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Efficient Routes to Carbon–Silicon Bond Formation for the Synthesis of Silicon-Containing Peptides and Azasilaheterocycles

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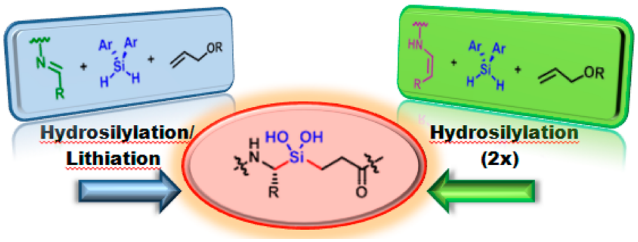
CONSPECTUS



Silasubstitution, where silicon is substituted for carbon at specific sites of the substrate, has become a growing practice in medicinal chemistry. Introducing silicon into bioactive compounds provides slight physical and electronic alterations to the parent compound, which in certain instances could make the substrate a more viable candidate for a drug target. One application is in the field of protease inhibition. Various silane diol isosteres can act as potent inhibitors of aspartic and metalloproteases because of their ability to mimic the high-energy tetrahedral intermediate in peptide bond hydrolysis. In particular, since 1998, the Sieburth group has prepared a number of functionalized peptide silane diol isosteres. In a seminal study, they demonstrated that these molecules can bind to the active site of the enzymes. Inspired by these results, we initiated a study to develop a concise and straightforward route to access highly functionalized silicon diol based peptidomimetic analogs, which we describe in this Account. The synthesis of such analogs is challenging because the dipeptide mimics require the formation of two carbon–silicon bonds as well as two chiral carbon centers.

Our first strategy was to assemble the two C–Si bonds from diphenylsilane through an initial regioselective hydrosilylation step of a terminal alkene, followed by lithiation of the formed alkyldiphenylsilane by a simple lithium metal reduction. Subsequent diastereoselective addition of this silyllithium species to a *tert*-butylsulfinimine provided a rapid method to assemble the dipeptide mimic with stereochemical control at the new chiral carbon center adjacent to the silicon. This strategy worked with a wide range of functional groups. However, there were some limitations with the more elaborate targets. In particular, we needed to exchange the phenyl groups of the diphenylsilane with aryl groups that were more labile under acidic conditions in order to introduce Si–O bonds in the end product. We demonstrated that a variety of Ar_2SiH_2 compounds with methyl substituents on the aromatic core could effectively undergo hydrosilylation and reductive lithiation with a soluble reducing agent, lithium naphthalenide. The electron-rich aromatic groups were more acid labile and, depending on the conditions, could produce either the silane diol or the silanol.

In an alternative strategy, we used a highly regioselective Rh-catalyzed sequential double hydrosilylation to form the two C–Si bonds with a single catalyst. This approach is a more efficient, atom economical way to synthesize a wider range of highly functionalized organosilanes with the added possibility of extending this method into an asymmetric protocol. By this method, various functional groups that were not previously tolerated in the lithiation protocol, including OBn, OAc, furyl, and thiophenes, could now be incorporated. Hydrosilylation of a terminal olefin and a peptide functionalized with an enamide at the C-terminus achieved the desired silane in high yields in a one pot reaction without compromising the stereochemical integrity of the peptide. As an extension of this work, we used these methods to efficiently generate a variety of chiral azasilaheterocycles, including silapiperidines and silaindolizidines.

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I. Introduction

Silasubstitution, also known as the "silicon switch", of bioactive molecules has become a growing practice in medicinal chemistry. This is primarily due to the pioneering work of Reinhold Tacke and co-workers whose interest was to evaluate whether "silicon switch" could enhance the biological activity of muscarinic receptor antagonists.[1] Although silicon is not a naturally occurring element in bioactive compounds, comparable physical and electronic similarities with some slight differences from carbon makes it a viable choice toward replacing a carbon center of a drug candidate.[2]

II. Silicon: A Carbon Substitute

Silicon is the most similar element to carbon as depicted in Figure 1.[3,4] However despite its strong resemblance, silicon possesses its own inherent character that is slightly altered from its carbon counterpart. It possesses an approximately 65% larger radius than carbon and has slightly altered bond angles and longer bond lengths (typically 20% longer when Si–C bond is compared with C–C).[2a,b,3,4] There are also some electronic differences from carbon. Silicon is more lipophilic. It is also more electropositive allowing for stronger Si–OH and Si–F bond strengths than its respective C–OH and C–F bonds.[2c] SiO–H also exhibits a better hydrogen bond donor ability than carbinols.[2b,c] These slight differences from the parent carbon compound allows the "silicon switch" to be an attractive strategy toward improving the substrate's pharmacokinetic properties (Table 1).[2a–c]

One of the major emerging applications for silicon is its ability to mimic the active transition state of protease-mediated

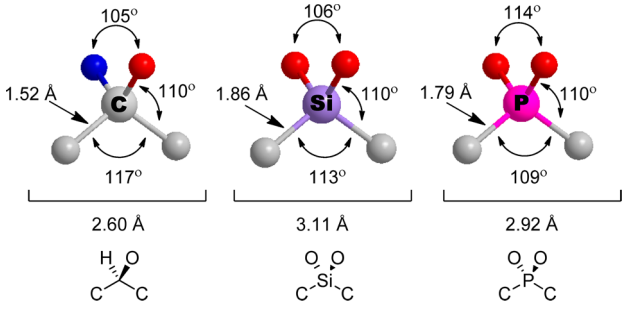


FIGURE 1. Silicon's and phosphorus's physical similarity to carbon.

TABLE 1. Key Physical and Electronic Differences between Carbon and Silicon

	carbon	silicon
radius	77 ppm	117 ppm
bond length	1.52 Å (C–C)	1.86 Å (Si–C)
electronegativity	2.50	1.74
lipophilicity	cLogP = 3.97 (Ph*t*Bu)	cLogP = 4.72 ($PhSiMe_3$)

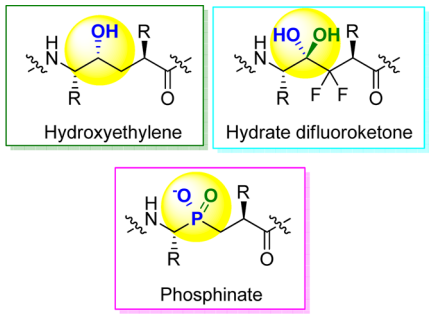
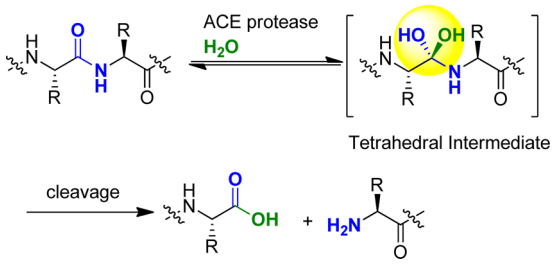


FIGURE 2. Uncleavable isosteres mimicking the tetrahedral intermediate.

SCHEME 1. ACE Protease Amide Bond Cleavage



peptide hydrolysis. The first successful case was the inhibition of the angiotensin converting enzyme (ACE) protease, a metalloprotease possessing a zinc metal in its active site.[5] This metal activates water, which then promotes the cleavage of the amide bond (Scheme 1).[6] A way to inhibit this activity is to introduce a synthetic mimic of the tetrahedral intermediate that will bind to the active site more readily than the peptide.[5,7] Investigations of various uncleavable isosteres (hydroxylethylene, hydrated difluoroketone, and phosphinate) that can permanently maintain the tetrahedral state were explored (Figure 2).[5] It was postulated that silicon would also serve as an excellent candidate for mimicking the tetrahedral intermediate due to it being the closest carbon analog. Unlike carbon, silicon prefers residing as the silane diol form rather than as the silanone.[8] Also, the lengthening of Si–OH bonds would allow easier access for the metal to bind to the hydroxyl groups. Therefore despite having a strong resemblance to the parent compound, its slight alterations to the physical and electronic properties would make the silicon diol analog a viable candidate to be investigated.

For several years, the exploration into this field was limited primarily due to the lack of methodology to incorporate the silicon element into highly functionalized systems. Thus, only simple silanes were investigated. Galardy and Kortylwicz tested a simple dimethylsilane diol **1** in 1985, while Curley and Pratt used a more functionalized silane triol

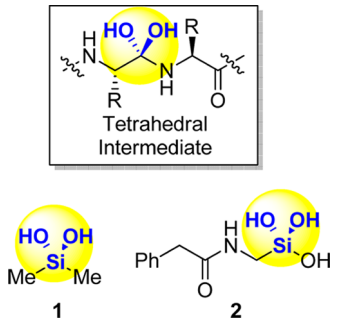


FIGURE 3. First silicon substrates used to mimic the tetrahedral intermediate for ACE protease inhibition.

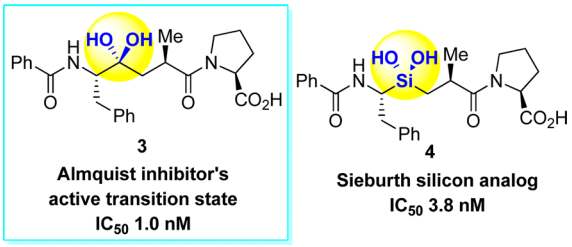


FIGURE 4. Sieburth's silicon analog mimic **4** to Almquist inhibitor **3**.

2 nearly a decade later (Figure 3). Unfortunately, enzyme inhibition was not observed in both cases.[9,10]

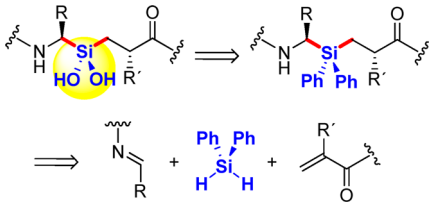
A major contribution came from Sieburth and co-workers in 1998, who took a known ACE protease inhibitor, the Almquist inhibitor **3**, and synthesized a silicon-based mimic **4**. In their study, they not only proved that the silicon analog **4** had comparable biological activity to its parent carbon compound but also provided the first strategy toward incorporating silicon diols into a highly functionalized system (Figure 4).[4,11,12] Inspired by these results, our group believed that incorporating silane diols into peptides had high potential in medicinal chemistry. Therefore, we were interested in pursuing a concise and straightforward route toward incorporating the silane diol motif as depicted in Scheme 2 and investigating its utility in protease inhibition.

III. Hydrosilylation/Lithiation Strategy

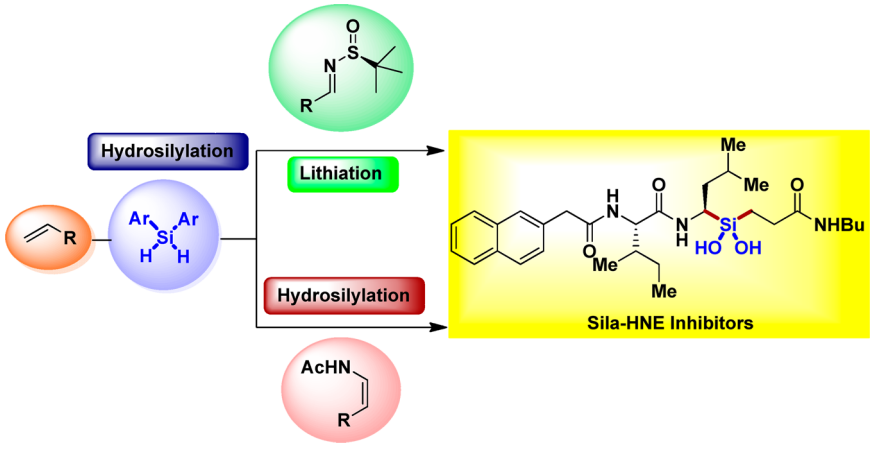
From a retrosynthetic viewpoint, two simple disconnections can be made concerning the two C–Si bonds (Scheme 3). Our group envisioned that we could access the silane diol peptidomimetic analogs via hydrosilylation of an olefin followed by a lithiation and addition to an imine to form the two necessary C–Si bonds. As the final step, the silane diols would be furnished by an acid induced hydrolysis of the aromatic group. Initial studies were focused on the lithiation step. It was anticipated that high diastereoselectivity could be achieved using chiral sulfinimines despite the potential competing aza-Brook rearrangement.[13,14] This method had numerous advantages. Optically pure sulfinimines **5** could easily be obtained via condensation of (*R*)-*tert*-butanesulfinamide onto various aldehydes while the generation of $Ph_2MeSiLi$ can be achieved using $Ph_2MeSiCl$ and Li metal. The *tert*-butanesulfoxide auxiliary can be subsequently removed using acidic conditions and thereby furnish a free amine for further functionalization (Scheme 4).

Imines possessing enolizable protons were previously postulated to be problematic due to the limited success

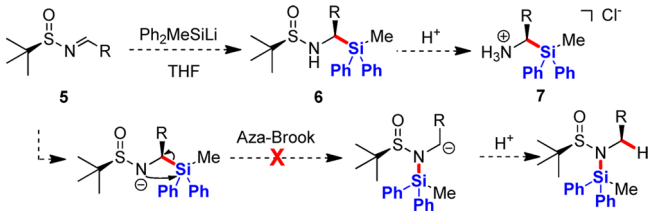
SCHEME 3. Retrosynthetic Analysis of Silicon Peptidomimetic Analogs



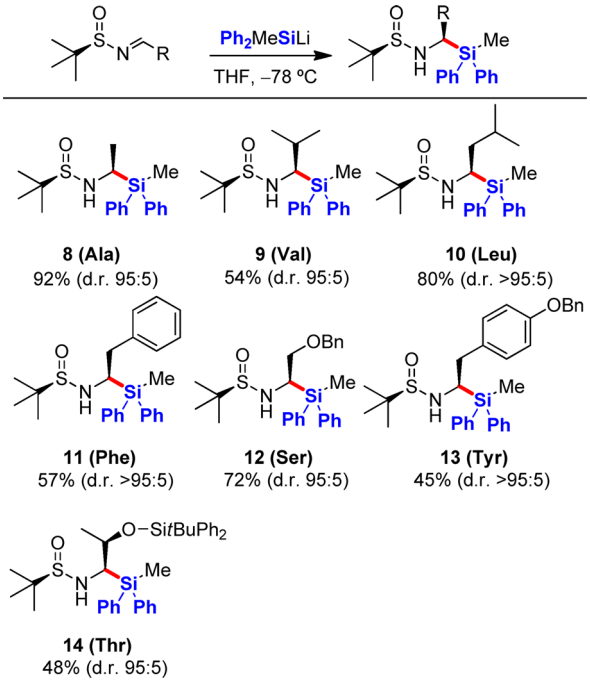
SCHEME 2. Designed Approaches towards Silicon-Based Peptidomimetic Analogs



SCHEME 4. Silyllithium Attack onto Chiral Sulfinimine Strategy towards Synthesis of α-Alkylsilyl Amine



SCHEME 5. Synthesis of Silicon Mimics of Simple Amino Acid

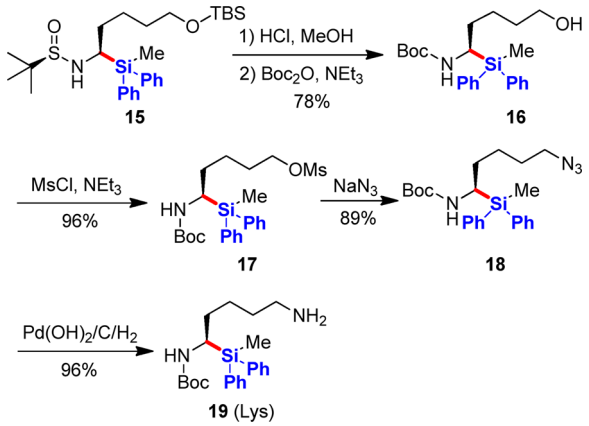


using a chiral sulfinimine derived from acetophenone.[13] We decided to probe a variety of imines generated from aldehydes that are less prone to enolization and discovered that this method could indeed provide moderate to high yields of the α-silylamines with high diastereoselectivity (Scheme 5).[15,16]

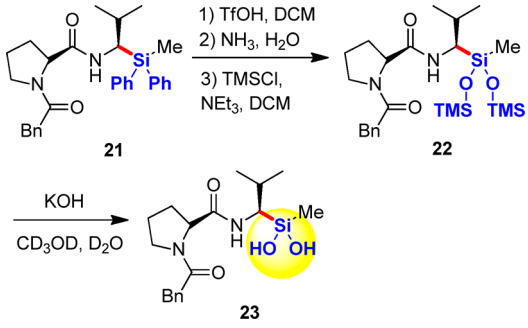
More complex amino acid mimics could also be accessed using this strategy. In order to generate a silicon analog of lysine, the addition product **15** (Scheme 6) underwent global deprotection followed by protection of the primary amine to its corresponding Boc carbamate **16**.[16] The hydroxyl group was mesylated and treated with NaN_3. Azide **18** was subsequently converted to the free amine to achieve the desired lysine mimic **19**. Similar strategies were employed to access aspartic acid, proline, and arginine.[16]

The N-terminus was then coupled to various amino acids and was subsequently converted to the silane diol from the

SCHEME 6. Synthesis of the Silicon Mimic of Lysine



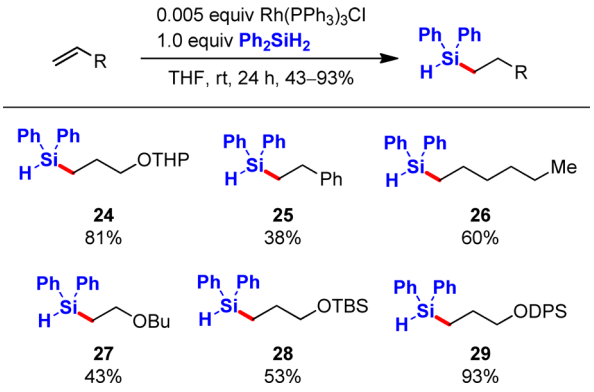
SCHEME 7. Silane's Phenyl Cleavage and Hydrolysis



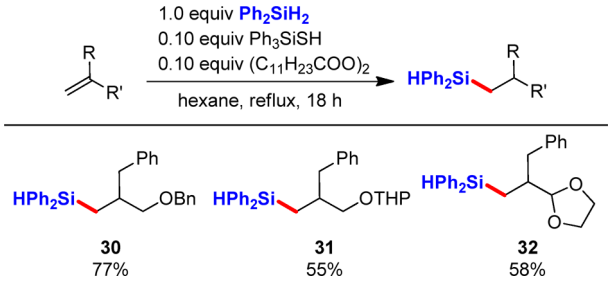
diphenylsilane moiety by treatment with TfOH followed by aqueous hydrolysis as reported by Sieburth and co-workers (Scheme 7).[12,15] Isolation of the silane diol **23** directly after TfOH and hydrolysis, however, was not possible due to the propensity for silane diols to form oligomers when concentrated or in nonpolar solvents.[12] In a previous report, the crude silane diol was converted to the corresponding difluorosilane by treatment with HF.[12] The difluorosilane is reported to be stable for purification via extraction. In hopes to avoid the usage of caustic hydrofluoric acid, the crude silane diol was subjected to TMS protection of the hydroxyl groups to obtain a stable and isolable disiloxane **22**. This derivative could be hydrolyzed under aqueous basic conditions to provide the silane diol product in solution.[4] A number of peptide mimics were synthesized using this strategy thereby demonstrating the methods viability.

With the silyllithium attack onto chiral sulfinimines investigated, our group focused on the other C–Si bond formation via hydrosilylation protocol. Organ and Combs had previously reported that hydrosilylation of a terminal olefin with chlorodiphenylhydridosilane achieved complete

SCHEME 8. Rh-Catalyzed Hydrosilylation of Terminal Linear Olefins



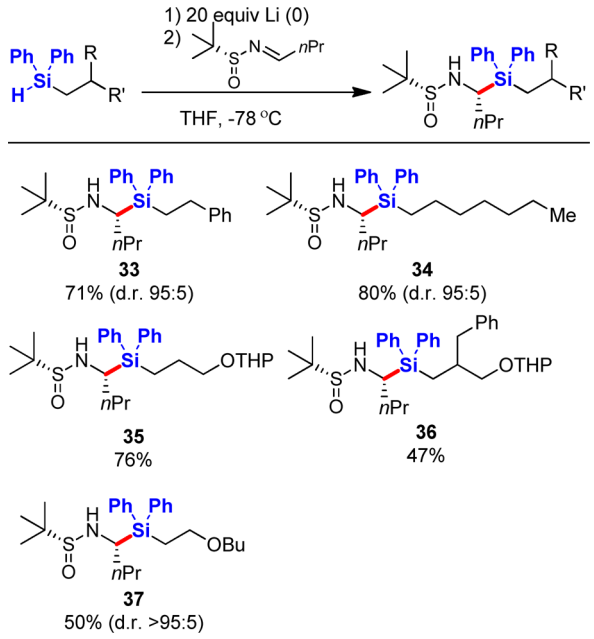
SCHEME 9. Radical-Catalyzed Hydrosilylation of 1,1-Disubstituted Olefins



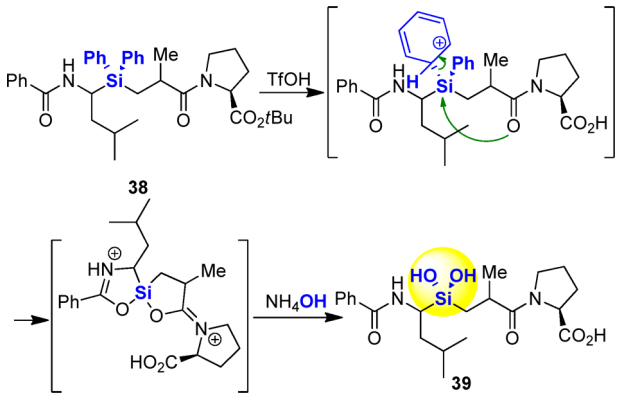
regioselectivity for the anti-Markovnikov product. The resulting chlorosilane underwent lithiation and subsequently attacked an *in situ* generated imine.[17] Due to various chlorosilanes being problematic in the purification and handling, our group hoped to exchange the chlorodiphenylhydridosilane with diphenylsilane, the product of which should be susceptible to chromatographic purification unlike the corresponding chloride.

The hydrosilylation of a terminal olefin achieves moderate to excellent yields of the desired product with catalyst loading as low as 0.5 mol % $Rh(PPh_3)_3Cl$ (Scheme 8).[18] Surprisingly, no double hydrosilylated product was observed in this study. These mild conditions tolerated various functionalities. However, using styrene, enol ether, or 1,1-disubsituted olefins as the terminal olefin provided none or at most low yields of the product. With the 1,1-disubsituted olefins, a radical-catalyzed hydrosilylation proved more successful leading to the desired anti-Markovnikov product in moderate to good yields (Scheme 9).[18] Importantly, the resulting silanes from both linear and branched olefins could subsequently be converted to their corresponding silyllithium anion upon subjection to Li metal, which then upon subjection to

SCHEME 10. Lithiation of Hydridosilane Followed by Attack onto Chiral Sulfinimines



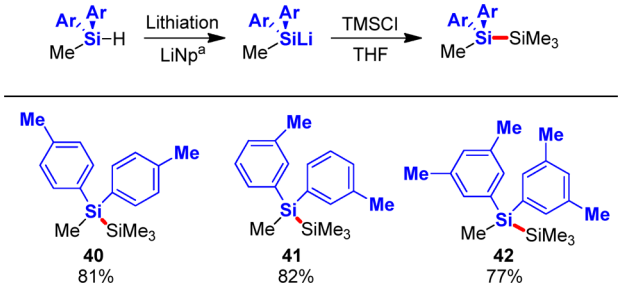
SCHEME 11. Silane's Phenyl Group Cleavage Mechanism



the chiral sulfinimine provided the product with high diastereoselectivity (Scheme 10).[18]

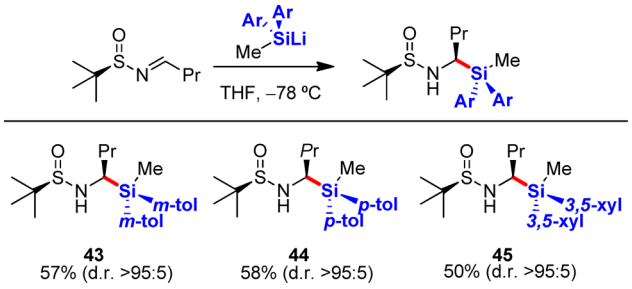
This method allowed us to access a diverse collection of diphenylsilanes. As the final strategy to furnish the silane diol moiety, acidic conditions were employed. This method was first introduced by Sieburth and co-workers who postulated the cleavages occurred according to the mechanism depicted in Scheme 11.[11] As previously stated, the reaction often required harsh conditions such as the use of triflic acid to promote the cleavage of the silane's phenyl groups. However, in certain cases, the phenyl cleavages were not possible using this strategy.

SCHEME 12. Silyllithium Formation Followed by Attack onto TMSCl[a]



[a]Li (10.0 equiv), naphthalene (1.0 equiv), THF, rt, 1h; then diarylsilane was added, and the mixture was stirred for 3–4 h.

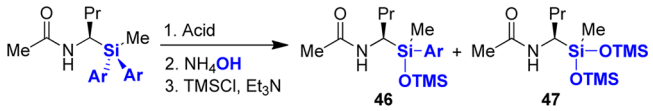
SCHEME 13. Silyllithium Attack of Chiral Sulfinimine



Therefore, our group hoped to introduce an electron-rich aromatic group on the silicon that would be inert in the removal of the chiral auxiliary but be more labile than Ph using the previously reported conditions for the aromatic group cleavage.

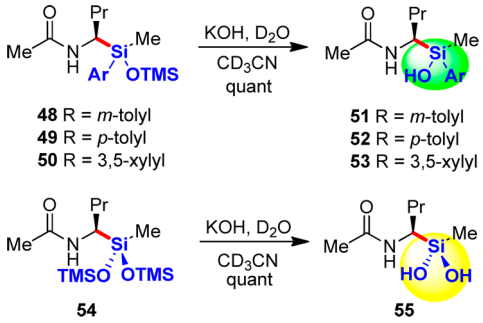
Initial work demonstrated that the lithiation protocol employing Li metal was not compatible with a number of diarylsilanes, where Ar ≠ Ph. A protocol developed previously to reduce disilanes using a soluble reducing agent, lithium naphthalenide (LiNp),[19] was therefore examined. To demonstrate that silyllithium compounds were being successfully generated, the reaction was quenched with TMSCl to provide their respective disilanes **40**–**42**. These disilanes were synthesized in good yields (Scheme 12).[20] This strategy was then employed to access α-aminosilanes. The incorporation of electron-rich diaryl groups using this protocol provided the α-aminosilanes in moderate yields with high diastereoselectivity (Scheme 13).[20] The electron-rich aryl groups tolerated HCl conditions allowing for the subsequent sulfonamide cleavage followed by acetylation of the resulting amine. However when treated with TfOH, the aromatic groups were cleaved to furnish the protected silane diol in higher yields than in previous reports (Scheme 14). The protected silane diols can also be accessed in some cases with 1:1 ratio of TFA/CH_2Cl_2.[20] Interestingly, cleavage of

SCHEME 14. Representative Examples of Acid-Mediated Cleavage of Electron-Rich Diarylsilanes to Furnish Silane Diol or Silanol



aryl group	acid conditions	**46**	**47**
m-tolyl	TfOH (10 equiv), CH_2Cl_2	--	71%
m-tolyl	TFA/ CH_2Cl_2 (1/1)	77%	--
p-tolyl	TfOH (10 equiv), CH_2Cl_2	--	70%
p-tolyl	TFA (10 equiv), CH_2Cl_2	79%	--
p-tolyl	TFA/ CH_2Cl_2 (1/1)	--	80%

SCHEME 15. Hydrolysis To Access the Silanol and Silane Diol



only one of the aryl groups to generate a silanol is also possible when using a dilute concentration of TFA. The following hydrolysis provides the silane diol or the silanol in quantitative yields (Scheme 15). Hence, this method may be viable for generating not only the silane diol but also the silanol depending on the acidic conditions employed.

IV. Double Hydrosilylation: An Alternative Strategy

The lithiation strategy to attack a chiral sulfinimine represents a general and straightforward route toward the synthesis of two C–Si bond in the silicon-based peptidomimetics. However, there are some limitations with this strategy. Certain functional groups, OBn, OAc, etc., tethered to the olefin or variations of the silane's aryl substituents are not tolerated. Also, these processes demand the use of a stoichiometric amount of the chiral auxiliary to induce stereochemical control during the silyllithium attack, which will subsequently be discarded in the following step.

In order to achieve a potentially more efficient, atom-economical process of accessing a wider range of highly functionalized organosilanes, an asymmetric metal-catalyzed protocol was needed. Our group envisioned that diphenylsilane could serve as an appendage point in which on one end,

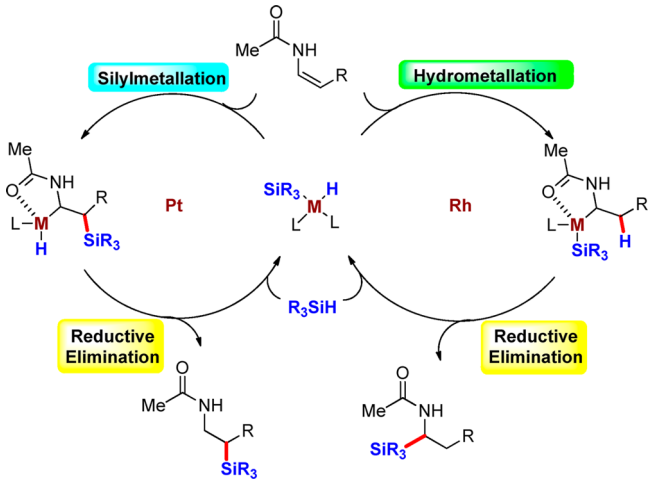
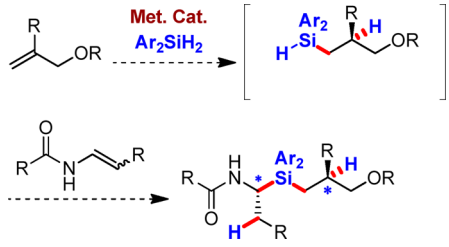


FIGURE 5. Proposed mechanism for Rh- versus Pt-catalyzed hydrosilylation.

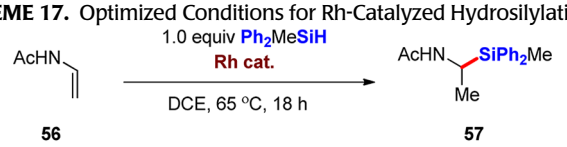
SCHEME 16. Sequential Hydrosilylation



the hydride would undergo metal-catalyzed hydrosilylation onto a terminal olefin to form the first C–Si bond and the other remaining hydride could undergo another hydrosilylation onto an enamide (Scheme 16). This would provide a highly convergent method of synthesizing silicon-based peptidomimetic analogs with the stereochemical control dictated by a chiral metal catalyst.

Since hydrosilylation of terminal olefins has been thoroughly investigated in the literature, initial studies were conducted to determine whether hydrosilylation of an enamide could display good regioselectively for the α-position in useful yields using alkyldiphenylsilane. We anticipated this reaction would be regioselective due to Skoda Földes' earlier reports of silylation at the α-position of 1-vinyl-2-pyrrolidinone when employing a Rh catalyst.[21] A complete reversal of regioselectivity can be obtained when using a Pt catalyst. Later, Murai and Kato claimed that the *N*-carbonyl group directed the hydrosilylation to the α-position of the enamide as depicted in Figure 5.[22] On the other hand, Sieburth and co-workers' investigation of this reaction between diphenylmethylsilane and Boc-substituted enamines provided only low yields of the silicon-containing product.[23] It became therefore evident that an initial optimization study

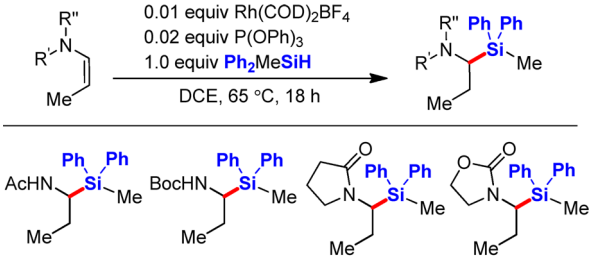
SCHEME 17. Optimized Conditions for Rh-Catalyzed Hydrosilylation



56 **57**

Rh cat	isolated yield (%)
0.005 equiv. $Rh_2(OAc)_4$	87
0.01 equiv. $Rh(COD)_2BF_4$	78

SCHEME 18. Effect of N-Substituent



58 97% **59** 54% **60** 78% **61** 37%

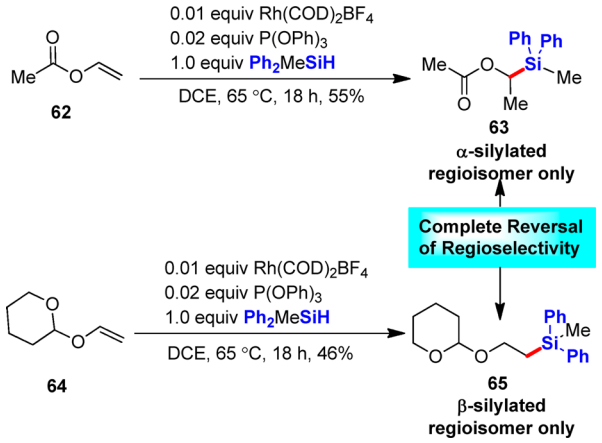
was required in order to obtain good yields of the hydrosilylated product as one regioisomer.

In our studies, $Rh_2(OAc)_4$ and $Rh(COD)_2BF_4$ with $P(OPh)_3$ proved to be the best catalyst when *N*-vinylacetamide was hydrosilylated with Ph_2MeSiH achieving 87% and 78% yields, respectively (Scheme 17).[24] This demonstrated that despite using a bulkier silane, good yields of the desired product could still be obtained. The monomeric Rh catalyst system was employed in the subsequent studies instead of the Rh dimer because it would provide us the increased flexibility to extend this methodology toward the development of an asymmetric protocol.

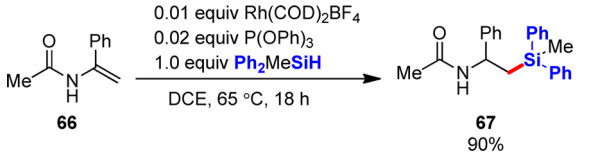
The differences seen in the results obtained from Murai and Kato versus Sieburth and co-workers indicated that perhaps the N-substituent played a crucial role in not only the regioselectivity but also the obtained yield. This was confirmed when the N-substituent was varied from an Ac to a Boc protecting group.[24] Silane **58** provided a 43% higher yield than silane **59** (Scheme 18). The yield lowers with another N-substituent, but the same trend is observed between silane **60** and **61**.

Having determined the N-substituent's effect on the obtained yield, we also investigated its role in the regioselectivity. Murai and Kato had previously proposed that the carbonyl group directs the hydrosilylation to the α-position.[22] Interestingly, when it was switched to vinyl acetate **62**, only the α-silylated regioisomer **63** was obtained.[24] If the acetyl group is replaced with a THP group, this regioselectivity is

SCHEME 19. Regioselectivity Governed by N-Substituent



SCHEME 20. Reversal of Carbonyl-Directing Effect by Sterics

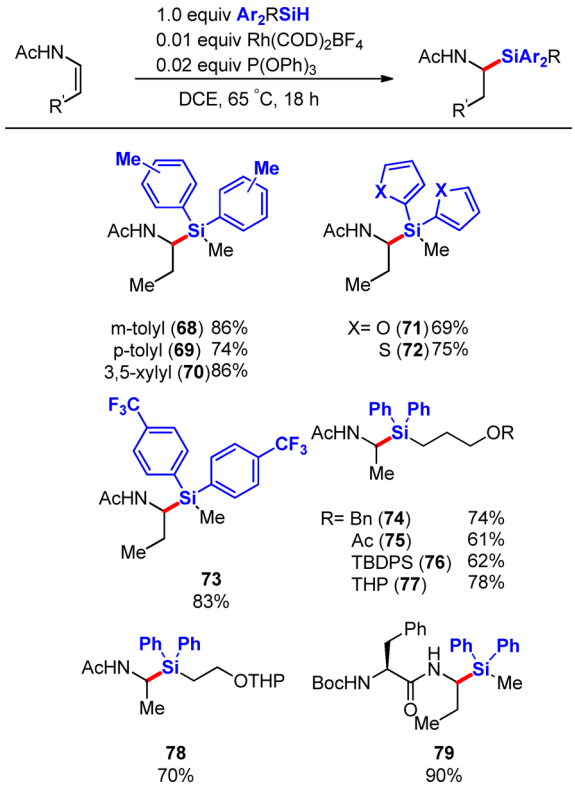


reversed to the β-position (Scheme 19), further supporting Murai and Kato's speculation of a carbonyl directing effect. Nevertheless, this effect can be overruled if a 1,1-disubstituted enamide **66** is used instead, whereby sterics prevent silylation from occurring at the α-position (Scheme 20).

Once the necessary components for a high yielding regioselective hydrosilylation were determined, the alkyl substituent and aryl groups on the silane were varied (Scheme 21). The reaction provided moderate to good yields of the desired product tolerating a wide range of different functionality. Its mild conditions allowed access to substrates that could not be previously synthesized via hydrosilylation/lithiation protocol. Silanes with electron-rich aryl groups (**70**–**72**), which have previously been demonstrated to promote a more facile cleavage to furnish either the silane diol or the silanol in the subsequent step, could be easily accessed using this strategy. Also, for the first time, furans and thiophenes could be incorporated (**71** and **72**). These particular organosilanes are highly attractive as silane diol precursors primarily because they are anticipated to undergo cleavage and hydrolysis by simply using dilute HCl instead of TfOH, TFA, or HF.

Substituents on the β-position of the enamide were also varied (Scheme 22).[24] The reaction tolerated aryl halides, slightly electron-rich aromatic groups, and alkyl groups. If

SCHEME 21. Representative Hydrosilylated Products Varying Silane's Aryl Group and Alkyl Group

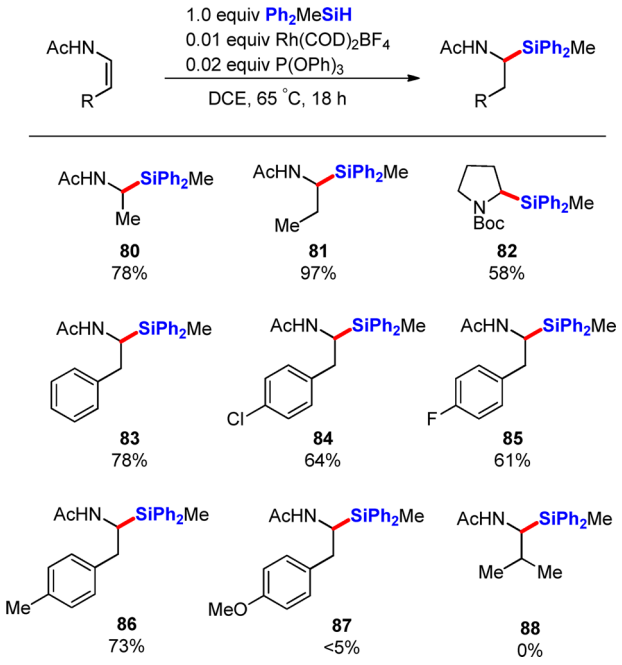


the aromatic group is too electron-rich, only trace product is observed. Trisubstituted enamides were not tolerated due to the increased sterical encumberance for efficient coordination of the metal to the olefin.

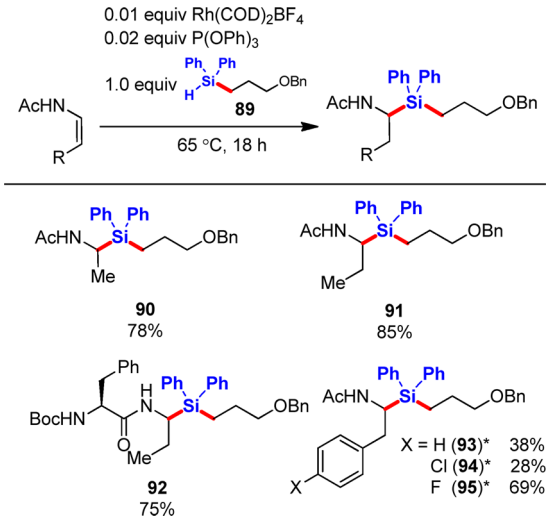
There were some other limitations. When silane **89** was paired with enamides containing an aromatic group at the β-position, trace amount of product was obtained using $Rh(COD)_2BF_4$ as the catalyst. This was attributed to the slightly increased steric bulk on the silicon center retarding the reaction and allowing for catalyst decomposition. Therefore, $Rh_2(OAc)_4$, which is known to be a less reactive but more stable catalyst, was employed instead (Scheme 23),[24] providing higher yields than $Rh(COD)_2BF_4$. However, with this catalyst, enamide isomerization to the *trans* configuration occurred. For an alkyl substituent at the β-position of the enamide, a *trans*-configuration can still provide comparable yields to the *cis*-enamide, but when the substituent is an aryl group, no product is observed. Therefore, further studies must be conducted in order to access these substrates.

Having investigated the hydrosilylation of both the olefin and the enamide separately, we turned our attention toward the development of a one-pot sequential hydrosilylation.

SCHEME 22. Hydrosilylation of Various Enamides



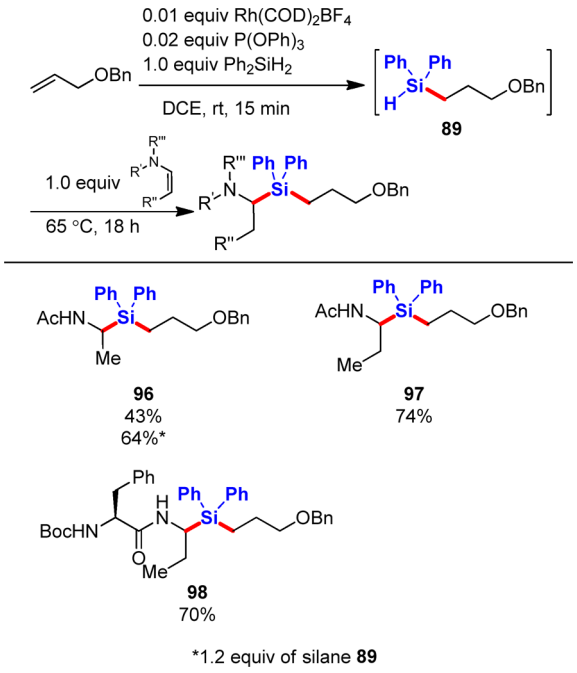
SCHEME 23. Hydrosilylation with Silane **89**[a]



[a]For entries marked with asterisk, 0.005 equiv $Rh_2(OAc)_4$ was used.

When the previously reported $Rh_2(OAc)_4$ was used, the first hydrosilylation only achieved a 54% NMR conversion after 18 h, and thus, it was not further utilized in the sequential hydrosilylation studies. With the benzyl protected allyl alcohol as the terminal olefin, hydrosilylation occurred in 15 min using $Rh(COD)_2BF_4$ after which the catalyst activity begins to drop thus lowering the yield for the second hydrosilylation. Therefore, addition of the enamide after 15 min was necessary.

SCHEME 24. One-Pot Sequential Hydrosilylation



*1.2 equiv of silane **89**

This one pot procedure can be applied to simple enamides, as well as more functionalized systems, affording silanes **96**–**98** in 43–74% yields (Scheme 24).[24] These mild conditions tolerated various functionalities, as well as preserving the stereochemical integrity of the original substrate. No epimerization was observed in silane **98**. Since we have now established double hydrosilylation as a viable method toward forming the two C–Si bonds and have also demonstrated its potential for a sequential one pot procedure to access these silicon-based peptidomimetic analogs, we are currently investigating development of an asymmetric version of this protocol.

V. Application toward Stereocontrolled Synthesis of 2-Substituted-1,3-Azaheterocycles

In recent years, there has been a growing interest in the preparation of heterocycles in which one of the ring's carbons has been replaced by silicon. A few bioactive silicon–nitrogen containing heterocycles have already been synthesized (e.g., the spirocyclic σ receptor ligands **99**, the neurotropic tetrahydroisoquinoline sila-analog **100**, silicon analog **101** of the antidepressive agent dimetracrine, and sila-haloperidol **102** (Figure 6).[25,26]

Different approaches have been developed to prepare these heterocyclic systems containing silicon and nitrogen;[12k,27] however, to this date, no synthesis has targeted 2-substituted 1,3-azasila-heterocycles with stereochemical control.

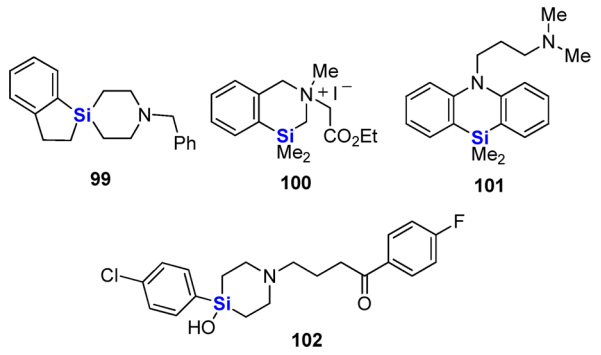
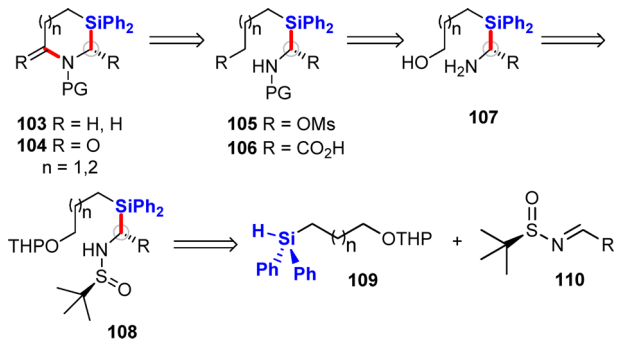


FIGURE 6. Examples of bioactive silicon–nitrogen heterocycles.

SCHEME 25. Retrosynthetic Analysis of the Silaheterocycles **103**/**104**



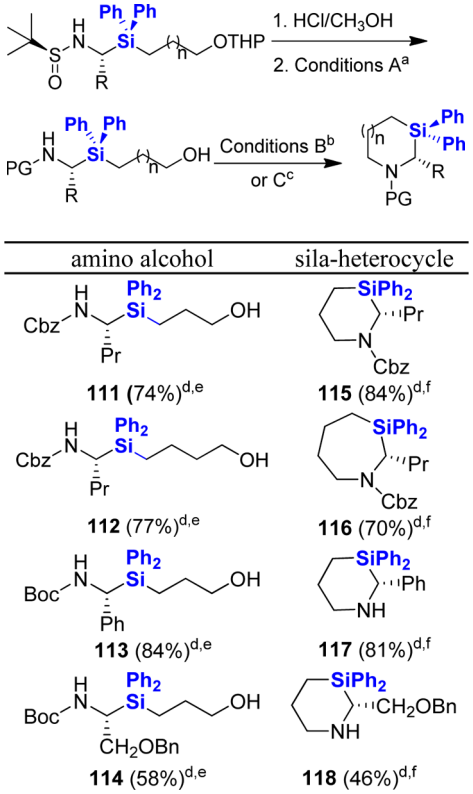
We proposed that these various sila-based azaheterocycles could be accessed by employing our lithiation strategy to control the generated stereocenter as depicted in Scheme 25. The azasilaheterocycles **103** and **104** can be formed by an intramolecular cyclization of amino alcohols **107** either via an intramolecular S_N2 substitution from the sulfonate **105** or by an EDC-promoted intramolecular coupling of amino acid **106**.

Ring closure by an intramolecular nucleophilic substitution of an amino alcohol was first investigated.[28] The best results obtained are depicted in Table 2. The synthesis starts with the global deprotection of the sulfonamides under acidic conditions followed by the protection of the amine and mesylation of the hydroxyl group. Deprotection of the amine and cyclization using NaH or NEt_3 furnished the corresponding silaheterocycles.

Silaheterocycle **115** is a coniine analog, and **118** represents a deoxynojirimycin derivative displaying only one protected hydroxy group in the side chain. A representative building block of more complex alkaloids, chiral 2-substituted piperidinones, could also be accessed using the alternative method of ring closure, involving EDC-promoted intramolecular coupling (Scheme 26).[28]

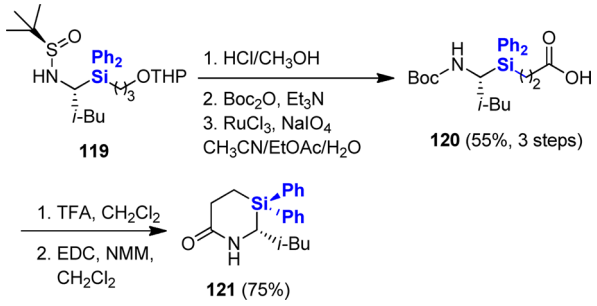
The synthesis of the sila-analog of the glycosidase inhibitor *epi*-lentiginosine **125** was also reported (Scheme 27).

TABLE 2. Preparation of 1,3-Azasilaheterocycles



[a]Conditions A: CbzCl, $NaHCO_3$, H_2O, THF or Boc_2O, Et_3N, CH_2Cl_2. [b]Conditions B: (a) MsCl, Et_3N, CH_2Cl_2; (b) NaH, THF. [c]Conditions C: (a) MsCl, Et_3N, CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) Et_3N, CH_2Cl_2. [d]Isolated yields after column chromatography on silica gel. [e]Yields after two steps. [f]Yields after three steps.

SCHEME 26. Preparation of Piperidinone **121**



The necessary aldehyde was prepared from an L-tartaric acid derivative and condensed with (*S*)-*tert*-butanesulfinamide. The resulting sulfinimine was applied in the synthetic sequence shown previously (Scheme 25). The addition of the silyllithium reagent to chiral sulfinimine **122** provided silane **123** in a 62% yield. Sequential deprotection with DDQ and HCl, followed by Boc protection of the amine afforded diol **124**. This intermediate was transformed into a bis-mesylate and cyclized to form azasilaheterocycle **125** in good overall

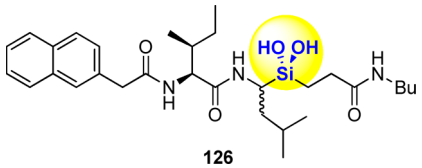
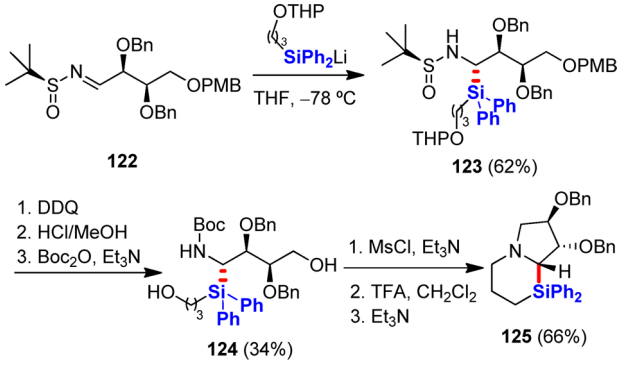


FIGURE 7. Silicon diol based serine protease HNE Inhibitor.

SCHEME 27. Synthesis of Sila-analogue of (+)*epi*-Lentiginosine **125**



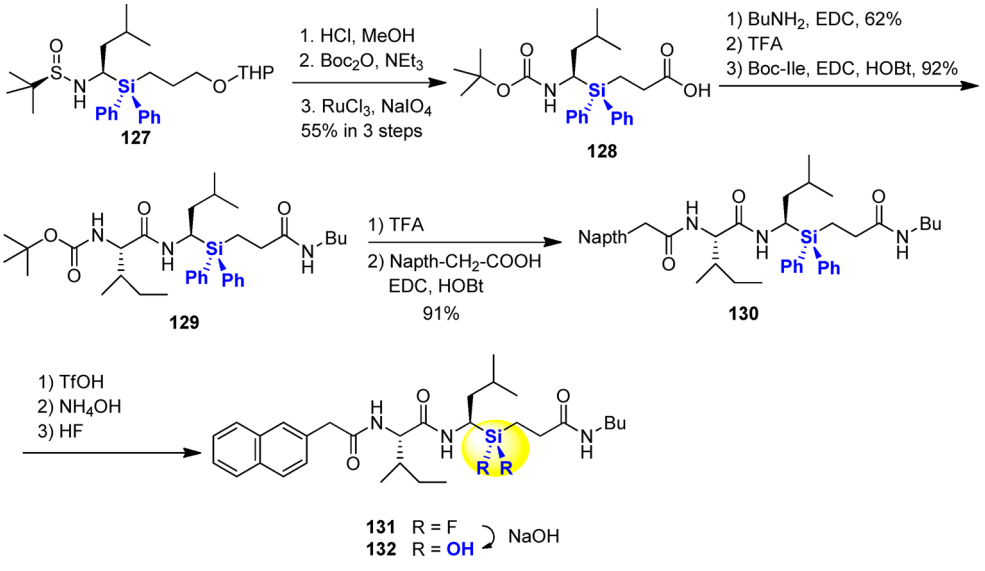
yield for the last three steps with its stereochemical configuration corresponding to that of *epi*-lentiginose.[28] Now that we have accessed the diphenyl analog, we are currently investigating the incorporation of electron-rich aromatic rings on the silicon to help facilitate the double aromatic group cleavage to furnish the silane diol on these sila-azaheterocycles.

VI. Inhibition of HNE Protease

The silane diol **126** as depicted in Figure 7 has previously been demonstrated to exhibit good inhibitory properties against the serine protease, human neutrophil elastase (HNE).[29] However, the original reported synthetic strategy to access this compound provided a 1:1 mixture of stereoisomers at the α-position to the silicon atom.[29b] Obtaining each diastereomer as a single compound and testing it for HNE inhibition could facilitate the identification of the more active stereoisomer. Therefore, a strategy was devised to access these analogs using the lithiation protocol.[16]

Silylsulfinamide **127**, prepared using our lithiation conditions, was oxidized to the corresponding acid **128**, which was coupled directly to *n*-butylamine. Two successive cycles of N-terminal deprotection using TFA followed by peptide coupling afforded the fully protected peptide **129**. Treatment with TfOH followed by aqueous basic hydrolysis and reaction with HF afforded the difluorosilane **131**. Conversion to the silane diol **132** could then be readily achieved by treatment with aqueous NaOH. The approach depicted in Scheme 28 is not only shorter and higher yielding than the previously reported synthesis of **132** but also generated the target as a single diastereoisomer. During the course of this report,[16] the synthesized silicon diol peptidomimetic analog **132** had been determined to have a good inhibitory effect on the HNE protease. In a following report, this synthesis[16] was applied toward the generation of various sila-based HNE inhibitor derivatives to further elucidate the mechanism and the optimal substrate functionality, which would provide the highest inhibitory effect.[30] The inhibitory activity did not increase by incorporating the silane diol motif. However, compared with inhibitors **133** and **134**, the silane diol isostere **132** displayed a different mode of inhibition

SCHEME 28. Synthesis of Serine Protease HNE Inhibitor **132**



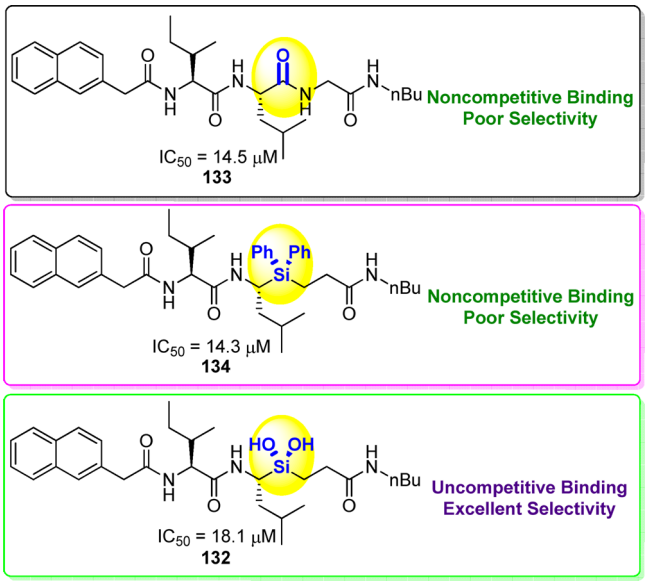


FIGURE 8. Mode of binding, selectivity, and IC_{50} value of parent carbon based-isostere **133**, diphenyl silane isostere **134**, and silane diol isostere **132**.

from noncompetitive to uncompetitive and proved to be far more selective for HNE protease inhibition than other similar serine proteases (Figure 8). This account demonstrated that incorporating the silane diol moiety not only can provide a highly selective isostere but can also change the mode of inhibition to afford a new class of potential drug candidates.

VII. Conclusions and Future Perspectives

In this Account, we have described our recent efforts toward developing concise and straightforward routes toward the incorporation of silicon into functionalized peptides exploiting a hydrosilylation/lithiation strategy or a sequential double hydrosilylation protocol. Both methods allow for the rapid assembly of two carbon–silicon bonds from simple silicon-containing precursors. These strategies were also extended to include the synthesis of HNE inhibitors displaying unusual enzyme inhibition kinetics and various azasilaheterocycles, some of which resemble a class of potent glycosidase inhibitors.

As stated in the Introduction, the replacement of carbon with silicon at strategic sites of a bioactive molecule is a growing field. Yet, its extensive use has been hampered by the limitations of introducing silicon into highly functionalized organic molecules. We believe our research contributes to this area and will also facilitate access to a number of new silicon containing compounds of pharmaceutical interest. Although further developments are still necessary, our work on the Rh(I)-catalyzed double hydrosilylation protocol provides rapid access to molecules containing two carbon–silicon bonds. Additional studies are though needed to increase its utility by introducing an asymmetric variant. Finally, another avenue to be pursued is the preparation of more complex azasilaheterocycles, which are mimics of bioactive nitrogen containing ring systems possessing hydroxyl groups. Replacement of such groups by Si–OH would provide compounds possessing more acidic hydroxyl groups, which could eventually lead to increased binding in the active site and hence higher potency than the parent compound. Examples of interesting heterocycles are the potent glycosidase inhibitors nojirimycin, swainsonine, and castanospermine. Work is currently underway and will be reported in due course.

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BIOGRAPHICAL INFORMATION

Geanna K. Min graduated from Boston University in 2006 with a B.A. degree in chemistry at Boston University, Massachusetts, doing her undergraduate research with Professor John A. Porco, Jr. She obtained her M.S. degree in 2008 from University of North Carolina, Chapel Hill, NC, with Professor Jeffrey S. Johnson and her Ph.D. degree in 2012 with Professor Troels Skrydstrup at Aarhus University, Denmark.

Dácil Hernández studied at the University of La Laguna, Tenerife, receiving her Bachelor Degree in Chemistry in 2001. She completed her Ph.D. in synthetic organic chemistry in 2007 under the scientific supervision of Drs. Rosendo Hernández González and Alicia Boto Castro. In 2009, she moved to Aarhus University, Denmark, for a postdoctoral fellowship with Professor Troels Skrydstrup. She is currently a contracted researcher in the Instituto de Productos Naturales (IPNA), belonging to the Spanish Research Council (Consejo Superior de Investigaciones Científicas, CSIC).

Troels Skrydstrup received a B.Sc. (Eng.) degree from Queen's University, Kingston, Canada (1983), and his M.Sc. and Ph.D. degrees from the Technical University of Denmark (1985 and 1988) under the supervision of Prof. Anders Kjær. After several postdoctoral periods at the Institute de Chimie des Substances Naturelles, Gif-sur-Yvette (1988–1989 with Prof. G. Ourisson, 1990–1992 with Dr. D. Grierson), and at the Carlsberg Laboratories (1989–1990 with Prof. K. Bock), Troels Skrydstrup was employed as Chargé de Recherche (CR1) both at the Université d'Orléans and Université Paris XI (1992–1997). In 1997, he became Associate Professor at the Department of Chemistry, Aarhus University, and was promoted to full Professor of Organic Chemistry in 2002. Troels Skrydstrup was Head of Department in the period 2001–2004 and 2010. In 2001,

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FOOTNOTES

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