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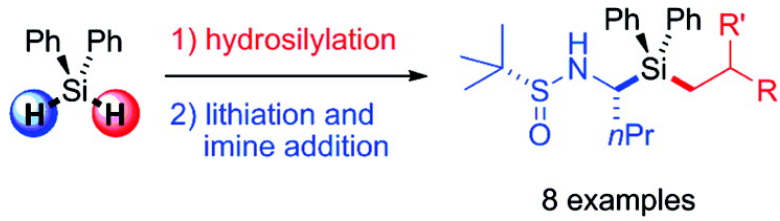

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Sequential C−Si Bond Formations from Diphenylsilane: Application to Silanediol Peptide Isostere Precursors

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Abstract: The report of silanediol peptide isosteres as highly active inhibitors of proteolytic enzymes has triggered an increased interest for these compounds, thereby necessitating a general and direct synthetic access to this unusual class of protease inhibitors. In this paper, we report on the two-step assembly of the carbon−silicon backbone of a silane-containing dipeptide fragment. The synthetic scheme is comprised of an alkene hydrosilylation step with the simple precursor, diphenylsilane, using either a radical initiator or $RhCl(PPh_3)_3$, Wilkinson's catalyst, for the creation of a hydridosilane and the first new carbon−silicon bond. The next step is the reduction of this hydridosilane with lithium metal providing a silyl lithium reagent, which undergoes a highly diastereoselective addition to an optically active *tert*-butanesulfinimine, thus generating the second C−Si bond. This method allows sequential functionalization of the two hydrides in diphenylsilane by chemoselective discrimination.

Introduction

Background. Proteases play a crucial role in both physiological and pathological metabolism, and therefore, great interest has been paid to the development of inhibitors hereof.[1] As a general design criterion to such inhibitors, many research groups in academia and industry have focused on replacing the scissile bond of a peptide substrate with nonlabile tetrahedral intermediate mimics, for example, hydroxyethylene, phosphinate, and difluoroketone isosteres (Figure 1). Even more fundamental than the development of new, specific protease inhibitors is the discovery of new motifs to be applied for these designs. The silanediol represents such a new motif owing to its many desirable properties: It closely resembles the tetrahedral intermediate of peptide hydrolysis. It favors the hydrated diol form over a silicon−oxygen double bond due to the poorer $P_\pi-P_\pi$ overlap in silanones, whereas its carbon counterpart favors the ketone over its hydrate, a geminal diol. The Si−C and Si−O bond distances are increased compared to those of the corresponding carbon analogs by approximately 25%, thereby enhancing the resemblance to the transition state of the peptide bond cleavage. Furthermore, the hydrogen bond donating properties are improved owing to a more acidic SiO−H bond in comparison to CO−H, which facilitates tight binding in the active site of the protease.[2] Unlike the phosphinate motif, the silanediol is uncharged at physiological pH, and while this excludes the possibility of electrostatic interactions in the active site, it offers a potential beneficial effect in relation to membrane permeability and hence bioavailability.

This general concept of silanediols as potent protease inhibitors was introduced by Sieburth and co-workers in 1998

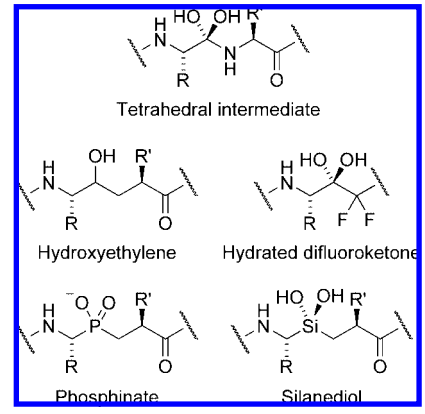


Figure 1. Common tetrahedral intermediate-mimicking motifs used in the design of aspartic- and metalloprotease inhibitors.[1]

and since then a number of silanediols with high inhibitory activities against both aspartic and metalloproteases have been reported by the same group (Figure 2).[3] These inhibitors contain a silanediol methylene unit in place of the scissile bond of a peptide or peptide-like compound. In this context, it is interesting to note that currently no silicon-containing drugs have entered the commercial market, although large efforts have been made

(1) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305–341.

(2) (a) Sieburth, S. M.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812–814. (b) Mutahi, M. W.; Nittoli, T.; Guo, L.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363–7375.

(3) (a) Chen, C.-A.; Sieburth, S. M.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B.; Jeffry, S.; Klabe, R. M. *Chem. Biol.* **2001**, *8*, 1161–1166. (b) Kim, J.; Glekas, A.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3625–3627. (c) Kim, J.; Sieburth, S. M. *J. Org. Chem.* **2004**, *69*, 3008–3014. (d) Kim, J.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2853–2856. (e) Kim, J.; Hewitt, G.; Carroll, P.; Sieburth, S. M. *J. Org. Chem.* **2005**, *70*, 5781–5789. (f) Juers, D. H.; Kim, J.; Matthews, B. W.; Sieburth, S. M. *Biochemistry* **2005**, *44*, 16524–16528. (g) Sieburth, S. M.; Chen, C. A. *Eur. J. Org. Chem.* **2006**, 311–322.

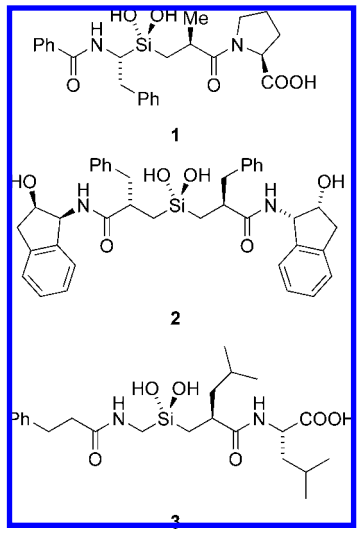


Figure 2. Silanediol-based protease inhibitors of angiotensin-converting enzyme (**1**), HIV protease (**2**), and thermolysin (**3**) as published by Sieburth.[3a,b,d]

to take advantage of the unique properties of organosilanes by incorporating silicon into bioactive compounds.[4]

Previous Syntheses. The first syntheses of the silanediol protease inhibitors reported by Sieburth and co-workers involved nucleophilic substitution of halosilanes as the means to construct the carbon−silicon bonds. This strategy was successfully applied to the synthesis of nine inhibitors against three different proteases, but it relied on a linear strategy and involved several functional group manipulations. The general applicability of masking the silanediol as a more synthetically tolerant diphenylsilane throughout the syntheses was nicely demonstrated.[5] Recently, the Sieburth group published a more direct route to a β-silyl acid precursor involving a magnesium-mediated addition of dichlorodiphenylsilane to a diene followed by hydroboration and ring opening in HF (Scheme 1).[6] This method allowed control of the stereocenter β to silicon and the resulting fluorosilane was further elaborated into an α-aminosilane.

Another approach to the silanediol peptide mimics was reported by Organ and Combs and involved a platinum-catalyzed hydrosilylation of a protected allyl alcohol with chlorodiphenylsilane followed by reduction of the resulting chlorosilane to a silyl lithium reagent and addition to an achiral imine (Scheme 1).[7] This method constructed the two carbon−silicon bonds in two consecutive steps with the simultaneous introduction of the required functional groups or their immediate precursors, but it did not offer control of the formed stereocenter. Also, the presence of a labile chlorosilane in the intermediate is not practical and complicates isolation and purification procedures.

We have previously shown that methyldiphenylsilyl lithium, generated from chloro(methyl)diphenylsilane by lithium metal reduction, undergoes diastereoselective addition to a variety of *tert*-butanesulfinimines as an expansion of the work by Scheidt and co-workers.[8] This route provides a method for controlling the stereochemistry of the stereogenic carbon center adjacent to silicon and shows functional group tolerance.[9]

Retrosynthetic and Synthetic Analysis. Examining the diphenylsilane dipeptide isostere from a retrosynthetic viewpoint, two simple disconnections can be made concerning the two carbon−silicon bonds (Scheme 2). From a synthetic perspective, these disconnections represent two formal hydrosilylations of a carbon−carbon and a carbon−nitrogen double bond with diphenylsilane. Catalytic hydrosilylation of the imine will not lead to the desired product, but to its regioisomer.[10] However, silane addition to the C═N bond of a *tert*-butanesulfinimine giving the desired regioisomer should be possible as we have demonstrated earlier,[9] if the required silyl lithium reagent can be formed. Silane addition to the C═C bond could in principle occur *via* either a radical-induced or a transition-metal-catalyzed hydrosilylation.[11] Regioselectivity is in both cases highly dependent on the alkene in use.

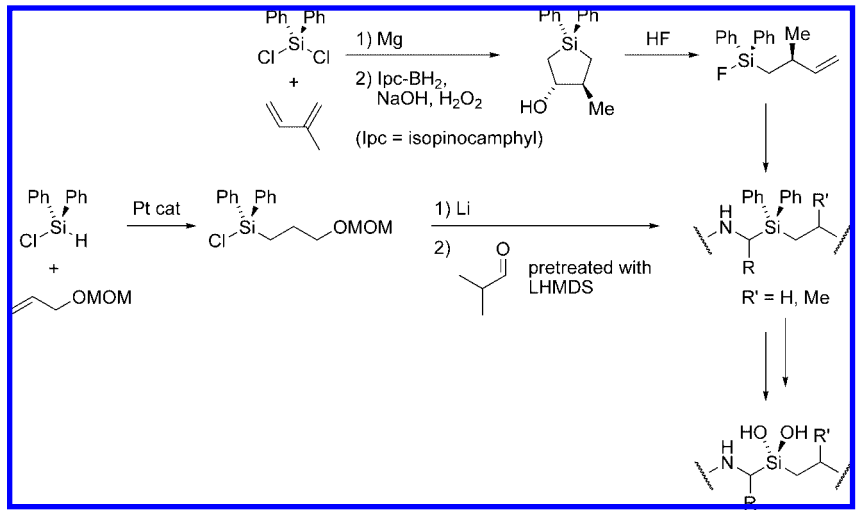
One of these two consecutive derivations of diphenylsilane must favor monofunctionalization, either by masking one of the hydrides by a different functionality, for example, a chloride, or by a reaction that selectively forms the monoalkyldiphenylsilane. The former strategy has already been adapted by Organ and Combs,[7] but the intrinsic problem of isolating and purifying the highly moisture-sensitive chlorosilane intermediate is a considerable disadvantage of this strategy. The latter strategy affords a hydridosilane intermediate, and these are stable to chromatographic purification techniques and do not require handling or storage under inert atmosphere. As already indicated, this strategy raises two important questions concerning its feasibility: (1) can alkene hydrosilylation with diphenylsilane be accomplished with selective monofunctionalization; and (2) is it possible to convert the resulting hydridosilane into its corresponding silyl lithium? The reversed order is not very likely, since hydridodiphenylsilyl lithium is not a stable intermediate.[12] In short, we wish to develop a method for the sequential functionalization of diphenylsilane through the creation of two carbon−silicon bonds from reactions with two different, unsaturated starting materials. This paper describes our successful work in this area providing our initial results directed to the development of a general synthetic strategy to silanediol protease inhibitors starting from a very simple silicon-containing compound, diphenylsilane. It demonstrates that stable alkyldiphenylsilanes can be suitable substrates for the preparation of alkyldiphenylsilyl lithium reagents.

Results and Discussion

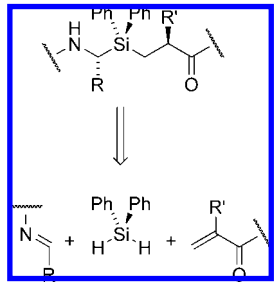
Hydrosilylation Studies. A direct, stereoselective, and ideally general synthetic route to silanediol peptide mimics is preferable in order to expand the scope of these silicon-containing derivatives as protease inhibitors. Our goal was to devise a strategy for the hydrosilylation of functionalized alkenes with diphenylsilane, conversion of the resulting hydridosilanes into silyl lithium reagents followed by addition to chiral sulfinimines. In two consecutive steps this would yield difunctionalized

(4) For two recent reviews, see: (a) Showell, G. A.; Mills, J. S. *Drug Discov. Today* **2003**, *8*, 551–556. (b) Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526–543.
(5) See also: (a) Glekas, A.; Sieburth, S. M. *Tetrahedron Lett.* **2001**, *42*, 3799–3801.
(6) Sen, S.; Purushotham, M.; Qi, Y.; Sieburth, S. M. *Org. Lett.* **2007**, *9*, 4963–4965.
(7) Organ, M. G.; Buon, C.; Decicco, C. P.; Combs, A. P. *Org. Lett.* **2002**, *4*, 2683–2685.
(8) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403–1406.
(9) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035–10044.
(10) See for example: (a) Tamao, K.; Kawachi, A. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: New York, 2002; Vol. 4, p 451f.
(11) Marciniec, B. *Silicon Chem.* **2002**, 155–175.
(12) Kawachi, A.; Tamao, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 945–955.

Scheme 1. Synthetic Strategies Towards Silanediol Peptide Isosteres by Sieburth (top) and Organ/Combs (bottom)



Scheme 2. Retrosynthesis of a Diphenylsilane Dipeptide Fragment with High Atom Efficiency



diphenylsilanes as precursors of silanediol peptide analogs. Since an ester or similar protecting groups of the carboxylic functionality in the alkene substrate would likely be unstable to the silane reduction conditions, we opted for using protected allyl alcohols as the alkene reactants.

Catalytic hydrosilylation of alkenes has been achieved with a wide range of catalysts including nucleophiles, Lewis acids, supported metals, and transition metal complexes.[11] The selective monoalkylation of diphenylsilane via hydrosilylation has also been obtained with various catalysts, although this has only been demonstrated with simple hydrocarbon olefins.[13] In consideration of catalyst availability and stability, we chose to initiate our investigations with Wilkinson's catalyst ($RhCl(PPh_3)_3$), although other catalytic systems may show equal or improved activities.

Alternatively, hydrosilylation can be achieved under radical conditions applying a radical initiator and a polarity-reversal catalyst according to the principle described by Roberts.[14] In the uncatalyzed radical chain hydrosilylation, the rate-determining step is hydrogen atom abstraction by the newly formed, nucleophilic, carbon-centered radical from the electron-rich hydridosilane. Adding a thiol catalyst, which delivers an electron-poor hydrogen atom to the carbon radical, reverses this electronic mismatch. Thereby, an electrophilic thiyl radical is generated, which subsequently abstracts hydrogen from the silane. The two thiol-mediated hydrogen transfers occur faster than the direct transfer.[15]

The syntheses of the functionalized alkenes to be used in the hydrosilylation reactions were carried out as follows: Alkenes **10**, **11**, **20**, and **21** were obtained by standard protection procedures of allyl alcohol. The disubstituted alkenes **7**, **8**, and **9** were prepared from dihydrocinnamaldehyde (**4**) exploiting a Mannich reaction followed by reduction and/or protection (Scheme 3).[16]

Radical chain-propagated hydrosilylation of alkenes with excess diphenylsilane (2 equiv) was accomplished in refluxing hexane over a period of 18 h using dilauroyl peroxide (10 mol%) as the radical initiator and triphenylsilanethiol (10 mol%) as the polarity-reversal catalyst (Table 1). Gratifyingly, these conditions were tolerated by the two alcohol protecting groups examined in entries 1−4, the dioxolane in **9** (entry 5) and by a benzyl substituent in the 2-position of the alkene (entries 3−5). The yields obtained were in general good for radical reactions ranging from 55−77% yield. Although the use of diphenylsilane carries the risk of double alkylation, none of the dialkylated products were observed which may be accounted for by the slower hydrogen transferring abilities of the trisubstituted silane derivatives due to potential sterical factors as well as the stronger Si−H bond for the trifunctionalized silane compared to diphenylsilane.[14d] Roberts and co-workers have reported enantioselective hydrosilylations applying homochiral carbohydrate-derived thiols as catalyst,[14b,17] but preliminary attempts to employ some of these catalysts for the synthesis of optically active silane **14** were met with little success.

(13) (a) Fuchikami, T.; Ubukata, Y.; Tanaka, Y. *Tetrahedron Lett.* **1991**, *32*, 1199–1202. (b) Takahashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 8564–8566. (c) Kira, M.; Hino, T.; Sakurai, H. *J. Am. Chem. Soc.* **1992**, *114*, 6697–6700. (d) Baruah, J.; Osakada, K.; Yamamoto, T. *J. Mol. Catal. A: Chem.* **1995**, *101*, 17–24. (e) Hou, Z.; Zhang, Y.; Tardif, O.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9216–9217. (f) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794–13807. (g) Ura, Y.; Gao, G.; Bao, F.; Ogasawara, M.; Takahashi, T. *Organometallics* **2004**, *23*, 4804–4806.

(14) (a) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1995**, *36*, 2875–2878. (b) Cai, Y.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, *n/a*, 467–475. For a review, see: (c) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35. For a recent monograph on organosilanes in radical chemistry, see: (d) Chatgilialoglu, C. *Organosilanes in Radical: Chemistry, Principles, Methods and Applications*; John Wiley & Sons Ltd: Chichester, 2004.

(15) Diphenylsilane has been reported to yield only the monoalkylated product in a silyl radical addition to an α,β-unsaturated ester, see: Smadja, W.; Zahouily, M.; Journet, M.; Malacria, M. *Tetrahedron Lett.* **1991**, *32*, 3683–3686.

(16) (a) Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* **1988**, *110*, 531–538. (b) Banik, B. K.; Chapa, M.; Marquez, J.; Cardona, M. *Tetrahedron Lett.* **2005**, *46*, 2341–2343.

Scheme 3. Preparation of Alkene Precursors

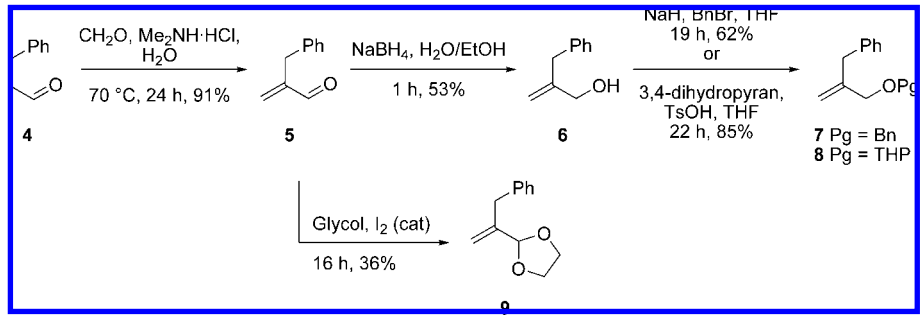
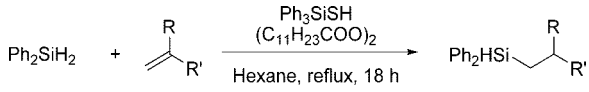


Table 1. Hydrosilylation of Alkenes using Radical Initiator and Thiol Catalyst[a]

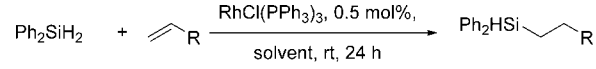


entry	alkene	silane	yield[b]
1	OBn **10**	Ph$_2$HSi OBn **12**	72%
2	OTHP **11**	Ph$_2$HSi OTHP **13**	76%
3	Ph OBn **7**	Ph$_2$HSi Ph OBn **14**	77%[c]
4	Ph OTHP **8**	Ph$_2$HSi Ph OTHP **15**	55%[d]
5	Ph O O **9**	Ph$_2$HSi Ph O O **16**	58%[c]

[a] Silane (2 equiv), alkene (1 equiv), Ph_3SiSH (0.1 equiv), $(C_{11}H_{23}COO)_2$ (2 × 0.05 equiv). [b] Isolated yields after column chromatography. [c] As a racemic mixture. [d] As a diastereomeric mixture.

Transition metal-catalyzed hydrosilylation of a number of alkenes with diphenylsilane was next undertaken and performed using $RhCl(PPh_3)_3$ with catalyst loadings of 0.5 or 1 mol% and a reaction time of 24 h (Table 2). Initially, the THP-protected allylic alcohol **11** was examined. The reactions showed little variation among the solvents THF, CH_2Cl_2, and toluene (entries 1, 3, and 4), but acetone proved to be a poor choice (entry 5). This is not unexpected since $RhCl(PPh_3)_3$ has the potential of catalyzing the hydrosilylation of ketones as well,[18] and indeed the silyl ether derived from acetone was detected in the ^{1}H NMR spectrum of the reaction mixture. Hydrosilylation of the carbonyl is expected to occur faster than that of the alkene, and it is therefore somewhat surprising that a small amount of product is actually formed despite the large excess of acetone.[19] When one equivalent of acetone was added to the reaction with **11** in THF (entry 6), it appeared that the ketone and the alkene underwent hydrosilylation at similar rates. Finally, it is also interesting to observe that the yield of hydrosilylation of **11** was not improved upon increasing the number of equivalents of the silane (entry 2).

Table 2. Hydrosilylation of Alkenes using Wilkinson's Catalyst[a]



entry	alkene	silane	solvent	yield[b]
1	OTHP **11**	Ph$_2$HSi OTHP **13**	THF	81%
2[c]	**11**	**13**	THF	75%
3[d]	**11**	**13**	CH_2Cl_2	71%
4[d]	**11**	**13**	Toluene	85%
5[d]	**11**	**13**	Acetone	17%
6[d]	**11**	**13**	THF + 1 equiv acetone	50%
7	Ph **17**	Ph$_2$HSi Ph **22**	THF	38%[e]
8	**18**	Ph$_2$HSi **23**	THF	60%
9	O **19**	Ph$_2$HSi O **24**	THF	43%
10	OTBS **20**	Ph$_2$HSi OTBS **25**	THF	53%
11	ODPS **21**[f]	Ph$_2$HSi ODPS **26**[f]	THF	93%[g]

[a] Silane (1 equiv), alkene (1 equiv). [b] Isolated yields after column chromatography. [c] Entry performed with silane (2 equiv), alkene (1 equiv). [d] Entry performed with 1 mol% catalyst loading. [e] Higher yields for this reaction have been reported (ref 13d). [f] DPS = *tert*-butyldiphenylsilyl. [g] Isolated yield.

The yields of these reactions were highly dependent on the alkene investigated. Fortunately, the THP- and DPS-protected allyl alcohols (**11** and **21**), which are interesting in terms of peptide analog synthesis as they elaborate into β-silyl acids, provided the highest hydrosilylation yields in 81 and 93%, respectively (entries 1 and 11). Use of the less sterically demanding TBS group was less effective most likely due to the lability of this hydroxyl protecting group under the reaction

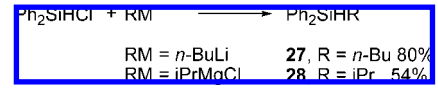
conditions (entry 10). Formation of silane **22** from styrene **17** in up to 89% yield under similar reaction conditions and with the same catalyst has been reported elsewhere, but this reaction proved troublesome in our hands for reasons not known (entry 7).[13d] In all cases, the anti-Markovnikov product was obtained selectively.[20]

Double alkylation is again a potential problem, but the dialkylsilanes were not observed under this hydrosilylation protocol. This reluctance for double addition involving diphenylsilane was further supported by treating silane **13** with one equivalent of alkene **11** under the same reaction conditions, after which no dialkylated product was observed. Attempts to apply the alkenes bearing a C2-benzyl substituent (**8** and **9**) unfortunately did not yield the hydrosilylation product under these conditions.

To conclude, it is notable that both the silyl radical addition and catalytic hydrosilylation occur with full atom economy and only substoichiometric additives and in addition, stoichiometric amounts of reagents are applied in the catalytic hydrosilylation. Hence, further work is currently underway to examine other hydrosilylation conditions to improve the scope of this reaction to more functionalized alkenes, particularly those possessing C2-substituents.

Silyl Lithium Generation and Sulfinimine Addition Studies. The preparation of arylsilyl lithium reagents from corresponding aryl(chloro)silanes with lithium metal in THF solution has been known for decades and is a widely used procedure for the preparation of these reagents.[21] As discussed in the Introduction section, chlorosilanes are not attractive as synthetic intermediates due to stability issues, and the direct lithiation of hydridosilanes could in certain cases replace the use of chlorosilanes in synthetic schemes. Owing to their hydridic nature, however, hydridosilane are not easily deprotonated with bases. Deprotonation and generation of silyl lithium reagents have been achieved using strong bases like *tert*-butyl lithium and lithium diisopropylamide, but only for the special cases of dihydridodisilylsilanes.[22] Reduction to give silyl potassium reagents has been achieved with sodium/potassium alloys or potassium hydride.[23] The reaction of arylhydridosilanes with lithium metal has only been mentioned briefly in the literature, but is noted to lead to an number of side reactions including disilane formation and disproportionation, and is thus considered unsuitable for the formation of silyl lithium reagents.[21a,c,24] To the best of our knowledge, silyl lithium reagents generated from hydridosilanes and lithium metal have not been applied in the synthesis of functionalized silanes. The sparse reports on the lithium reduction of hydridosilanes led us to speculate whether this reaction was indeed as unreliable as first anticipated.

Scheme 4. Nucleophilic Substitution of Chlorodiphenylsilane



To commence this investigation, three simple alkyldiphenylsilanes **27**, **28**, and **30** were examined for lithiation. The methylsilyl derivative (**30**) is commercially available, and the other two silanes were prepared from chlorodiphenylsilane using commercial solutions of *n*-butyl lithium or isopropyl magnesium chloride as nucleophiles (Scheme 4).[25] This method is straightforward for the introduction of simple alkyl substituents but may become difficult if elaborate Grignard reagents or alkyl lithiums are to be applied.

With an array of simple and functionalized alkyldiphenylsilanes at hand, we were ready to challenge the previous literature assumptions of hydridosilanes being poor substrates for lithium reduction. The synthesized hydridosilanes were treated under similar conditions as the chlorosilanes for the generation of silyl lithium reagents and then reacted with the chiral sulfinimine **29**,[26] the results of which are displayed in Table 3. For example, methyldiphenylsilane reacted with lithium metal in dry and degassed THF over the course of several hours forming a dark brown solution characteristic for lithiation as seen with the chlorosilanes. Subsequently, this solution was added to a cooled solution (−78 °C) of the sulfinimine, providing after workup and chromatographic purification an 86% yield of the α-silylsulfinamide **31** with high diastereoselectivity (>95:5) as shown in entry 1. The reaction of seven other alkyldiphenylsilanes with sulfinimines also gave the expected α-silylsulfinamides in yields ranging from 47−84%, and in most cases with excellent diastereoselectivities. It was pleasing to observe that even the alkyldiphenylsilane **15** carrying a β-benzyl group in the alkyl chain could be coupled to the sulfinimine by lithiation of a stable silane precursor, providing product **38** in a yield close to 50% (entry 8).

The general trend in diastereoselectivities was interrupted by the case with a secondary alkyl substituent on the silicon atom (entry 3), in which the diastereoselectivity was noticeably lower. Diastereoselectivities were determined from ^{1}H NMR spectra as previously described,[9] except for the products containing THP protecting groups (**37** and **38**, entries 7 and 8). The presence of an additional stereocenter in this protecting group (and in the case of **38**, the benzyl side chain) caused these products to be

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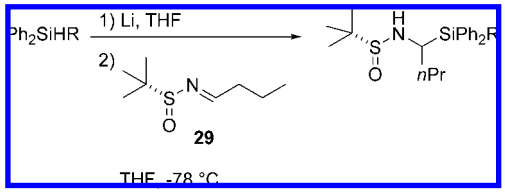
Table 3. Lithiation of Hydridosilanes and Subsequent Addition to Sulfinimine[a]



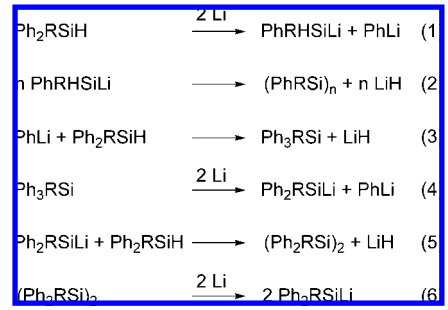
entry	silane	sulfinamide	yield[b]	dr[c]
1	Ph_2MeSiH **30**	**31**	86%	95:5
2	**27**	**32**	78%	95:5
3	**28**	**33**	84%	80:20
5	**22**	**34**	71%	95:5
4	**23**	**35**	80%	95:5
6	**24**	**36**	50%	>95:5
7	**13**	**37**	76%	n.d.[d]
8	**15**	**38**	47%	n.d.[d]

[a] Silane (2 equiv), Li (20 equiv), sulfinimine (1 equiv). [b] Isolated yields after column chromatography. [c] Determined from ^{1}H NMR. [d] Not determined due to the presence of additional stereocenters.

formed as diastereomeric mixtures rendering the detection and quantification of minor diastereomers difficult. Further, unambiguous assignment of the minor/major diastereomeric relation to arise from the stereocenter α to silicon and not the one in the protecting group was not easily given. Despite this ambiguity, we believe that the diastereoselectivities for formation of products **37** and **38** were comparable to those for the other reactions in Table 3.

The silane bearing a benzyl ether (**12**) was also subjected to lithiation, but did not yield the addition product due to the possible removal of the benzyl group under the reaction conditions with lithium metal. Similarly, the silanes bearing

Scheme 5. Suggested Route to Formation of Silyl Lithiums from Hydridosilanes and Lithium Metal



silyl-protected alcohols (**25** and **26**) displayed some instability under these reaction conditions leading to partial deprotection of the starting material and a number of byproducts.[27]

The mechanism for generation of the silyl lithium reagents from their corresponding hydridosilanes is suggested to occur via a number of steps as illustrated in Scheme 5. Fleming and co-workers have studied the formation of arylsilyl lithiums from chlorosilanes extensively.[28] They suggest that any hydridosilane present in the solution (from protonation of the silyl lithium reagent) will react with the formed silyl lithium to give a disilane, which is again reduced by lithium to reform the silyl lithium ((5) and (6), Scheme 5). In terms of the hydridosilane reductions, this means that any source of silyl lithium reagent will initiate the conversion.

Tetraphenylsilane has been reported to react with lithium in THF to give triphenylsilyl lithium and phenyl lithium;[29] and recently, functionalized silyl lithiums have been prepared from lithium reduction of phenyl-substituted silanes.[30] We suggest that a similar C−Si bond cleavage may comprise the initial step in the hydridosilane reduction (1). The formed hydridosilyl lithium probably collapses to oligo- or polysilanes (2),[12,21a] while phenyl lithium may react with another molecule of the alkyldiphenylsilane to give an alkyltriphenylsilane (3). This tetrasubstituted silane is prone to further C−Si bond cleavage to give phenyl lithium and the desired alkyldiphenylsilyl lithium (4). If this is indeed the case, it entails that either phenyl lithium or the silyl lithium reagent will catalyze the reduction of hydridosilane. Whichever is the dominant, or whether it is a combination of the two, will depend on the relative rates of the reactions. Relative reaction rates also determine if the major fate of the hydridosilane is conversion to the desired silyl lithium or to oligosilanes or oligosilanyl lithiums, and therefore if the silyl lithium reagent will be formed in near quantitative amounts or not. We have used two equivalents of the hydridosilanes in the reactions to compensate for any loss of material; however, we have not challenged the necessity for using this excess. The formation of phenyl lithium, lithium hydride, and potential oligosilanyl lithiums may hamper the yield of the desired product by reacting with the sulfinimine, but we have not detected any of these byproducts and thus cannot conclude if this is an actual problem.

Finally, to emphasize the direct accessibility of the addition products shown in Table 3, a "one-pot" hydrosilylation, lithiation

(27) In accordance with notions mentioned in ref 21c.
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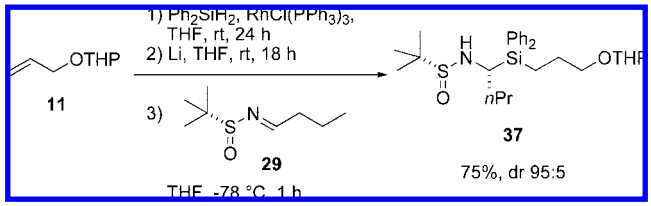
Scheme 6. One-Pot Hydrosilylation, Lithiation, and Addition to Sulfinimine[a]



[a] Conditions: Diphenylsilane (2 equiv), alkene (2 equiv), $RhCl(PPh_3)_3$ (0.01 equiv), crude mixture transferred to suspension of Li (20 equiv) and added to imine (1 equiv).

and addition were attempted with alkene **11**. The catalytic hydrosilylation was performed in THF, and the crude reaction mixture subjected to lithiation and subsequent sulfinimine addition (Scheme 6). The addition product (**37**) was obtained in a good 75% yield and a 95:5 diastereomeric ratio. The 'one-pot' yield thus surpassed the two-step yield (62%) without compromising the diastereoselectivity. This further demonstrates that complex dialkyldiphenylsilanes are readily accessible compounds using this strategy.

We envision silanes **37** and **38** to undergo protecting group manipulations and oxidation to give the overall structure of a silane-containing dipeptide fragment. In combination with our previous application of sulfinimines bearing side chains of both natural and non-natural amino acids, we believe this strategy will give access to a wide range of Aa-[Si]-Gly and Aa-[Si]-Phe dipeptide analogs,[31] with the possibility of expanding the strategy to other amino acids bearing alkyl side chains. Further work will nevertheless be required to improve the scope of the hydrosilylation step to introduce such side chains, as well as the possible development of an asymmetric version.

Overall, our hydrosilylation/lithiation strategy describes the use of diphenylsilane as a representative of the general synthons **39** and **40** (Figure 3), and chlorodiphenylsilane a representative

(31) Aa represents any natural or non-natural amino acid.

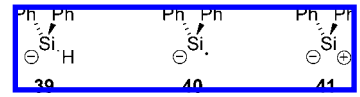


Figure 3. General diphenylsilyl synthons as applied in this paper.

of the general synthon **41** (Figure 3). Therefore, with these two simple starting materials, a variety of transformations and access to a wide range of diphenylsilanes can possibly be made accessible in a facile manner.

Conclusions

We have reported on the two-step synthesis of a dipeptide mimic precursor containing a central diphenylsilane group. Diphenylsilane, one of the simplest precursors, undergoes two consecutive carbon−silicon bond formations to give the desired C−Si framework with appropriate functionalities for further elaborations. To the best of our knowledge, this is the first report on the successful synthetic application of a silyl lithium reagent generated from a hydridosilane by lithium metal reduction, and compared to chlorosilanes, they exhibit the conspicuous advantage of being stable to chromatographic purification. In our continued search for a divergent and versatile synthesis of silanediol peptide isosteres, our next goal will be to improve the scope of these reactions for the general, efficient, and stereoselective introduction of the side chain on the C-terminal end of the silane. The successful outcome of this study will be reported in due course.

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Supporting Information Available: Experimental methods for the preparation of **5**−**16**, **20**−**29**, **31**−**38**. Copies of ^1H NMR and ^{13}C NMR spectra for compounds **12**−**16**, **24**−**26**, and **32**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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