Deuterium-Labeled Silanes as a Simple Mechanistic Probe not Requiring Absolute Configuration Determination**

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***Abstract:*** *A new stereochemical probe for mechanisms at the silicon atom that is based on a deuterium-labeled silolane is synthesized and evaluated. The key synthetic step involves the hydrogenation of a 2,5-dihydrosilole with deuterium gas, giving a complex mixture of isochronic stereoisotopologues. The overall stereochemical imbalance of this mixture is evident in its $^2H$ NMR spectrum, which provides a good qualitative measure of changes in the configuration at the silicon atom. The technique is rapid, easy to use, and overcomes limitations and biases of traditional methods. The utility of this new procedure is demonstrated by tracking the stereochemical course of several classical reactions as well as contemporary catalytic transformations involving bond formation at the silicon atom.*

Our mechanistic understanding of chemical reactions at the silicon atom relies heavily on our ability to interpret the stereochemical course of a given reaction. This task has traditionally been accomplished using silicon-stereogenic silanes (Figure 1, top).[1] Using chiral silane **1** and its derivatives, Sommer's pioneering and extensive research program on the stereochemistry at silicon mapped out classical reactivity.[2] Corriu developed cyclic chiral silane **2**[3] recognizing that greater rigidity around the stereocenter offers distinct advantages. Recently, we designed and employed a new family of chiral silanes based on the general structure **3**.[4] Our group elucidated the mechanisms of a range of modern catalytic reactions, including Si–H bond activation with Lewis acidic boranes,[5] Cu–H-catalyzed dehydrogenative Si–O coupling,[6] and $Ir^{III}$-catalyzed carbonyl hydrosilylation.[7] Despite these achievements, the use of silicon-stereogenic silanes as mechanistic probes remains a challenging technique. At a practical level, their preparative resolution is usually laborious, and the analytical separation of enantiomers is generally demanding. More fundamentally, for any given reaction, the absolute configuration needs to be determined, that is, the reaction product has to be stereochemically correlated to its starting material through a known reaction sequence. This is a particularly difficult task in the realm of Si–C bond-forming reactions.

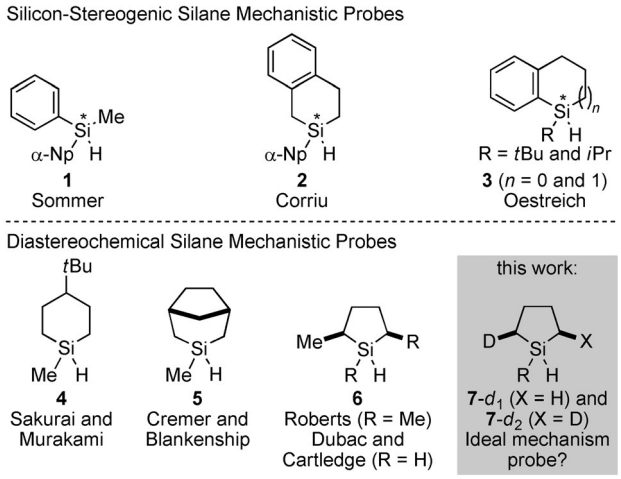


***Figure 1.*** Silicon stereochemical probes. Np = naphthyl.

The logical alternative to chiral non-racemic mechanistic probes is to track the configuration at the silicon atom using a diastereochemical relationship to another stereocenter elsewhere in the molecule (Figure 1, bottom). Several examples of such probes have already been developed and evaluated. Sakurai and Murakami prepared and studied *meso*-configured silane **4**[8] whereas Cremer and Blankenship employed **5**.[9] Diastereomeric silanes that are based on stereochemical information at the α position(s) of silolane systems **6** were developed by Roberts[10] as well as Dubac and Cartledge.[11] The latter system witnessed significant use as a mechanistic probe.[12] One problem with this approach is that the preparative and analytical separation of the diastereomers is difficult. More importantly, the two diastereomers are likely to differ substantially in their physical and chemical properties.

We began to consider whether a cyclic silane, suitably labeled with deuterium, could provide a "silent" diastereochemical relationship to the configuration at the silicon atom. Our design settled on silolane **7**, which can be monodeuterated at the α position to give a chiral racemic compound **7**-$d_1$ or *syn*-dideuterated to provide isotopologue **7**-$d_2$ with *meso* configuration. Inversion of the configuration at the silicon atom in both silanes **7**, that is, racemic **7**-$d_1$ and *meso* **7**-$d_2$, would produce the corresponding diastereomers. These diastereomeric pairs would be isochronic in their $^1H$ and $^2H$ NMR spectra yet present converse intensity patterns for the signals corresponding to their α positions.[13] A useful

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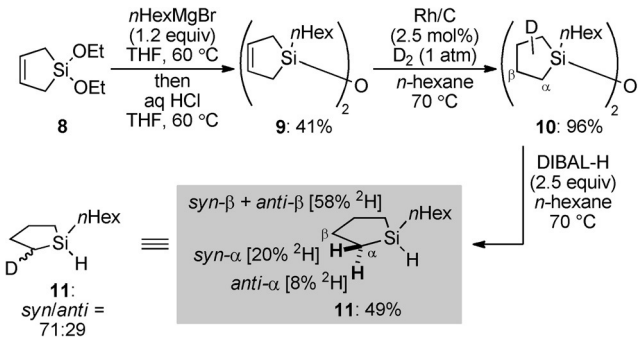
property of silolanes is that their α protons are generally well resolved and unobscured in their NMR spectra. Importantly, the two diastereomers would have, to all practical intents and purposes, the same physical and chemical properties, with any potential difference in reactivity at the silicon atom silenced to the level of a tertiary isotope effect. Whereas the stereoselective synthesis of silolane **7** presents a daunting challenge, we succeeded in preparing a deuterium-labeled silolane as a mixture of stereoisotopologues to serve as a proxy for **7**. The synthesis and evaluation of this new probe are presented herein and cast new light on several modern catalytic reactions.

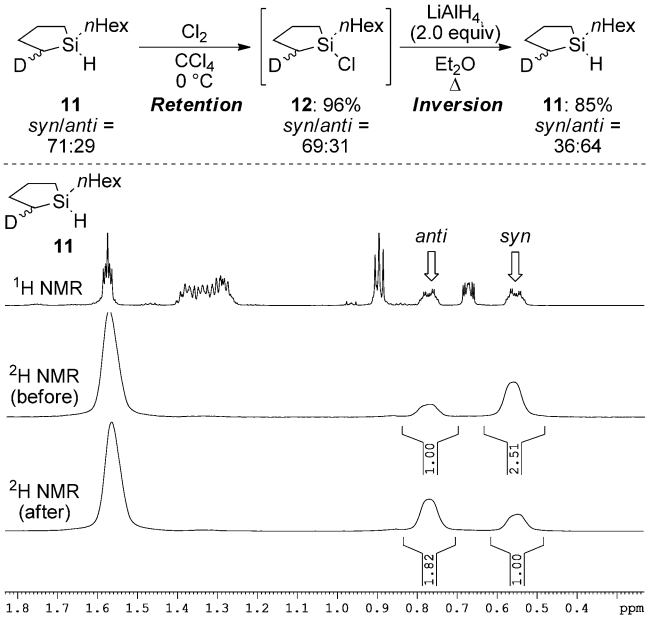
The synthesis is described in Scheme 1. The commercially available 2,5-dihydrosilole **8** was treated with *n*HexMgBr to




***Scheme 1.*** Preparation and $^2$H NMR analysis of silolane **11**. DIBAL-H = diisobutylaluminum hydride.

effect monosubstitution at the silicon atom, and the intermediate was directly converted into siloxane **9** using aqueous HCl. Treatment of this material with a catalytic amount of Rh/C under an atmosphere of $D_2$ reduced the double bond to form silolane **10** in 96% yield. Inspection of the $^2$H NMR spectrum of **10** revealed that deuterium had been incorporated at both the β and α positions of the silolane ring. Deuteration at the allylic position of cyclic alkenes under hydrogenation conditions was previously noted,[14] but the mechanistic details of this process have not been examined yet. This material was treated with DIBAL-H to give silane **11**, for which the deuterium incorporation was measured. The overall incorporation was 58% at the β positions (unresolved), 20% at the *syn*-α position, and 8% at the *anti*-α position, giving a modest but significant *syn*-α/*anti*-α ratio of 71:29.[15] Even though the exact composition and distribution of this complex mixture of isotopologues cannot be determined, the overall imbalance of deuterium incorporation at the α position will reliably track configurational changes at the silicon atom. With silane **11**, we have developed a proxy for **7** and a viable prototype.

With this new probe in hand,[16] we initially sought to perform a classical Walden cycle[17] using reactions of known stereochemical outcome (Scheme 2, top). Silane **11** was treated with a solution of $Cl_2$ in $CCl_4$ at 0 °C to give chlorosilane **12** in high yield with retention of configuration at the silicon atom. This was followed (in a separate run) by reduction with $LiAlH_4$ to give back **11** with overall inversion

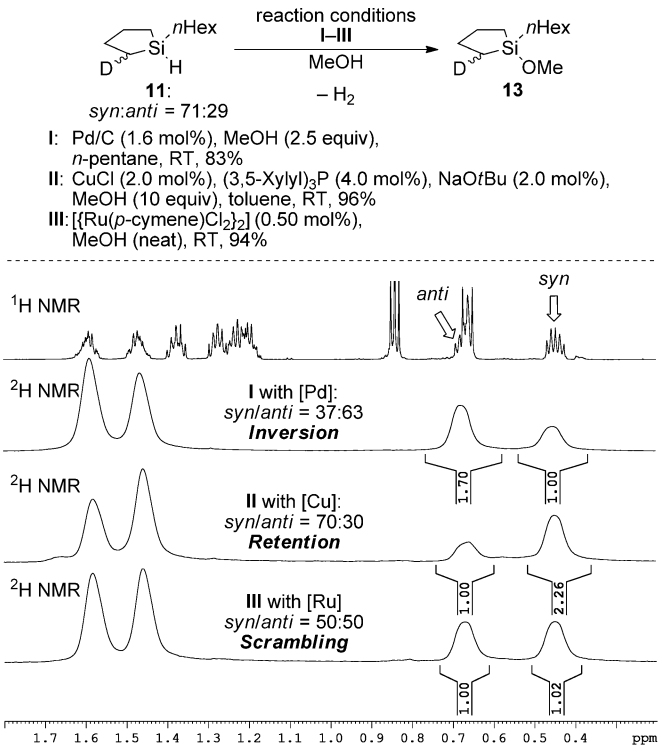



***Scheme 2.*** Tracking the Walden inversion at the silicon atom during chlorination of the Si–H bond and subsequent chloride/hydride displacement.

of configuration.[18] A comparison of the $^2$H NMR spectra of the starting and final material revealed that the α position signals had swapped their intensities (Scheme 2, bottom). An important feature of this sequence is that unlike for the traditional chiral silane approach, the configurational change at the silicon atom of **12** is seen without the need for chemical correlation.

Dehydrogenative couplings of hydrosilanes and alcohols are achieved using many catalysts and pass through a variety of mechanistic manifolds. Using hydrosilane **1**, Sommer and Lyons have already shown that Pd/C catalyzes a Si–O coupling with inversion of configuration at the silicon atom.[19] Several years ago, our laboratory developed a Cu–H-catalyzed version for the kinetic resolution of racemic donor-functionalized alcohols using hydrosilane **3**.[6] Mechanistic experiments together with quantum-chemical calculations established that this reaction proceeded with retention of configuration at the silicon atom. Recently, the [{Ru(*p*-cymene)$Cl_2$}$_2$] dimer was recognized as a particularly potent catalyst for this class of reactions.[20] Couplings of **11** and methanol under the above setups give silyl ether **13** and provide a useful setting for illustrating our method (Scheme 3, top). These reactions also highlight its ability to detect the three stereochemical extremes, namely inversion, retention, and scrambling/racemization (Scheme 3, bottom). The Pd/C- and Cu–H-catalyzed reactions proceeded as expected with a minimal decrease in the diastereomeric ratios. The $Ru^{II}$-catalyzed reaction showed complete scrambling with a 1:1 integration ratio in the $^2$H NMR spectrum. Mizuno and coworkers had studied this reaction using Sommer's hydrosilane **1** and found that it proceeded with inversion of configuration at the silicon atom. However, they observed extensive racemization when an excess of the alcohol component was

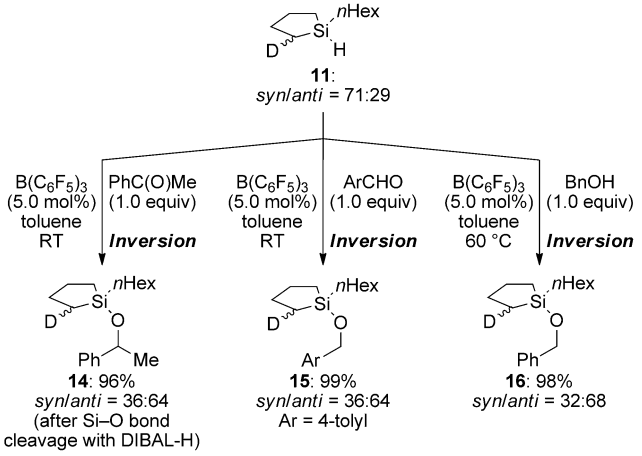
  




***Scheme 3.*** The three stereochemical extremes of dehydrogenative Si–O couplings.

used. This result is in line with our observations as methanol was used as the solvent.

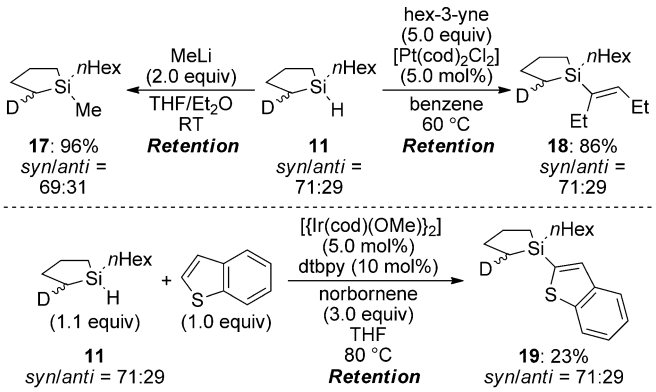
We then turned our attention to Si–H bond activation with $B(C_6F_5)_3$,[21] a process that we had shown to obey an $S_N2$-Si mechanism.[5,22] To further demonstrate the utility of our probe, we (re-)investigated the $B(C_6F_5)_3$-catalyzed carbonyl hydrosilylation and the related Si–O coupling (Scheme 4). Hydrosilylation of acetophenone with **11** afforded the corresponding silyl ether **14** in high yield. The new stereogenic center at the carbinol carbon atom breaks the symmetry of the silolane ring, rendering all eight protons magnetically




***Scheme 4.*** Stereochemical course of $B(C_6F_5)_3$-catalyzed reactions at the silicon atom. Bn = benzyl.

non-equivalent. For **14**, we therefore could not resolve and assign the key α position signals. Reduction to **11** with DIBAL-H allowed us to interpret the hydrosilylation as occurring with the expected inversion of configuration at the silicon atom (not shown). We also conducted the hydrosilylation of 4-methylbenzaldehyde, which provided a similar result. As expected, the dehydrogenative coupling of **11** and benzyl alcohol proceeded with inversion. These results are consistent with our earlier work[5] and that of Kawakami and co-workers.[22] Additional control experiments allowed us to throw further light on this class of reactions. Probe **11** was combined with $B(C_6F_5)_3$ (10 mol%), and the solution was analyzed using $^2$H NMR spectroscopy. The configuration at the silicon atom was seen to slowly scramble over the course of days. Conversely, treatment of **11** with $B(C_6F_5)_3$ (5.0 mol%) and di-*tert*-butyl ketone (5.0 mol%) resulted in a configurational scrambling process that was complete within minutes (see the Supporting Information for details). This suggests that **11** is subject to a donor-promoted configurational scrambling process, leading to racemization for silicon-stereogenic hydrosilanes, that competes with hydrosilylation or Si–O coupling to some extent.[23]

Finally, we investigated a class of reactions that have been difficult, if not impossible, to study using the traditional silicon-stereogenic silane approach: Si–C bond-forming reactions. For the elucidation of the absolute configuration, complex and indirect chemical correlation networks need to be constructed. Sommer built such a network within his family of silicon-stereogenic silanes and was able to interrogate the mechanisms of a range of alkylation and hydrosilylation reactions.[24] As chemical correlation is not a requirement of our method, we were able to directly examine examples of Si–C bond-forming reactions (Scheme 5). Both




***Scheme 5.*** Representative stoichiometric and catalytic Si–C bond-forming reactions. cod = cycloocta-1,5-diene, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

alkylation with MeLi (**11**→**17**) and $Pt^0$-catalyzed alkyne hydrosilylation (**11**→**18**) occurred with the expected retention of configuration at the silicon atom. Catalytic dehydrogenative C–H silylation has emerged as a powerful method for the direct functionalization of arenes, heteroarenes, and alkanes.[25] Current proposals as well as a recent detailed mechanistic study[26] predict Si–H bond activation to occur

through traditional oxidative addition and reductive elimination pathways. Based on this hypothesis, the process was predicted to occur with retention of configuration at the silicon atom. Obtaining experimental evidence of this important mechanistic detail using traditional chiral triorganosilane probes (cf. Figure 1, top) is likely to fail owing to the severe structural constraints of the reaction with respect to the silane component. Our silane, however, being fully alkyl-substituted and sterically compact, is suitable for this task. Lu and Falck have developed and optimized the $Ir^{I}$-catalyzed C–H silylation of heteroarenes using triethylsilane.[27] We adapted these conditions to couple silane **11** and benzo[*b*]thiophene (**11**→**19**, Scheme 5). The reaction worked, and $^{2}H$ NMR analysis revealed that it did indeed proceed with complete retention at the silicon atom.

In conclusion, we have designed and employed a new type of silane mechanistic probe to conveniently track the configuration at the silicon atom. The simple technique is fast to use and overcomes the limitations of previous methods by monitoring of the stereochemical changes by straightforward NMR analysis. In future, a synthetic strategy that provides access to silane **7** as a single isotopologue as well as alternatively substituted examples will be devised. This would further improve the sensitivity of the technique and allow for quantitative analysis.

**Keywords:** configuration determination · hydrogenation · isotopic labeling · reaction mechanisms · silicon

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*Angew. Chem.* **2015**, *127*, 12666–12670

[1] For a recent review on the chemistry of silicon-stereogenic silanes, see: L.-W. Xu, L. Li, G.-Q. Lai, J.-X. Jiang, *Chem. Soc. Rev.* **2011**, *40*, 1777–1790.
[2] a) L. H. Sommer, C. L. Frye, *J. Am. Chem. Soc.* **1959**, *81*, 1013; b) L. H. Sommer, C. L. Frye, G. A. Parker, K. W. Michael, *J. Am. Chem. Soc.* **1964**, *86*, 3271–3276; c) L. H. Sommer, *Stereochemistry, Mechanism, and Silicon*, McGraw-Hill, New York, **1965**.
[3] a) R. J. P. Corriu, C. Guerin, J. J. E. Moreau in *Topics in Stereochemistry, Vol. 15* (Ed.: E. L. Eliel), Wiley, New York, **1984**, pp. 355–374; b) R. J. P. Corriu, C. Guerin, *Adv. Organomet. Chem.* **1982**, *20*, 265.
[4] a) M. Oestreich, U. K. Schmid, G. Auer, M. Keller, *Synthesis* **2003**, 2725–2739; b) S. Rendler, G. Auer, M. Keller, M. Oestreich, *Adv. Synth. Catal.* **2006**, *348*, 1171–1182; for an account, see: c) M. Oestreich, *Synlett* **2007**, 1629–1643.
[5] S. Rendler, M. Oestreich, *Angew. Chem. Int. Ed.* **2008**, *47*, 5997–6000; *Angew. Chem.* **2008**, *120*, 6086–6089.
[6] a) S. Rendler, G. Auer, M. Oestreich, *Angew. Chem. Int. Ed.* **2005**, *44*, 7620–7624; *Angew. Chem.* **2005**, *117*, 7793–7797; b) S. Rendler, O. Plefka, B. Karatas, G. Auer, R. Fröhlich, C. Mück-Lichtenfeld, S. Grimme, M. Oestreich, *Chem. Eur. J.* **2008**, *14*, 11512–11528.
[7] T. T. Metsänen, P. Hrobárik, H. F. T. Klare, M. Kaupp, M. Oestreich, *J. Am. Chem. Soc.* **2014**, *136*, 6912–6915.
[8] a) H. Sakurai, M. Murakami, *J. Am. Chem. Soc.* **1972**, *94*, 5080–5082; b) H. Sakurai, M. Murakami, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3185–3189.
[9] S. E. Cremer, C. Blankenship, *Organometallics* **1986**, *5*, 1329–1336.
[10] H.-S. Dang, B. P. Roberts, D. A. Tocher, *J. Chem. Soc. Perkin Trans. 1* **1995**, 117–123.
[11] F. K. Cartledge, J. M. Wolcott, J. Dubac, P. Mazerolles, P. Fagoaga, *Tetrahedron Lett.* **1975**, *16*, 3593–3596.
[12] a) F. K. Cartledge, J. M. Wolcott, J. Dubac, P. Mazerolles, M. Joly, *J. Organomet. Chem.* **1978**, *154*, 187–201; b) J. Dubac, J. Escudie, C. Couret, J. Cavezzan, J. Satge, P. Mazerolles, *Tetrahedron* **1981**, *37*, 1141–1151; for an application of this system to the study of hydrosilane activation on heterogeneous copper, see: c) M. Bartók, Á. Molnár, *J. Chem. Soc. Chem. Commun.* **1982**, 1089–1090.
[13] Isotope effects will cause minute differences in magnetic resonance frequencies but this is insignificant relative to the overall line broadening observed in $^{2}H$ NMR spectra. For an examination of these effects in a tritium-labeled pyrrolidine, see: F. M. Kaspersen, C. W. Funke, E. M. G. Sperling, F. A. M. van Rooy, G. N. Wagenaars, *J. Chem. Soc. Perkin Trans. 2* **1986**, 585–591.
[14] M. Güngör, F. H. Jardine, J. D. Wheatley, *J. Chem. Soc. Dalton Trans.* **1988**, 1653–1656.
[15] Throughout, we refer to the *syn* and *anti* stereochemical descriptors as relative to the *n*-hexyl substituent. The assignment of signals is based on nOe correlations of non-deuterated material (see the Supporting Information for details).
[16] All operations were initially screened with non-deuterated material. For full details as well as a convenient synthesis of non-deuterated silane **11**, see the Supporting Information.
[17] a) P. Walden, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 133–138; b) Ref. [2a].
[18] The partial loss in stereochemical purity is likely the result of fast chloride-induced scrambling of chlorosilane **12**; see: M. Oestreich, G. Auer, M. Keller, *Eur. J. Org. Chem.* **2005**, 184–195, and references therein.
[19] L. H. Sommer, J. E. Lyons, *J. Am. Chem. Soc.* **1969**, *91*, 7061–7067.
[20] Y. Ojima, K. Yamaguchi, N. Mizuno, *Adv. Synth. Catal.* **2009**, *351*, 1405–1411.
[21] For a review on Si–H and H–H bond activation catalyzed by boron Lewis acids, see: M. Oestreich, J. Hermeke, J. Mohr, *Chem. Soc. Rev.* **2015**, DOI: 10.1039/C4CS00451E.
[22] For preliminary mechanistic evidence, see: S. Shinke, T. Tsuchimoto, Y. Kawakami, *Silicon Chem.* **2007**, *3*, 243–249.
[23] For related processes, see: a) Ref. [7]; b) M. Iglesias, P. J. Sanz-Miguel, V. Polo, F. J. Fernández-Alvarez, J. J. Pérez-Torrente, L. A. Oro, *Chem. Eur. J.* **2013**, *19*, 17559–17566.
[24] For alkylations, see: a) L. H. Sommer, P. G. Rodewald, G. A. Parker, *Tetrahedron Lett.* **1962**, *3*, 821–824; b) L. H. Sommer, W. D. Korte, P. G. Rodewald, *J. Am. Chem. Soc.* **1967**, *89*, 862–868; for $Pt^{0}$-catalyzed hydrosilylation, see: c) L. H. Sommer, K. W. Michael, H. Fujimoto, *J. Am. Chem. Soc.* **1967**, *89*, 1519–1521.
[25] For leading references, see: a) T. Ureshino, T. Yoshida, Y. Kuninobu, K. Takai, *J. Am. Chem. Soc.* **2010**, *132*, 14324–14326; b) C. Cheng, E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 8984–8989; *Angew. Chem.* **2013**, *125*, 9154–9159; c) E. M. Simmons, J. F. Hartwig, *Nature* **2012**, *483*, 70–73; d) C. Cheng, J. F. Hartwig, *Science* **2014**, *343*, 853–857.
[26] C. Cheng, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 12064–12072.
[27] B. Lu, J. R. Falck, *Angew. Chem. Int. Ed.* **2008**, *47*, 7508–7510; *Angew. Chem.* **2008**, *120*, 7618–7620.

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