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Synthesis, Reactivity, Functionalization, and ADMET Properties of Silicon-Containing Nitrogen Heterocycles

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Supporting Information

ABSTRACT: Silicon-containing compounds have been largely ignored in drug design and development, despite their potential to improve not only the potency but also the physicochemical and ADMET (*a*bsorption, *d*istribution, *m*etabolism, *e*xcretion, *t*oxicity) properties of drug-like candidates because of the unique characteristics of silicon. This deficiency is in large part attributable to a lack of general methods for synthesizing diverse organosilicon structures. Accordingly, a new building block strategy has been developed that diverges from traditional approaches to incorporation of silicon into drug candidates. Flexible, multi-gram-scale syntheses of silicon-containing tetrahydroquinoline and tetrahydroisoquinoline building blocks are described, along with methods by which diversely functionalized silicon-containing nitrogen heterocycles can be rapidly built using common reactions optimized to accommodate the properties of silicon. Furthermore, to better clarify the liabilities and advantages of silicon incorporation, select compounds and their carbon analogues were challenged in ADMET-focused biological studies.

1. INTRODUCTION AND BACKGROUND

1.1. State of the Art. The routine incorporation of silicon as a carbon isostere in drug discovery would present innovative solutions to medicinal chemistry problems and greatly expand the state of the art, largely because the unique physicochemical properties of silicon render it ideal for medicinal applications that no other element can effectively achieve. Although vertically adjacent in Group 14, silicon and carbon are substantially different: (1) silicon is more electropositive than carbon and possesses a larger covalent radius and longer bonds, all characteristics that allow for the fine-tuning of neighboring functional group properties;[1] (2) silicon may expand its valence from four to higher order five- and six-coordinated species,[2] presenting unique possibilities not realizable by carbon, e.g., improving membrane permeability in a manner analogous to benzoxaboroles;[3] (3) silicon can form stable silanediols, the silicon equivalent of carbon-based geminal diols—a highly sought pharmacophore feature in protease transition-state inhibition;[4] and (4) by virtue of its inability to form stable double bonds with carbon or oxygen, and its lack of recognition by metabolic enzymes, strategic substitution by silicon may provide a valuable tactic in eliminating toxic metabolites and improving the ADMET (*a*bsorption, *d*istribution, *m*etabolism, *e*xcretion, *t*oxicity) profile of drug candidates.[5]

Despite all of these potential attributes, the "carbon−silicon" switch[6] has been successful only in the agrochemical industry (e.g., flusilazole and silafluofen),[7] and despite significant interest in the pharmaceutical industry, no silicon-containing drugs have been approved in any U.S. or Western European market. In Eastern Europe, the only marketed example is the steroid silabolin, in which silicon exists as a silyl ether in a prodrug capacity.[8] This lack of success in the pharmaceutical industry may be attributed to two key factors: (1) an absence of general and accessible synthetic methods for the construction of appropriately functionalized silicon-containing molecules and (2) ineffective approaches to the utilization of silicon, of which the "carbon/silicon switch" is the most common. To address these shortcomings, we envisioned a different strategy in the development of a pluggable building block approach that not only is complementary to existing methods but also allows for flexible and innovative employment of silicon at all stages of the drug discovery process. Ultimately, we believe that new classes of compounds based upon the unique properties of silicon will be most effectively utilized in the form of simple silicon-containing building blocks that are amenable to synthetic manipulation and applications in fragment-based drug design.[9] We therefore developed general synthetic methods that render silicon-containing heterocycles (silaheterocycles) both strategically accessible and diversifiable to allow for the routine, user-friendly employment of silicon in medicinal chemistry.

1.2. Selection of Targeted Structures. In view of the prevalence of heterocycles in drug discovery, priority was given to the development of general and robust synthetic methods amenable to the construction of benzannulated silicon-containing silaheterocycles with six-membered rings that possessed at least one other heteroatom (Figure 1). Drug structures are dominated by five- and six-membered heterocyclic compounds, and it was therefore logical to prioritize the development of synthetic methods for accessing analogous silaheterocycles, but six-membered rings were specifically targeted due to their greater diversity potential. For the purpose of narrowing the large number of potential candidates into a manageable survey, emphasis was placed upon

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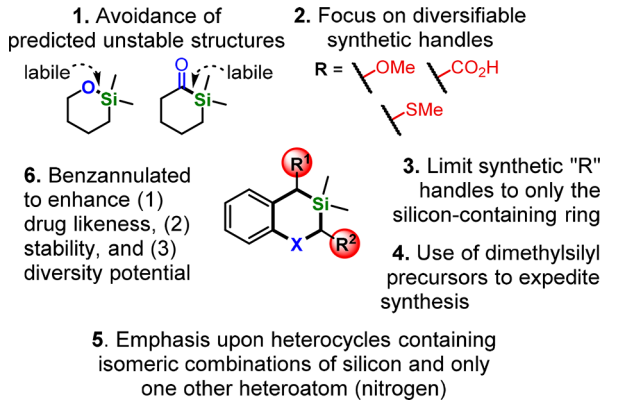

Figure 1. Structural targeting and design logic.

silaheterocycles containing silicon and only one other heteroatom; nitrogen was selected because of its ability to function as both a point of diversity and an anchor for directing groups. An annulated benzene ring was included to provide drug-likeness, stability, and diversity potential, and the silicon atom was decorated with methyl groups to simplify studies of the effect of silicon on the ring chemistry. Additional considerations that guided structural selection were inclusion of functional groups that could serve as diversifiable synthetic attachment points and avoidance of acyl silanes and silaheterocycles bearing silicon−heteroatom bonds because of expected hydrolytic instability.[10] Following these criteria, five silicon-containing nitrogen heterocycles **1**−**5** were selected for investigation (Figure 2).

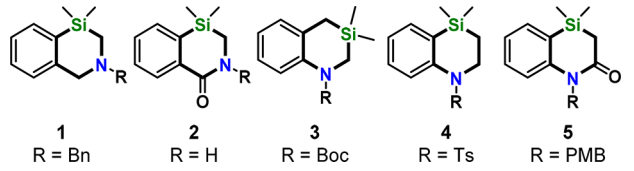

Figure 2. Targeted silicon-containing N-heterocycles.

1.3. Synthetic Design. Early-stage introduction of functional groups would force the development of unique procedures to accommodate the inherent reactivities of each individual functional group, necessitating the time-consuming discovery of alternative cyclization conditions. Therefore, we implemented a two-phase strategy for the construction of functionalized silaheterocycle building blocks (Figure 3). The first phase involved the development of synthetic procedures for constructing relatively *unfunctionalized* silicon-containing heterocyclic cores, which were in turn elaborated in the second phase to provide diverse *functionalized* silaheterocycle fragments. This approach allowed for the rapid and flexible elaboration of key late-stage intermediates and is inclusive of functionalities beyond those reported herein.

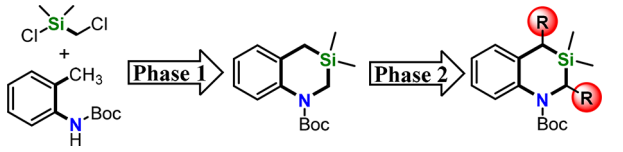

Figure 3. Two-phase synthetic strategy.

The first component of the two-phase approach—the synthesis of unfunctionalized core structures—was guided by the following defining criteria: the syntheses had to be (1) multi-gram scalable, (2) capable of yielding analytically pure core structures, and (3) based on the utilization of affordable and available reagents. Although an impressive body of research exists for the general installation of acyclic silicon-containing groups, relatively little is reported regarding the assembly of silaheterocycles. Most known procedures report the construction of rings bearing kinetically stable endocyclic silicon−heteroatom bonds,[11] which we sought to avoid. Syntheses of silaheterocycles containing carbon-flanked silicon are more relevant,[12] but only a few construct rings bearing sites for functionalization, which necessitated either the development of new synthetic procedures or optimization of existing methods for multi-gram-scale preparations.

The second component of the two-phase approach was defined by the elaboration of the unfunctionalized cores into useful silaheterocycle building blocks. A critical feature of this phase was to access silaheterocyclic, reactive intermediates that could be trapped with appropriate nucleophiles or electrophiles to produce diversely functionalized silicon-containing fragments by reactions both compatible with silicon and also simple to employ. Two classes of diversity elements were introduced, named here as "terminal" diversity and "functional" diversity. Terminal diversity is defined as the introduction of groups that cannot be easily manipulated through methods common to medicinal chemistry but demonstrate the utility of a functionalization reaction. "Functional" diversity implies the installation of synthetic moieties to which diverse functional groups or drug fragments may be attached and manipulated. Importantly, this phase presented the opportunity to study the impact of silicon on the chemistry of azasilines and draw comparisons to the known behavior of analogous carbon-based azacycles. The reactivity and stability of these cores and their corresponding anionic or cationic reactive intermediates were evaluated, and behavior both similar to and divergent from classical tetrahydroquinolines and tetrahydroisoquinolines is reported. Finally, in view of the large number of compounds and permutations possible among targets defined by our structural criteria, we elected to ignore functionalization of the fused benzene ring and focus entirely upon the silicon-containing rings because the chemistry of these unique heterocyclic systems is completely unknown.

2. RESULTS

2.1. 1,3-Azasiline. The 1,3-azasiline core was expected to behave in a fashion akin to tetrahydroisoquinolines, and a variety C-and N-functionalization reactions were planned (Figure 4). In regard to C-functionalization, generation of reactive organolithium intermediates and trapping with diverse electrophiles was prioritized, but it was not clear where the site of lithiation would occur because of potential competition between the carbanion-stabilizing α-silyl group C(2) and the benzylic C(4) sites. Although oxidation of the C(4) position would present opportunities to introduce nucleophiles, this avenue was not investigated because the closely related 1,3-azasilin-4-one core allowed for more expedient access to this reactivity (see section 2.2). Finally, bearing the only aliphatic nitrogen among the targeted cores, the 1,3-azasiline was anticipated to engage in the broadest array of C−N bond-forming reactions.

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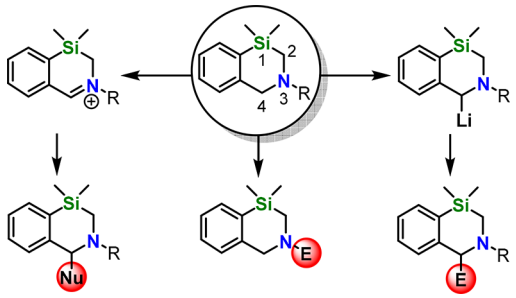
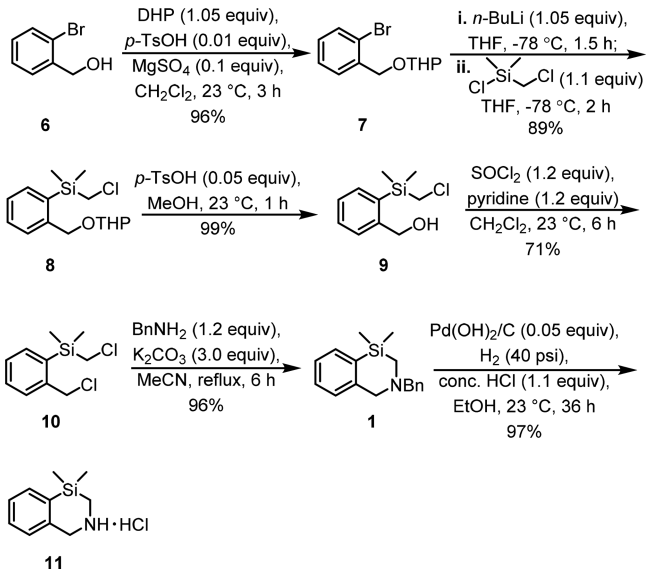


Figure 4. Targeted reactivities of the 1,3-azasiline core.

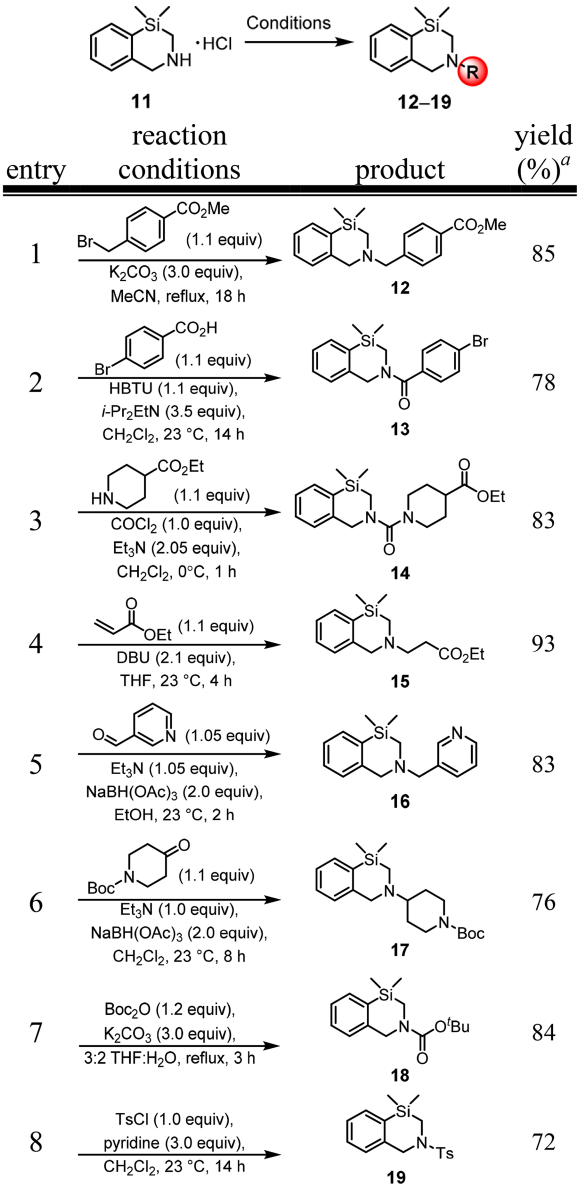
2.1.1. Synthesis of the 1,3-Azasiline Core. The N-benzyl-protected 1,3-azasiline core **1** has been reported previously by Sato,[13] but in our hands this route was low-yielding and insufficiently scalable for our purposes. Therefore, a new route was implemented (Scheme 1). Readily available 2-bromobenzyl alcohol was O-protected in high yield and silylated with (chloromethyl)dimethylchlorosilane after bromine−lithium exchange to afford **8**. O-Deprotection followed by chlorination provided the versatile intermediate **10** that could be cyclized by dual substitution with N-nucleophiles (including tosylamide), but benzylamine was preferred because of its greater reactivity and more facile deprotection. The synthesis of the 1,3-azasiline core **1** was overall high yielding, capable of producing up to 18 g of **1**, and all transformations were sufficiently clean that no chromatography beyond simple silica plugs was required. Furthermore, the core was easily purified by distillation to analytical purity. Finally, it was found that simple hydrogenation produced the novel hydrochloride salt **11** in high yield and purity.

Scheme 1. Synthesis of the 1,3-Azasiline Core



2.1.2. Nitrogen Functionalization of the 1,3-Azasiline Core. The 1,3-azasiline core nitrogen could easily be modified by a variety of common functionalization reactions (Table 1). Alkylation was simple, clean, and high yielding (entry 1). Carbodiimide amidation was best performed with uronium salts such as HBTU (entry 2) under N_2; the classical EDC/HOBT combination resulted in the formation of minor side-products, likely due to protodesilylation resulting from HCl and HOBT.

Table 1. N-Functionalization Reactions of the 1,3-Azasiline Core



entry	reaction conditions	product	yield (%)[a]
1	(1.1 equiv), K_2CO_3 (3.0 equiv), MeCN, reflux, 18 h	**12**	85
2	(1.1 equiv), HBTU (1.1 equiv), *i*-Pr_2EtN (3.5 equiv), CH_2Cl_2, 23 °C, 14 h	**13**	78
3	(1.1 equiv), $COCl_2$ (1.0 equiv), Et_3N (2.05 equiv), CH_2Cl_2, 0°C, 1 h	**14**	83
4	(1.1 equiv), DBU (2.1 equiv), THF, 23 °C, 4 h	**15**	93
5	(1.05 equiv), Et_3N (1.05 equiv), $NaBH(OAc)_3$ (2.0 equiv), EtOH, 23 °C, 2 h	**16**	83
6	(1.1 equiv), Et_3N (1.0 equiv), $NaBH(OAc)_3$ (2.0 equiv), CH_2Cl_2, 23 °C, 8 h	**17**	76
7	Boc_2O (1.2 equiv), K_2CO_3 (3.0 equiv), 3:2 THF:H_2O, reflux, 3 h	**18**	84
8	TsCl (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, 23 °C, 14 h	**19**	72

[a]Yields of isolated purified products.

Acylation reactions worked well, and asymmetrical ureas could be prepared when phosgene was employed (entry 3). Conjugate additions also performed well (entry 4). Reductive aminations of both aldehydes and ketones were facile (entries 5 and 6), but choice of solvent was important to prevent protodesilylation. Finally, carbamation was fast and clean, and it provided an essential directing group for carbon-functionalization reactions (entry 7). Transition metal-mediated N-arylation reactions were largely unsuccessful, yielding complex decomposition[14] in addition to protodesilylation (see Table S1).

An inert atmosphere (Ar or N_2) was critical in enhancing yield and suppressing side-product formation in N-functionalization reactions, especially in the case of functionalizations requiring reaction times longer than 2−3 h. Schlenk technique was not required; a simple solvent sparge and purge of the headspace was found to be sufficient. Solvent choice was not critical, but non-coordinating, aprotic solvents generally provided optimal results. For example, the reductive amination

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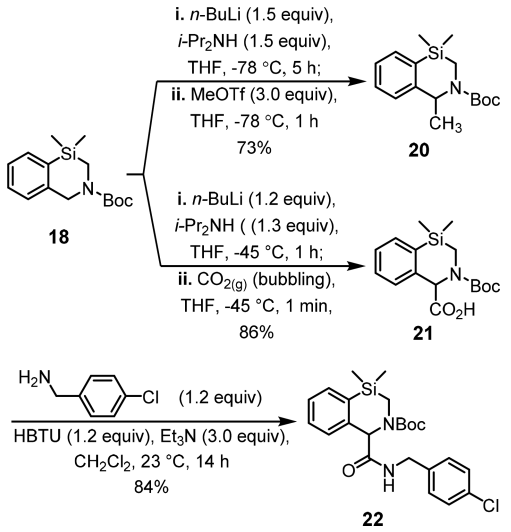
of azasiline **11** in EtOH with an aldehyde was facile (entry 5) but resulted in a complex product mixture with ketones, where dichloromethane was superior.

2.1.3. Carbon Functionalization of the 1,3-Azasiline Core. Functionalization of the N-Boc-protected 1,3-azasiline core **18** was achieved via a versatile organolithium intermediate (Scheme 2), although not all electrophiles could be productively captured. A range of metalation conditions was investigated. Whereas strong bases resulted primarily in benzylic C(4) metalation, some metalation also occurred at other sites. LDA proved superior, however, and exclusively lithiated the benzylic site at −45 °C for 1 h or at −78 °C for 5 h. Alkylation of the C(4) anion with alkyl triflates was accomplished without issue, although alkyl iodides resulted in complex product profiles likely stemming from one-electron events. Complex decomposition also followed aldehyde trapping. Alkyl chloroformates and alkyl cyanoformates could be captured but their liquid products were unstable to chromatography (silica, alumina) and could not be isolated (see Table S2). The basis for the observed instability was unclear, as the silicon is quite removed from the introduced C(4) functionality. Nevertheless, to circumvent this isolation problem, $CO_{2(g)}$ was used to quench the organolithium intermediate, and the resulting solid amino acid was isolated by crystallization in excellent yield and purity. Furthermore, the amino acid could be readily condensed with a benzyl amine to produce the desired amide in good yield (Scheme 2).

Scheme 2. C-Functionalizations of the 1,3-Azasiline Core



2.2. 1,3-Azasilin-4-one. The 1,3-azasilin-4-one core, containing a pre-installed C(4) carbonyl group, was expected to grant access to a variety of reactive intermediates that could enable functionalization at various sites (Figure 5).

2.2.1. Synthesis of the 1,3-Azasilin-4-one Core. A procedure for the preparation of the 1,3-azasilin-4-one core is available,[15] but was not suitable for multi-gram-scale synthesis because of the formation of side products; therefore, the execution and purification of each step was optimized (Scheme 3). Careful one-pot, double lithiation of *tert*-butyl benzamide and subsequent trapping with (chloromethyl)dimethylchlorosilane followed by cyclization provided the crystalline silicon-containing lactam **25**. Several metalation conditions were evaluated (*n*-BuLi—the originally described procedure—and *n*-BuLi/TMEDA) but *s*-BuLi was superior by far. The original N-deprotection protocol used conc. H_2SO_4, but this reagent led to significant protodesilylation, and alternative acidic conditions gave no reaction (neat TFA, concentrated HCl). However, heating **25** in toluene with sulfonic acids (TsOH, MsOH) proved expedient and clean, and up to 15 g of **2** could be easily prepared.

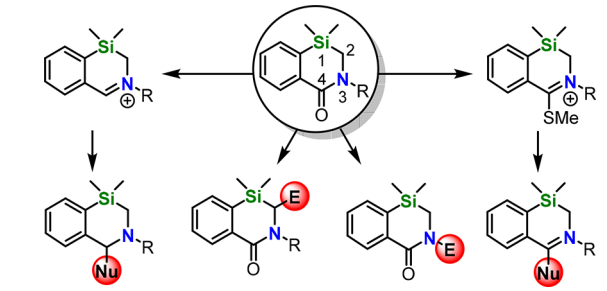
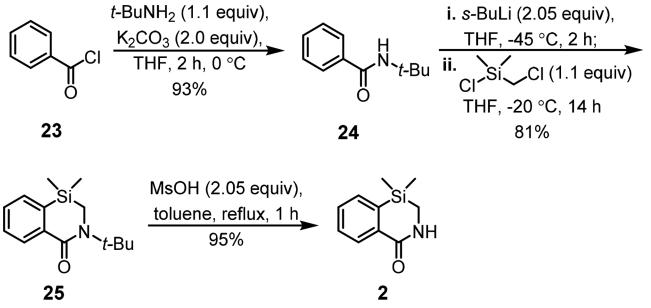


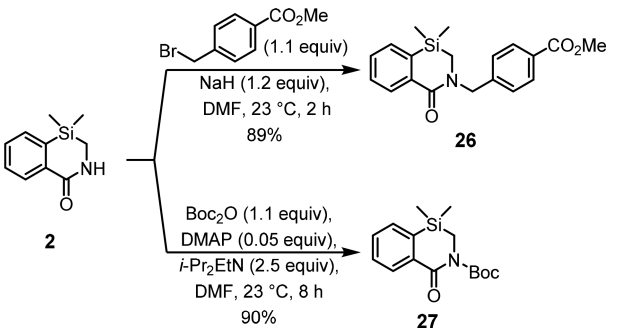
Figure 5. Targeted reactivities of the 1,3-azasilin-4-one core.

Scheme 3. Synthesis of the 1,4-Azasilin-3-one Core



2.2.2. Nitrogen Functionalization of the 1,3-Azasilin-4-one Core. Reactions of the nitrogen atom were selectively limited to only alkylation by alkyl halides and carbamation to furnish the Boc-protected azasiline (Scheme 4).

Scheme 4. N-Functionalization Reactions of the 1,3-Azasilin-4-one Core



2.2.3. Carbon Functionalization of the 1,3-Azasilin-4-one Core. Carbon functionalization of the 1,3-azasilin-4-one core focused on the two available sites, C(2) and C(4), but functionalization at C(2) was not possible under the conditions evaluated (see Table S3). The Boc group was envisioned to be a directing group to aid metalation at C(2), but attempts to access organometallic intermediates were unsuccessful. Decomposition was observed in all of the metal amide deprotonations, and no reaction was observed for organolithium deprotonations. Metalation of the aryl ring was never observed. Similarly, attempts at accessing iminium intermediates by oxidation (e.g.,

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DDQ, $LiClO_4$, MnO_2) were also unsuccessful, and only starting material was recovered.

The 1,3-azasilin-4-one core possessed a naturally electrophilic carbon at C4, and functionalization reactions of the native carbonyl and cationic intermediates were investigated. It was recognized that thioamides and their derivatives could provide a route to a wide variety of amidines and α,β-unsaturated esters. Therefore, the unsubstituted lactam **2** was thionated with Lawesson's reagent, and the resulting thiolactam was methylated to provide the methyl thioimidate **29** in excellent overall yield (Scheme 5). To prepare amidines, the thioimidate was heated at reflux in the presence of substoichiometric amounts of acid and an amine. Alternatively, the sulfur could be oxidized by *m*-CPBA, and the resulting sulfone (or sulfoxide) was treated with the appropriate nitrogen nucleophile in excess (Table 2).

Scheme 5. Synthesis of the Methyl Thioimidate of 1,3-Azasilin-4-one

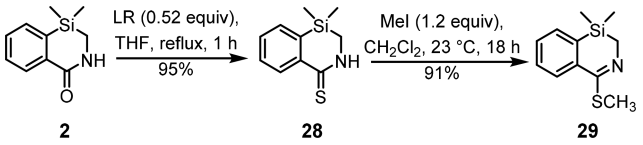
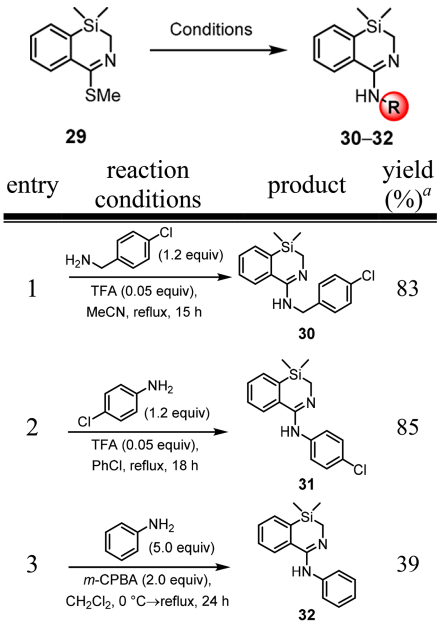


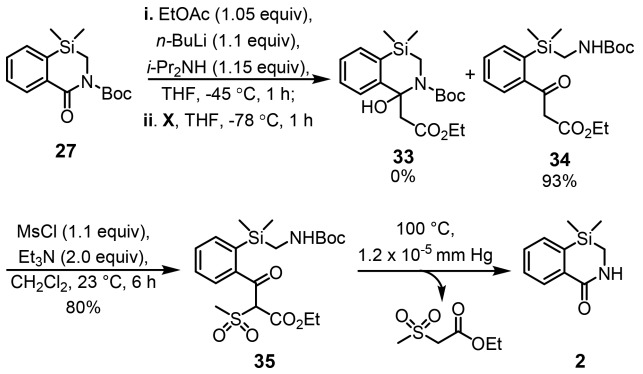
Table 2. Amidinations of the Azasiline Methyl Thioimidate



[a]Yields of isolated purified products.

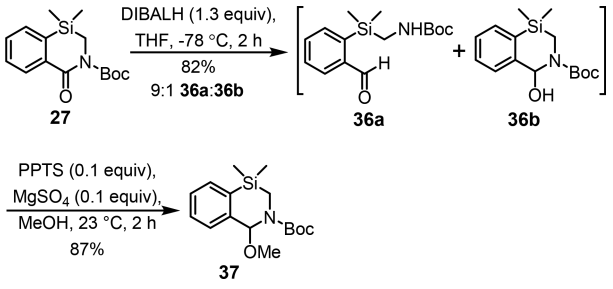
Attempts at forging α,β-unsaturated esters by an Eschenmoser sulfide contraction, the thio-Wittig reaction, or carbenoid insertion were unsuccessful (see Table S4), so aldol-type reactions of the native lactam were investigated. Although organolithium nucleophiles (*n*-BuLi, *s*-BuLi) preferentially attacked the Boc carbamate, enolates added exclusively into the amide carbonyl group. However, rather than the expected aldol product **33**, only the ring-opened β-keto ester **34** was isolated (Scheme 6). Ring-opening is the expected result for Boc-protected piperidones,[16] although use of tetrahydroisoquinolones in this capacity has never been reported and it was predicted (incorrectly) that the fused benzene ring would reinforce the heterocycle. Furthermore, mesylation of **34** produced, surprisingly, selective C-sulfonation and is noteworthy because selective C-sulfonations typically require stronger bases (e.g., NaH, LDA) or alternative non-halide nucleofuges.[17] Also interesting, attempted purification of the sulfonylated ester **35** by distillation resulted in rapid and quantitative cyclization concomitant with Boc-cleavage and elimination of ethyl 2-(methanesulfonyl)acetate to produce the original azasilinone core **2** (Scheme 6.)

Scheme 6. Aldol Addition and Ring-Opening of the 1,3-Azasilin-4-one Core



The *N*-Boc-protected lactam **27** presented an opportunity to install functionality via a reactive acyliminium intermediate. To achieve this, the lactam was first reduced at −78 °C by DIBALH, resulting in a 9:1 mixture of ring-opened and closed isomers. It is noteworthy that similar simple dihydroquinolones require half the reaction time and remain in cyclic form.[18] The isomers converged on the stable cyclic hemiaminal **37** in the presence of acidic methanol (Scheme 7). The hemiaminal could then react cleanly with mild nucleophiles in the presence of a Lewis acid such as $BF_3{\cdot}OEt_2$, although this could be substituted with anhydrous $ZnOTf_2$ with equal effect (Table 3).

Scheme 7. Acyliminium Substitutions of the 1,3-Azasilin-4-one Core



2.3. 2,4-Azasiline. The 2,4-azasiline, bearing an aniline-type nitrogen, was expected to behave in a manner consistent with tetrahydroquinolines, e.g., react with alkyl halides via a nitrogen-centered anion (Figure 6). Like the other azasiline cores, carbon functionalization focused on the preparation of organolithium (C(1) and C(3)) and iminium intermediates (C(3)), although it was not obvious if selective metalation could occur with the competitive presence of the resonance-stabilized C(1) and the directing-group-stabilized C(3) positions.

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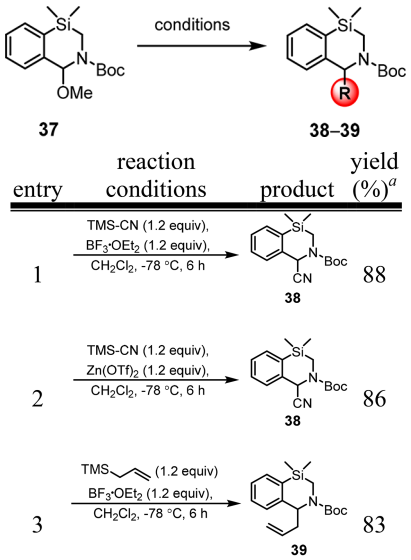
Table 3. C-Functionalization via a Carbamoyl Iminium Intermediate



[a]Yields of isolated, purified products.

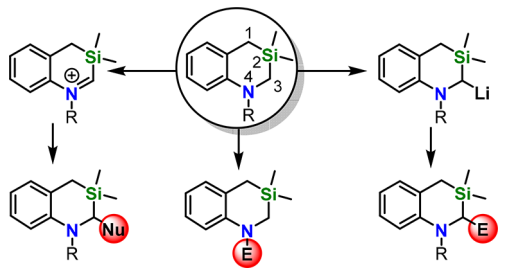
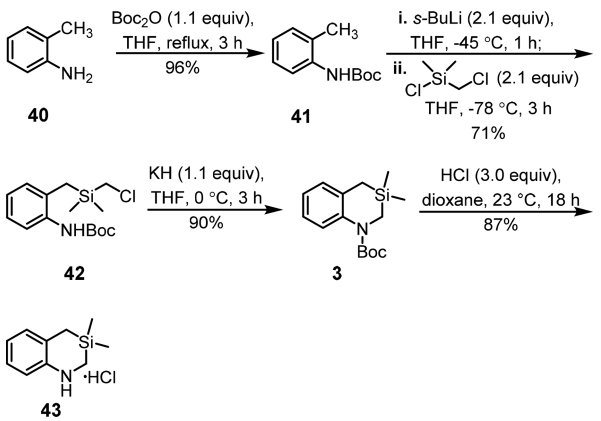


Figure 6. Targeted reactivities of the 2,4-azasiline core.

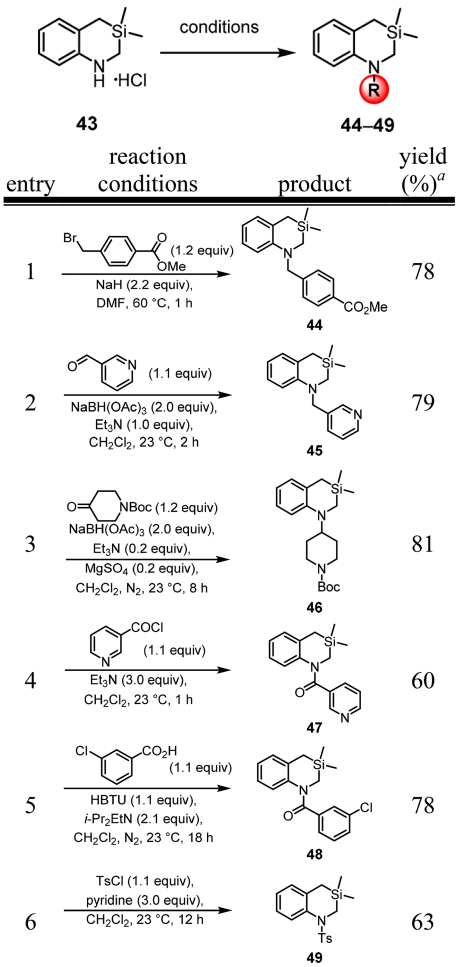
2.3.1. Synthesis of 2,4-Azasiline Core. The 2,4-azasiline core had been previously prepared by a sila-Matteson rearrangement, but only isomeric mixtures of the rearrangement products could be obtained in the absence of electronically biasing groups on the arene.[19] Therefore, a more direct approach was sought (Scheme 8). Lateral lithiation of Boc-protected 2-toluidine afforded a dilithium intermediate that was trapped with 2 equiv of the (chloromethyl)dimethylsilyl chloride to afford **42**. Initially, 1 equiv of (chloromethyl)-dimethylsilyl chloride was tested, on the basis that nitrogen would be silylated first and followed by favorable N-to-C transfer. However, 1 equiv resulted in a 2:1 mixture of the C-silylated to N-silylated species. Finally, cyclization was effected with potassium hydride in THF at 0 °C to afford up to 7 g of the core azasiline **3**. No cyclization was observed with the weak base K_2CO_3, and sodium hydride resulted in the formation of a small number of side products. Interestingly, extended reaction times with KH, and all reactions in DMF, resulted in complex mixtures.

Scheme 8. Synthesis of the 2,4-Azasiline Core



2.3.2. Nitrogen Functionalization of the 2,4-Azasiline Core. The 2,4-azasiline was one of two cores bearing an aniline-type nitrogen, and the reactions evaluated were selected based upon the expected behavior of this class (Table 4).

Table 4. N-Functionalizations of the 2,4-Azasiline Core



[a]Yields of isolated, purified products.

Deprotonation of **43** with NaH led to a stable anion that was easily substituted with methyl 4-(bromomethyl)benzoate (entry 1). Reductive amination of both aldehydes and ketones proceeded smoothly (entries 2 and 3), although the latter consistently resulted in multiple side products if performed exposed to air but performed well under N_2. The syntheses of amides with acid chlorides or carboxylic acids and uronium salts were also successful (entries 4 and 5), although, like that observed for the 1,3-azasiline **11**, peptide couplings utilizing EDC and HOBT afforded multiple side products.

The single most important factor for success of these reactions was the use of an inert atmosphere. The free base of

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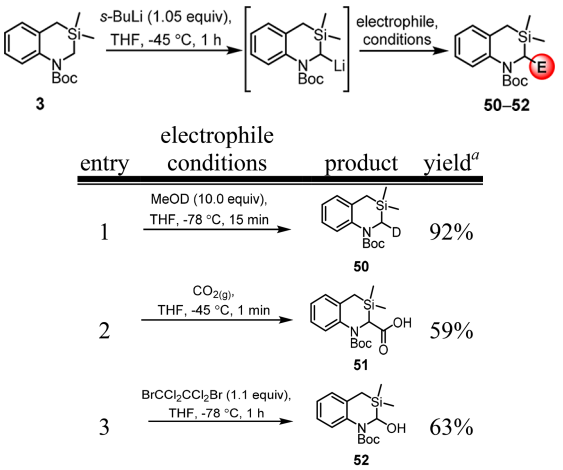
2,4-azasiline **43** (an α-silyl-substituted amine) was significantly more susceptible to autoxidation than even the free base of 1,3-azasiline **11**, and ketone reductive aminations (entry 3) and peptide couplings (entry 5) were possible only by excluding oxygen. Also, aprotic, non-coordinating solvents were found to provide optimal yields and purities in general. Interestingly, no sensitivity to light was observed. However, not all N-functionalizations were productive. Variations of the nucleophilic aromatic substitution of 2,4-dichloropyrimidine, for which each variant used a different base and counterion, also gave complex product mixtures. Common conditions, such as those involving a polar solvent like EtOH or DMF with an amine base, were not tested because of the lack of success observed with the 1,3-azasiline.

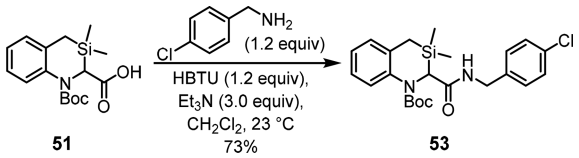
2.3.3. Carbon Functionalization of the 2,4-Azasiline Core. Lithiation/deuteration studies of **3** showed that metalation occurred exclusively at C(3), between nitrogen and silicon of the core, likely resulting from the directing effect of the Boc group (Table 5). Small electrophiles (deuterons) were cleanly captured (entry 1), but most carbonyl electrophiles (DMF, PhCHO, $ClCO_2Me$, $CNCO_2Et$) resulted in complex mixtures. However, capture of CO_2 allowed for the isolation of the crystalline amino acid **51** (entry 2). To demonstrate the viability of this amino acid as a building block, the carboxylic acid was treated with a uronium salt and an amine to produce the expected amide **53** (Scheme 9), which was stable to silica gel chromatography.

Table 5. C-Functionalization Reactions of the 2,4-Azasiline Core



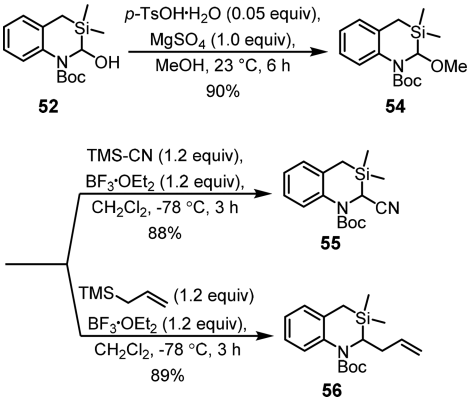
[a]Yields of isolated, purified products.

Scheme 9. Amidation of the 2,4-Azasiline Amino Acid



The lithiated azasiline could also capture bromine (from dibromotetrachloroethane, DBTCE), although the brominated intermediate was never isolated as aqueous work up led to rapid hydrolysis (Table 5, entry 3). The resulting hemiaminal **52** presented an opportunity to introduce functionality through the capture of weak nucleophiles by an acyl iminium ion. Therefore, after generation of the methyl hemiaminal **54**, treatment with a mild Lewis acid and nucleophiles resulted in the synthesis of allyl- and nitrile-containing azasilines in good yields (Scheme 10).

Scheme 10. C-Functionalization of the 2,4-Azasiline Core from a Carbamoyl Iminium Intermediate



2.4. 1,4-Azasiline. The 1,4-azasiline core was expected to behave in a manner consistent with tetrahydroquinolines (Figure 7). Therefore, the aniline-type nitrogen was predicted to react with a variety of electrophiles (e.g., alkyl halides, acyl chlorides) to produce interesting N-diversity. With regard to C-functionalization, careful selection of N-directing groups should provide access to reactive C(3) iminium and organolithium intermediates that may capture a variety of nucleophiles and electrophiles, respectively. Furthermore, the 1,4-azasiline core provided a platform for direct competitive comparison of the ability of silicon to stabilize α-carbanions to that of various directing groups (Ts, Boc, TBF) on nitrogen (C(2) versus C(3) lithiation).

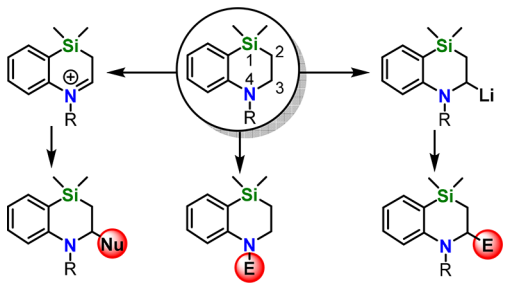


Figure 7. Targeted reactivities of the 1,4-azasiline core.

2.4.1. Synthesis of the 1,4-Azasiline Core. The tosyl-protected 1,4-azasiline core **4** was first synthesized and described by Durandetti and Maddaluno.[19] Their synthesis featured the silicon variant of the Matteson rearrangement, for which the tosyl group was essential for the formation of the desired isomer to the exclusion of the other (i.e., the 2,4-azasiline), whereas alternative common N-protecting groups resulted in isomeric mixtures. Each step required only minor optimization to meet our purity and scalability requirements (Scheme 11), and crystallization conditions were identified to replace column chromatography. With regard to the rearrangement, *s*-BuLi was significantly superior to *n*-BuLi (original protocol), cleanly affording up to 9 g of the desired azasiline **4** with enhanced yield and purity. Among various methods

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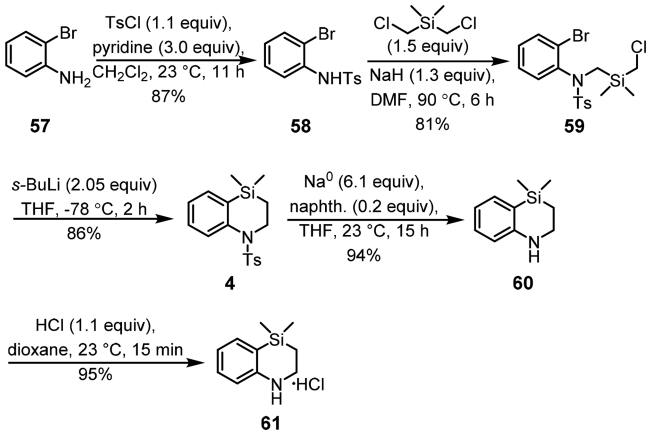
Scheme 11. Synthesis of the 1,4-Azasiline Core

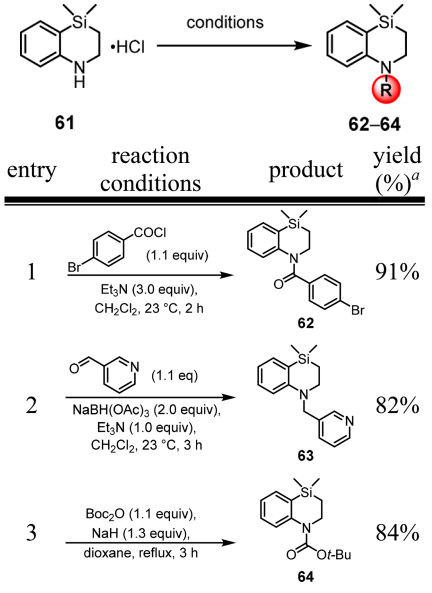


considered for removal of the *N*-tosyl group, reductive cleavage by sodium naphthalenide cleanly afforded the free base **60**. Despite the fact that higher stoichiometries of naphthalene resulted in dramatically reduced reaction times, we found that sub-stoichiometric quantities allowed for easier purification without affecting the yield. The free base **60** was not stable for extended storage at room temperature, but acidification with HCl provided a bench-stable, crystalline hydrochloride salt (**61**).

2.4.2. Nitrogen Functionalization of the 1,4-Azasiline Core. Functionalization reactions were selected on the basis of the expected aniline-like behavior of the 1,4-azasiline nitrogen (Table 6). Among the successful functionalizations, acylation of **61** with acid chlorides smoothly produced amides (entry 1), reductive amination of aldehydes resulted in alkylation (entry 2), and carbamoylation conditions allowed for the synthesis of the Boc-protected 1,4-azasiline (entry 3).

However, a large number of attempted nitrogen functionalizations unexpectedly resulted in formation of complex mixtures (see Table S6). Alkylation reactions with NaH rapidly gave multiple unidentified products, while other conditions, like that with the hindered base 2,6-lutidine in anhydrous DCE (both base and solvent chosen deliberately to suppress decomposition by virtue of their inability to coordinate to silicon), cleanly provided only the protodesilylated product. Although alkylation products could be derived from the reductive amination of *aldehydes*, the reductive amination of *ketones* consistently failed, regardless of reaction pH modulation. Amidations by carbodiimide peptide couplings were unsuccessful, as was nucleophilic aromatic substitution of 2,4-dichloropyrimidine. Finally, Buchwald–Hartwig amination conditions resulted in a mixture equal in complexity to that observed for the other reactions.

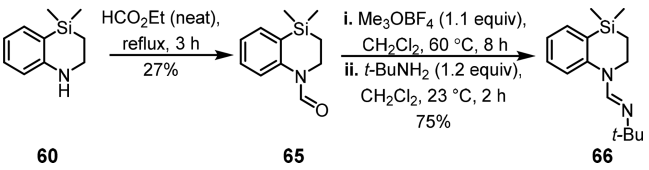
Table 6. Nitrogen Functionalizations of the 1,4-Azasiline Core



[a]Yields of isolated, purified products.

2.4.3. Carbon Functionalization of the 1,4-Azasiline Core. To facilitate directed lithiation, Boc- and *tert*-butyl formamidine (TBF)-protected azasilines **64** and **66** were prepared and treated with organolithium bases. All attempted N-Boc-directed metalations resulted in no observable conversion of starting material with either *n*-BuLi or *s*-BuLi at −78 °C, whereas at higher temperatures (−45 °C) only Boc cleavage occurred. No metalation of the arene was observed. The TBF-protected azasiline was expected to direct metalation alpha to nitrogen, on the basis of the tetrahydroquinoline behavior established by Meyers.[20] The synthesis of the analogous silicon heterocycle required only N-formylation, O-methylation with trimethyloxonium tetrafluoroborate, and substitution with *tert*-butylamine (Scheme 12). However, no lithiation of the TBF-protected 1,4-azasiline core **66** was observed with either *s*-BuLi or *t*-BuLi at the various temperatures evaluated (−78, −45, and −20 °C), which included temperatures under which lithiation of tetrahydroquinolines has been documented. Surprisingly, only unreacted starting material remained.

Scheme 12. Synthesis of the *tert*-Butyl Formamidine-Protected 1,4-Azasiline



In light of the resistance of the 1,4-azasiline core to lithiation, a range of oxidation reactions were carried out, with the downstream goal of accessing C(3) iminium intermediates (see Table S7). Oxidations on tosyl and Boc-protected cores, as well as the free base, produced no desired products. In fact, the 1,4-azasiline core proved as resilient to oxidative modification as it did toward lithiation, even under conditions known to oxidize related tetrahydroquinolines.

2.5. 1,4-Azasilin-3-one. Because of the stalwart resistance of the 1,4-azasiline core to chemical modification, substantial effort was made toward the synthesis of the unknown carbonyl-containing analogue, the 1,4-azasilin-3-one (Figure 8). The lactam provided a pre-installed handle for functionalization of the C(3) carbon by way of iminium intermediates, and functionalization of the C(2) carbon by classical enolate chemistry. Furthermore, because the nitrogen is part of an amide, the stability of the core was expected to exceed that of the 1,4-azasiline free base. Ultimately, the synthesis of the novel 1,3-azasilin-4-one was planned around the intramolecular

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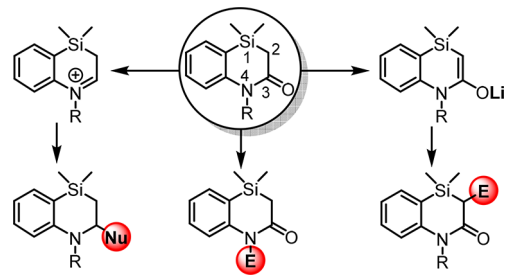


Figure 8. Targeted reactivities of the 1,4-azasilin-3-one core.

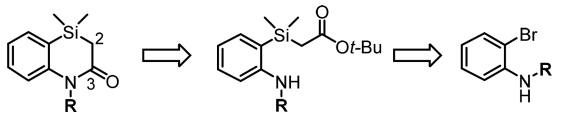
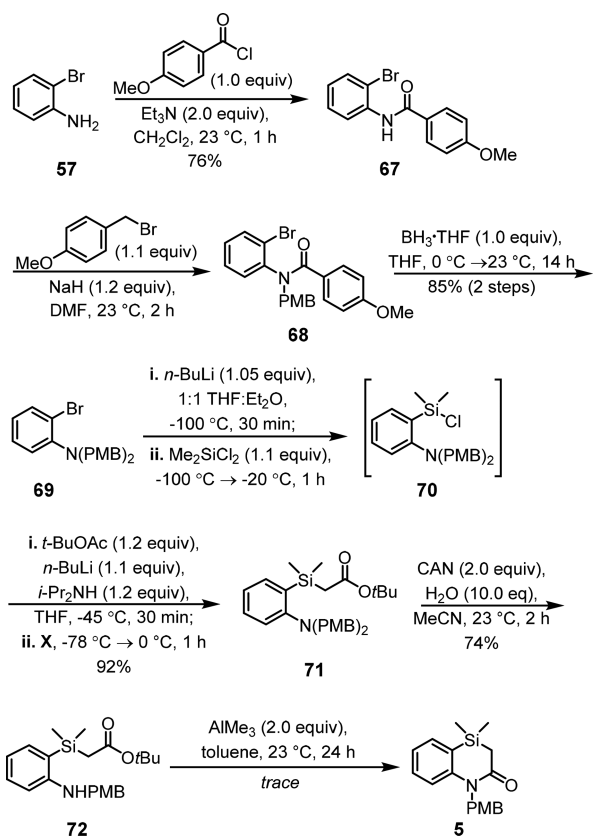


Figure 9. Planned cyclization approach to the 1,4-azasilin-3-one core.

condensation of an amine and an ester (or derivative) (Figure 9).

2.5.1. Synthesis of the 1,3-Azasilin-4-one Core. The key pre-silylated intermediate, 2-bromo-*N*,*N*-bis(4-methoxybenzyl)-aniline **69**, was prepared through a straightforward three-step procedure involving N-acylation of 2-bromoaniline with 4-anisoyl chloride, 4-methoxybenzylation of the resulting amide, and borane reduction (Scheme 13). Once in hand, intermediate **69** was subjected to a one-pot procedure involving bromine–lithium exchange and trapping the resulting anion with dichlorodimethylsilane to form the arylsilyl chloride **70**, which was then treated with the lithium enolate of *tert*-butyl acetate to provide the *tert*-butyl arylsilylacetate **71** in excellent yield. Use of *tert*-butyl acetate was critical in producing predominant C-silylation in such high yields. Cleavage of a single PMB group was effected oxidatively by CAN (DDQ resulted in the formation of side products). It is noteworthy that the second PMB could not be cleaved at room temperature, and heating at 80 °C for 3 h resulted in decomposition. Other methods of PMB deprotection also proved unsuccessful, as strong acids resulted in Si–C cleavage of the acetyl group, and—surprisingly—heterogeneous, catalytic reduction of the arene was favored over hydrogenolysis of the benzylic C–N bond.

Scheme 13. Synthesis of the 1,4-Azasilin-3-one Core 5



Initial cyclization tactics involved intramolecular attack by nitrogen on the ester **72** with the assistance of DMAP or by generation of the N-anion (see Table S9). However, no trace of reaction was observed in the case of DMAP and hot toluene. Treatment with KH gave divergent, solvent-dependent results. Rapid protodesilylation was observed in DMF, likely facilitated by coordination of the DMF carbonyl to silicon. In THF, cleavage of the acetyl-silicon Si–C bond was dominant. However, the problem of cyclization was also not resolved by use of $AlMe_3$, which provided the desired *N*-PMB-protected 1,4-azasilin-3-one core **5** in trace quantities detectable only by mass spectrometry, in addition to hydrolyzed and protodesilylated products.

3. DISCUSSION

3.1. Diversity at Nitrogen. Three types of nitrogen nucleophiles are represented in the five targeted azasiline cores: (1) the aliphatic amine class (tetrahydroisoquinoline analogue **1**), (2) the aniline class (tetrahydroquinoline analogues **3** and **4**), and (3) the amide class (tetrahydroisoquinolone analogue **2** and tetrahydroquinolone analogue **5**). Variations of these cores were evaluated for their ability to undergo electrophilic functionalization using reactions both common and representative of their anticipated chemistry. Several basic rules necessary to accommodate the effects of silicon were deduced from the survey, allowing for the optimization of nearly all reactions assessed.

Superior yields were observed for N-functionalization reactions of azasiline hydrochloride salts **11**, **43**, and **61** in aprotic, non-coordinating solvents (e.g., DCM, toluene) than in alcohols, for which decomposition was evident. For the former two azasilines, 1,3-azasiline **11** and 2,4-azasiline **43**, it was initially assumed that decomposition was induced by the protic, silophilic nature of alcohols, but NMR studies showed that both of these hydrochloride salts and their corresponding free base azasilines were stable to methanol-d_4, even for days at reflux; therefore, the solvent alone could not influence the reaction outcomes to the extent observed. However, it is well known that the oxidation potential of amines is strongly influenced by substitution, and the effect of α-substitution by Group 14 elements like silicon is to increase susceptibility to oxidation.[21] Furthermore, although nonpolar solvents are generally associated with higher rates of amine oxidation,[22] oxidations in polar solvents (e.g., methanol, water) operate by a different mechanism.[23] These processes favor the formation of N-oxides[24] and have even been shown to facilitate desilylation in electrochemical and photoinduced oxidations,[21c,25] which may explain the original observations of low yields and side-products in alcohols. Consequently, functionalizations of the α-silyl-substituted amine hydrochlorides **11** and **43**, once considered challenging (e.g., reductive aminations of ketones, peptide couplings), were rendered easily accessible by the simple

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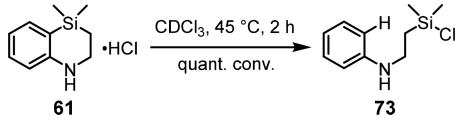
exclusion of oxygen in non-coordinating solvents, and *N*-alkylated products were prepared in high yields and with excellent purities. As expected, these conditions were unnecessary for the functionalization of 1,3-azasilinone **2**, which, as an amide, was not prone to autoxidation.

Solvent choice was much more critical for the successful functionalization of 1,4-azasiline **61**, but for a very different reason than that discussed for the α-silyl-substituted amines **11** and **43**. Being a β-silyl-substituted amine, autoxidation was not a limitation; instead, protodesilylation was the major route of decomposition, under both *acidic* and (ostensibly) *basic* conditions because of the *ortho* relationship of the electron-donating aniline nitrogen and silicon group, creating an electron-rich arylsilane prone to this kind of Si−C cleavage.[26] However, several important observations informed functionalization optimization: (1) it was found that protic, silophilic solvents (e.g., EtOH, MeOH) resulted in rapid decomposition of both the free base **60** and the hydrochloride salt **61**, no doubt because these solvents provide both a proton and a nucleophile necessary for protodesilylation; (2) protodesilylation in non-coordinating solvents (e.g., dichloromethane, toluene) was affected by temperature, and NMR studies showed that the hydrochloride salt **61** was quite stable at temperatures below 23 °C in $CDCl_3$, but protodesilylation occurred rapidly at 45 °C (Scheme 14); and (3) aprotic, coordinating solvents (e.g., DMF, DMSO) also promoted protodesilylation. Evidence for the coordinating effect of silophilic solvents comes from NMR studies (Figure 10), in which multiple species of **61** were observed in DMSO-d_6 at 23 °C that converged upon heating before succumbing to protodesilylation, whereas the $CDCl_3$ spectrum displayed no complexity.

Scheme 14. Protodesilylation of the 1,4-Azasiline Hydrochloride Core



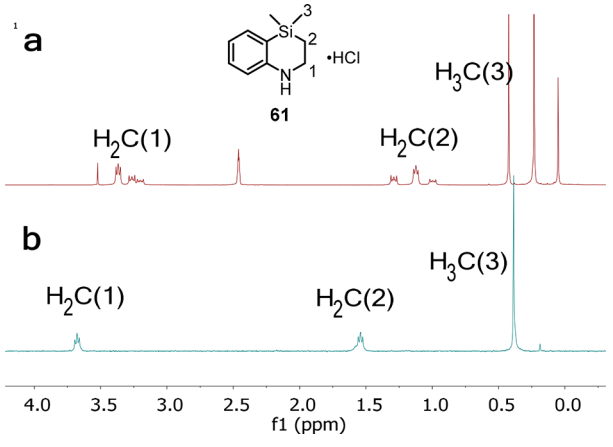


Figure 10. ^{1}HNMR spectra of **61** in DMSO-d_6 (a) and $CDCl_3$ (b) at 23 °C in a 4.0−0.0 ppm window.

These observations allowed for the design of conditions amenable to high-yielding N-functionalization of the 1,4-azasiline core. For example, Boc-protection was easily achieved by treating the 1,4-azasiline hydrochloride **61** with Boc anhydride and NaH in refluxing 1,4-dioxane (Table 6, entry 3), whereas DMF resulted in the formation of decomposition products, reflecting the greater coordinative ability of the C═O oxygen to silicon compared to the ethereal oxygen. For other functionalizations (e.g., reductive aminations, acylations) the use of non-coordinating solvents at room temperature or below permitted facile N-substitution. Furthermore, once substituted, N-acylated and N-alkylated products were *very stable* and were easily chromatographed, crystallized, or distilled.

The putative mechanisms of protiodesilylation, especially under conditions considered "basic," warrants discussion. Acid-mediated protiodesilylation likely proceeds through the expected steps, in which protonation of the arene *ipso* to silicon is followed by nucleophile-assisted desilylation and rearomatization (Figure 11a). The vicinal relationship of silicon and the electron-releasing nitrogen likely enhanced stabilization of the arenium intermediate, further favoring protiodesilylation.[27] Protiodesilylation under basic conditions, however, was surprising, but may be rationalized by addressing the proton source. With a heterogeneous base like NaH, deprotonation occurs relatively slowly; therefore, a population of the N-anion will exist in solution alongside the protonated species that ultimately provides the proton (Figure 11b). With homogeneous amine bases, however, protons are not actively removed from the reaction mixture and instead persist in the form of amine hydrochloride salts (Figure 11c).

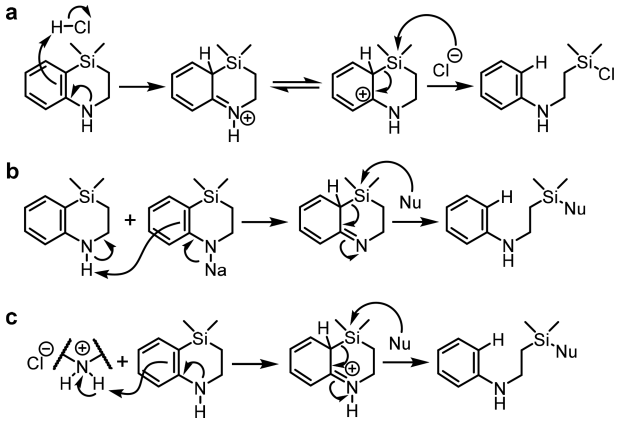


Figure 11. Protiodesilylation with various proton sources.

3.2. Diversity at Carbon. Two types of reactive intermediates were targeted for the C-functionalization of the azasiline cores, (1) organolithium compounds and (2) iminium ions, which were respectively treated with various electrophiles and nucleophiles selected specifically to probe the electronic and steric accessibility of carbon substitutions, as well as to install synthetic handles amenable for further, complex functionalization.

Exquisite site selectivity over metalation was achieved through careful optimization of the base and benefited from the complementary combination of the electronic stabilization of anions by silicon[28] and the directing effect of the Boc group.[29] Lithiation of Boc-protected 1,3-azasiline **18** at C(4) was selectively achieved with the relatively mild metal amide LDA whereas lithiation of Boc-protected 2,4-azasiline **3** at C(3) was best accomplished by *s*-BuLi, both of which could be performed at either −45 or −78 °C, flexible for the degree of functional group compatibility required. With these organolithium intermediates, alkylations, carboxylations, and bromi-

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nations all proceeded in excellent yields to furnish useful structures such as amino acids and hemiaminals. Similarly, a wide variety of functional groups could be installed in the **2** and **3** cores by the addition of nucleophiles into iminium ion intermediates, demonstrated by the synthesis of allyl- and nitrile-containing silicon heterocycles **38**, **39**, **55**, and **56**. Furthermore, it was shown that the amino acids **21** and **51** were themselves functional building blocks, evidenced by their transformation into amides.

Derivatives of the 2,4-azasiline were particularly remarkable for their stabilities, specifically amino acid **51** and amino nitrile **55**, because α-silyl amino acids are generally known to be quite unstable, significantly more so than even α-silyl amines, α-silyl esters, and β-silyl amino acids.[30] This instability is attributable to lengthening and weakening of the Si−C bond caused by the adjacent electron-withdrawing groups. However, **51** and **55** exhibited an incompatibility with silica gel and alumina, which can be explained by this relationship between α-substituted α-silyl amines and the electronic characteristics of the α substituent. This behavior is highlighted by the divergent stabilities of 1,3-azasiline and 2,4-azasiline series to silica gel (Figure 12).

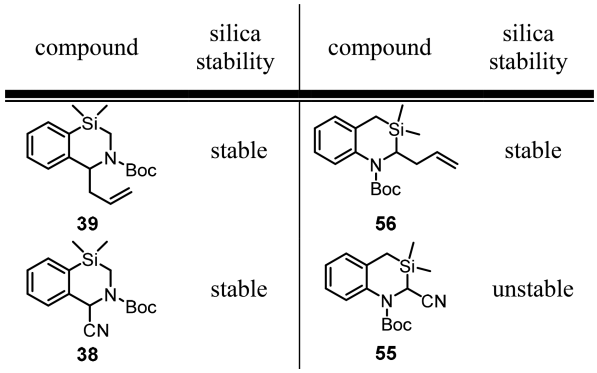

Figure 12. Comparative stabilities of 1,3- and 2,4-azasilines to silica gel.

On the other hand, weakening of the 2,4-azasiline Si−C(3) bond may account for the difficulty in cleanly capturing some carbonyl electrophiles (e.g., DMF, benzaldehyde) by organolithium intermediates (Figure 13, path a), although additional decomposition pathways may also be available depending on the substitution—e.g. the Peterson olefination for aldehyde

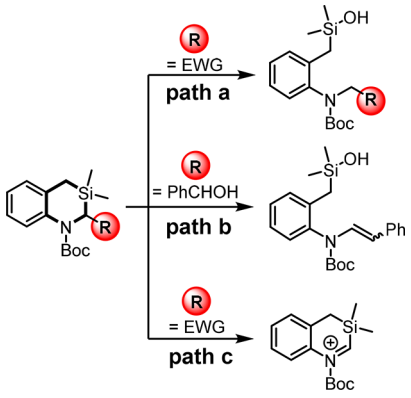

Figure 13. Possible decomposition products of electron-withdrawing 2,4-azasilines.

adducts (Figure 13, path b)—but this reactivity is unlikely and has been rarely reported for silacycles.[31] Predictably, carbon functionalization of the 1,3-azasiline core was significantly more tolerant of electron-withdrawing groups than the 2,4-azasiline core. However, attempted introduction of some carbonyl electrophiles resulted in decomposition, the basis of which is unclear as the 1,3-azasiline **18** silicon is quite removed from the introduced C(4) functionality. It is possible that the new group is undergoing elimination to form an iminium ion that subsequently decomposes,[32] implied by ^{1}H NMR and MS data of the crude reaction mixtures, in a manner similar to that depicted in Figure 13, path c.

The N-substituted 1,4-azasiline **4** and its Boc- and TBF-protected variants **64** and **66** were surprisingly resistant to C-functionalization; multiple attempted lithiations of the Boc- and TBF-protected cores resulted in *no detectable α-metalation*, which, as noted, starkly contrasts with Meyers's observations with tetrahydroquinolines.[20] The origin of this phenomenon remains difficult to pinpoint but may be referred to as a silicon *β-destabilizing* effect. Steric considerations provide one hypothesis for β-destabilization,[33] but it is not clear how the 1,4-azasiline methyl groups could shield the C(3) site, and the argument cannot account for the complete suppression of metalation observed in the 1,4-azasiline. From an inductive perspective, silicon is more electropositive than carbon, which may manifest as a higher C(3) C−H pK_a. Additionally, the longer C−Si bonds may distort the ring such that the directing properties of Boc and TBF are minimized. From a stereoelectronic perspective, the β-silicon effect[34] (classically, the stabilization of β-carbocations) would be expected to destabilize *carbanions* and may account for the inability of the 1,4-azasiline to lithiate. However, this effect is thought to be small[35] and the only dramatic manifestation is in the regioselective, trimethylsilyl-directed enolizations of cylcoheptanones and cyclohexanones.[36] If true, to the best of our knowledge this result represents the first example of destabilization of tetrahedral organolithium by silicon.

3.3. 1,4-Azasilin-3-one Core 5. Because of the unexpected behavior of the 1,4-azasilin-3-one core **5**, and the general formulation of its synthesis, a discussion separate from the other cores is warranted.

The different stabilities of analogues based on the mono-N-protected intermediate **71** was noteworthy (Figure 14, also see Table S10). Ignoring the Boc-PMB combination **71e**, which could not be synthesized (due to interception of the aryllithium intermediate by the Boc carbonyl following bromine−lithium exchange[37]) the diprotected compounds **71a**−**71d** were very stable, but oxidative PMB-deprotection[38] of **71b** (R^1 = Bn) and **71c** (R^1 = Me) led to complex mixtures (and PMB could not

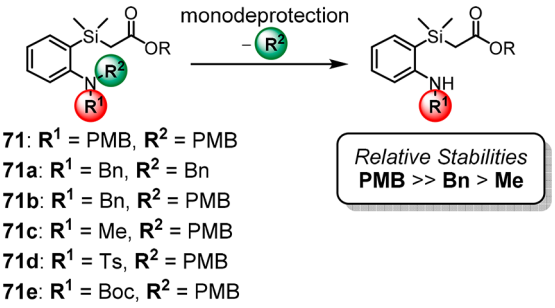

Figure 14. Relative stabilities of pre-cyclized intermediates.

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be cleaved if R^1 = Ts, **71d**). Only **71**, in which R^1 = PMB, was stable. In view of this behavior, and that of the related 1,4-azasiline core **4**, it was likely that protodesilylation was the major decomposition pathway (and was verified for $AlMe_3$-mediated cyclization). Therefore, the stability of the diprotected compounds may be attributed to (1) the absence of an NH, and (2) the nitrogen being most likely twisted out of the arene plane and thus unable to donate electron density into the benzene ring until after deprotection (Figure 15). However, this insight does not satisfactorily explain the observed difference between Bn and PMB, which are of similar steric bulk, strongly implying an electronic factor.

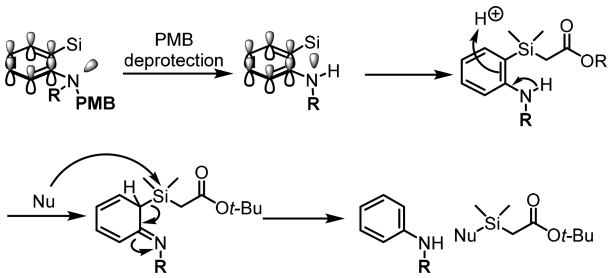


Figure 15. Proposed protiodesilylation pathway.

Furthermore, it was noted that deprotection of **71** was arrested after the loss of one PMB group. Extended reaction time or warming under the reported conditions (with ceric ammonium nitrate or anhydrous DDQ in dichloromethane) resulted in the formation of *p*-methoxybenzaldehyde, in addition to a complex mixture of additional products. This observation indicates that the deprotected, unsubstituted aniline **74** is unstable, most likely because of protiodesilylation. In contrast, the *para*-isomer **75** (Figure 16) is remarkably stable and can be readily isolated! A *para* relationship between silicon and the electron-donating group is expected to *enhance* the rate of protiodesilylation (e.g., $k_{rel}^{para}/k_{rel}^{ortho}$ for trimethylsilylphenol, 2.9; for trimethylsilylanisole, 3.8),[39] but this was not observed. Therefore, this result may be more accurately ascribed to rate acceleration by strain relief,[40] in which protonation of **74** is enhanced by a favorable change in dihedral angle between the silicon group and nitrogen as the *ipso* carbon adopts tetrahedral geometry.

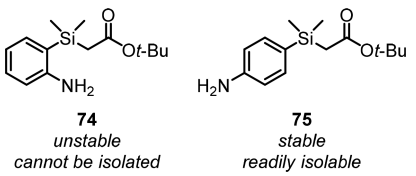
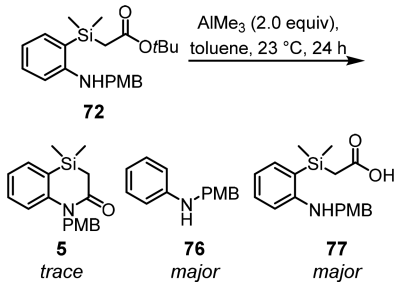


Figure 16. Relative stabilities of the 2- and 4-silylanilines.

Among the cyclization conditions evaluated, only that with $AlMe_3$ afforded 1,4-azasilin-3-one **5**, and then, only in a trace quantity detectable by mass spectrometry of the crude reaction mixture. The two major products were the protodesilylated *N*-(4-methoxybenzyl)aniline **76** and the silylacetic acid **77** (Scheme 15), the latter of which was unstable and quickly eliminated to afford acetic acid and the corresponding silanol. The presence of **77** strongly suggested that cyclization had occurred, and that silalactam **5** was susceptible to hydrolysis. Because this was unexpected, solvation-model calculations at

Scheme 15. Major Products of $AlMe_3$-Mediated Cyclization



the ωB97X-D/6-31G(d) level of theory were executed, with thermal corrections from B3LYP-D3(BJ)/6-31G(d). This level of theory indicates that the reaction modestly favors the hydrolyzed, ring-opened product (Figure 17) in both water (ΔG = −2.07 kcal/mol) and toluene (ΔG = −0.91 kcal/mol). This result again illustrates the dramatic influence of silicon on heterocyclic chemistry because analogous dihydroquinolones typically require strongly alkaline conditions (pH > 13) to undergo hydrolysis at 23 °C.[41]

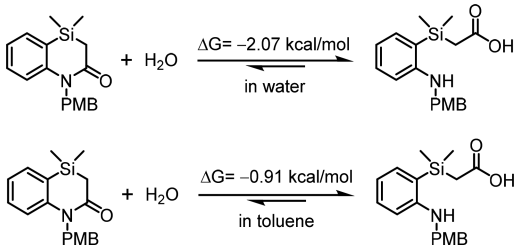


Figure 17. Calculated ΔG, from ωB97X-D/6-31G(d) with corrections from B3LYP-D3(BJ)/6-31G(d).

4. BIOLOGY RESULTS AND DISCUSSION

4.1. ADMET Properties of Silicon-Containing Heterocycles. Silicon-containing nitrogen heterocycles are underrepresented in the biological literature relative to compounds bearing exocyclic or linear silane groups.[42] Nonetheless, some information exists. For example, silaproline has received significant attention in the past two decades, albeit always as a proline isostere in peptides.[43] Among small molecules, the biological activity of azasilines has been studied in comparison with carbon analogues against influenza proton channels[44a] as well as CNS receptors like serotonin 5-HT_{1A} and dopamine D_2.[44b] In one example, acute toxicity and psychotropic activity in rats were investigated,[44c] while profiles of hepatic metabolites were analyzed in another.[44d] Recently, loperamide and its silicon analogue received a thorough *in vitro* and *in vivo* analysis.[44e] However, most silicon-containing nitrogen heterocycles have not received biological examination in any form.[44f,g]

4.2. In Vitro Assay Analysis. The aforementioned studies focused on activities at specific, medicinally relevant, biological targets rather than ADMET properties relevant to the general application of silicon in drug discovery. Introduction of silicon significantly increases compound lipophilicity[1,2] and increases the ClogP of azasilines by more than 2 log units over analogous carbon-based azacycles (Table 7). The consequence of this property may manifest as greater susceptibility to efflux transporters like P-glycoprotein (P-gp)[45] and Phase I metabolism.[46] Therefore, three types of biological assays were

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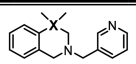
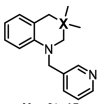
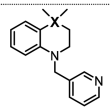
Table 7. Calculated Properties of *N*-Pyridylmethyl Azasilines[a]

entry	structure	X	MW	TPSA	ClogP
1		Si	268.4	16.1	5.8
2	X = Si, **16** X = C, **78**	C	252.4	16.1	3.6
3		Si	191.3	29.1	4.3
4	X = Si, **2** X = C, **79**	C	175.2	29.1	2.0
5		Si	268.4	16.1	4.3
6	X = Si, **45** X = C, **80**	C	252.4	16.1	5.3
7		Si	268.4	16.1	6.5
8	X = Si, **63** X = C, **81**	C	252.4	16.1	4.3

[a]Abbreviations: MW, molecular weight; TPSA, topological polar surface area; ClogP, calculated logP.

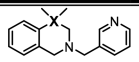
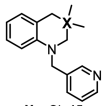
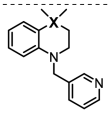
selected to measure the influence of silicon on small-molecule biological properties: (1) MDCK-MDR1 assays, to evaluate recognition by the P-gp efflux transporter; (2) liver microsome stability assays, to test susceptibility to Phase I metabolism in both rats and humans; and (3) cytochrome P450 (CYP) inhibition assays, to assess drug−drug interaction (DDI) risk against three major CYP isoforms. A representative member of each class of azasiline was selected and its direct tetrahydroquinoline or tetrahydroisoquinoline counterpart was synthesized (see Supporting Information for detailed schemes and procedures) and tested in parallel (Tables 7 and 8). With the exception of the lactam **2**, *N*-pyridylmethyl silaheterocycles were chosen due to the greater stability afforded by *N*-alkylation as well as the enhanced aqueous solubility conferred by the pyridine group.

In all cases, silaheterocycles showed no increased recognition by P-gp in the MDCK-MDR1 assay over their carbon azacycle counterparts (Table 8). Compounds that freely diffuse and show no recognition are expected to have BA/AB (basolateral→apical/apical→basolateral) ratios of 1.0 and will not be perturbed by addition of the P-gp inhibitor (Inh) cyclosporin (AB(Inh)/BA), and there is little deviation from this value among the tested compounds. However, high-confidence data could not be generated for 2,4-azasiline **45** (entry 5) because it tended to accumulate in MDCK cells or cell membranes which may be attributed to its lipophilicity and the reduced pK_a of the aniline-type nitrogen.

Unsurprisingly, all of the tested compounds were susceptible to metabolism in human and rat liver microsomes (Table 8). Although the silaheterocycles tended to be slightly more prone to metabolism than the azacycles, they were far less so than their ClogP values intimated. In fact, metabolic stability correlated more closely with topological polar surface area (TPSA) than with lipophilicity. Only the 1,3-azasiline **16** (entries 1 and 2, human liver microsomes) and azasilinone **2** (entries 3 and 4, rat liver microsomes) exhibited more than 2-fold shorter half-lives than their azacycle analogues. In the latter example, this modest difference was almost absent when measured in human liver microsomes (entries 3 and 4).

The CYP DDI assays showed that the presence of silicon did not increase cytochrome P450 inhibition (Table 8), and therefore, silaheterocycles did not constitute any more of a

Table 8. Azasiline Biological Data[a]

			MDCK-MDR1 permeability ratio		$t_{1/2}$ metabolic stability (min)[c]		CYP DDI IC_{50} (μM)		
entry	structure	X	BA/AB	AB(Inh)/AB[b]	human	rat	2C9	2D6	3A4
1		Si	1.0	1.0	9	<4	>20	6.2	6.3
2	X = Si, **16** X = C, **78**	C	0.7	0.9	21	<4	15.4	5.1	5.4
3		Si	1.3	1.0	55	61	>10	>10	>10
4	X = Si, **2** X = C, **79**	C	0.8	0.8	66	125	>10	>10	>10
5		Si	n/a	n/a	4	<4	12.5	11.7	0.4
6	X = Si, **45** X = C, **80**	C	0.9	1.0	6.5	<4	5.9	>20	1.4
7		Si	0.8	1.1	<4	<4	14.2	>20	0.5
8	X = Si, **63** X = C, **81**	C	1.1	1.0	<4	<4	12.9	>20	0.8

[a]Assayed and quantified by Cyprotex, Ltd. using established methods. [b]Inh = cyclosporin. [c]Stability assessed in liver microsomes. Abbreviations: MDCK, Madin−Darby canine kidney cells; MDR1, multi-drug resistance gene; $t_{1/2}$, half-life; CYP DDI, cytochrome P450 drug−drug interaction; BA/AB, basal−apical/apical−basal; IC_{50}, 50% inhibitory concentration.

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drug−drug interaction risk than analogous carbon azacycles through this mechanism (CYP induction was not examined). Inhibition was also not always uniform. In the case of the 2,4-azasiline **45** (entry 5) and its corresponding tetrahydroquinoline **80** (entry 6), the silaheterocycle was a 3-fold greater inhibitor of the CYP 3A4 isoform but a 2-fold lesser inhibitor of the CYP 2C9 isoform than the carbon azacycle.

4.3. Pharmacokinetic Analysis. Due to their lack of P-gp recognition, relatively high metabolic stabilities, and absence of CYP inhibition, azasilinone **2** and dihydroisoquinolone **79** were promoted to single-dose pharmacokinetic studies to compare their properties in complex organisms. Rats were dosed intravenously (i.v.) or orally (p.o.), plasma concentration was analyzed at various time points over 24 h, data were plotted logarithmically (Figure 18), and pharmacokinetic parameters were calculated (Table 9).

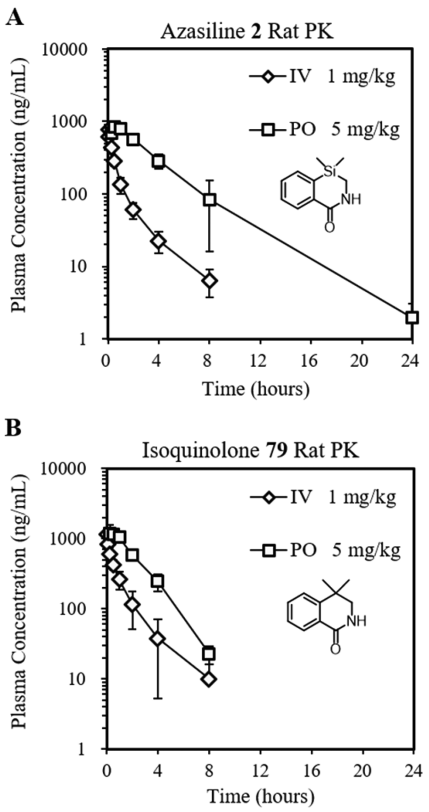

Figure 18. Single-dose pharmacokinetics (PK) for azasiline **2** (A) and isquinolone **79** (B). Cohorts of male Sprague−Dawley rats (n = 3/group) were dosed intravenously (i.v., tail vein) or orally (p.o., gavage solution) (20% HP-β-CD vehicle). Plasma was sampled at nine time points over 24 h, and concentration was determined by LC-MS/MS. Data plotted logarithmically. LLOQ: 1 ng/mL.

Azasilinone **2** and isoquinolone **79** exhibited similar pharmacokinetic profiles following intravenous administration (Table 9), with **79** possessing slightly greater initial concentration (C_0 = 1397 ± 57 vs 892 ± 105 ng/mL) and terminal plasma exposure (AUC_{term} = 937 ± 370 vs 556 ± 97 h·ng/mL). Azasilinone **2** had a marginally higher overall plasma clearance rate (CL = 30 ± 6 vs 19 ± 6 mL/min/kg) but this did not contribute significantly to the terminal-phase half-life $t_{1/2}$, which was similar to isoquinolone **79** (1.9 ± 0.2 vs 2.0 ± 1.2 h). Differences in volume of distribution V, in both the terminal phase (V_{dz} = 4.8 ± 0.7 vs 2.9 ± 0.6, **2** vs **79**) and at the steady-state point (V_{ss} = 2.8 ± 0.3 vs 1.8 ± 0.3, **2** vs **79**), were most likely driven by the different lipophilicities of **2** (ClogP 4.3) and **79** (ClogP 2.0). Absent other factors (e.g., plasma protein binding), lipophilicity is proportional to volume of distribution.[47]

Table 9. Pharmacokinetic Parameters (Observed and Calculated)[a]

PK parameter	compound: **2** (Si)	compound: **79** (C)	unit
	i.v. (1 mg/kg)		
C_0	892 ± 105	1397 ± 57	ng/mL
CL	30 ± 6	19 ± 6	mL/min/kg
AUC_{term}	556 ± 97	937 ± 370	hr·ng/mL
AUC_{∞}	574 ± 104	943 ± 369	hr·ng/mL
$t_{1/2\ term}$	1.9 ± 0.2	2.0 ± 1.2	h
V_{dz}	4.8 ± 0.7	2.9 ± 0.6	L/kg
V_{ss}	2.8 ± 0.3	1.8 ± 0.3	L/kg
	p.o. (5 mg/kg)		
C_{max}	847 ± 169	1266 ± 236	ng/mL
t_{max}	0.8 ± 0.3	0.5 ± 0.4	h
AUC_{term}	3171 ± 712	2893 ± 453	hr·ng/mL
AUC_{∞}	3179 ± 716	2935 ± 467	hr·ng/mL
$t_{1/2\ term}$	2.8 ± 0	1.3 ± 0.1	h
F	111 ± 25	62 ± 10	%

[a]Observed and calculated pharmacokinetic parameters from intravenous (i.v.) and oral (p.o.) single doses. Error reported as standard deviation. Abbreviations: C_0, plasma concentration at 0 min; CL, plasma clearance; AUC, area under the curve; $t_{1/2,term}$, terminal phase half-life; V_{dz}, terminal phase volume of distribution; V_{ss}, steady-state volume of distribution; C_{max}, maximum plasma concentration; t_{max}, time at C_{max}; F, bioavailability.

Following oral administration (Table 9), azasilinone **2** displayed a lower maximum concentration (C_{max} = 847 ± 169 ng/mL) and subtly longer onset (t_{max} = 0.8 ± 0.3 h) than isoquinoline **79** (1266 ± 236 ng/mL and 0.5 ± 0.4 h, respectively). However, plasma exposure was effectively identical between the two compounds (AUC_{term} **2** vs **79** = 3171 ± 712 vs 2893 ± 453 h·ng/mL). Surprisingly, despite the shorter half-life predicted by the rat microsomal stability assay (Table 8, entries 3 and 4), azasilinone **2** possessed a 2-fold longer half-life than isoquinolone **79** (2.8 ± 0 vs 1.3 ± 0.1 h, Table 9) and was still detectable at the 24 h time point (see Figure 18).

Remarkably, the oral bioavailability (F) of azasilinone **2** was significantly greater than that of the corresponding isoquinolone **79** (F = 111 ± 25 vs 62 ± 10%). Factors that strongly affect bioavailability include absorption and metabolism.[48] Because of the comparable plasma clearance rates of azasilinone **2** and isoquinolone **79** (Table 9), it is probable that absorption is the more influential factor and azasilinone **2** is more readily absorbed from the gut than its more hydrophilic isoquinolone counterpart. Additionally, **2** may also be better absorbed into tissue from the plasma, a possibility supported in part by the volumes of distribution (Table 9); conversely, the isoquinolone **79** may be more restricted to the aqueous environment of the plasma due to its potentially higher hydrophilicity (>400 μM at pH 7.4 vs 397 μM for **2**). Ultimately, these results show that incorporation of silicon does not necessarily present a liability and may potentially improve the PK profile of small-molecule heterocycles. Astute use of the building block strategy would

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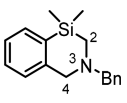
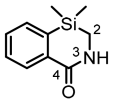
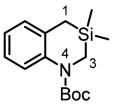
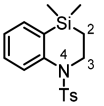
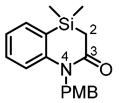
Table 10. Summary of Azasiline Core Reactivities

 1,3-Azasiline 1	 1,3-Azasilin-4-one 2	 2,4-Azasiline 3	 1,4-Azasiline 4	 1,4-Azasilin-3-one 5
Multi-Gram Scalable Simple Deprotection	Multi-Gram Scalable Simple Deprotection	Multi-Gram Scalable Simple Deprotection	Multi-Gram Scalable Simple Deprotection	Not Accessible
Multi-mmol Scale Functionalization	Multi-mmol Scale Functionalization	Multi-mmol Scale Functionalization	Multi-mmol Scale Functionalization	No Accessible Functionalization
***N*3 Diversity**	***N*3 Diversity**	***N*4 Diversity**	***N*4 Diversity**	***N*4 Diversity**
Acylation Alkylation Amidation Carbamation Conjugate Addition Reductive Amination	Alkylation Carbamation	Acylation Alkylation Amidation Carbamation Reductive Amination	Acylation Carbamation Reductive Amination	Not Accessible
***C*2 Diversity**	***C*2 Diversity**	***C*1 Diversity**	***C*2 Diversity**	***C*2 Diversity**
Not Evaluated	Not Evaluated	Not Evaluated	Not Evaluated	Not Accessible
***C*4 Diversity**	***C*4 Diversity**	***C*3 Diversity**	***C*3 Diversity**	***C*3 Diversity**
Alkylation Carboxylation	Iminium Addition Thionation Amidination	Alkylation Carboxylation Iminium Addition	Not Accessible	Not Accessible

allow these favorable features to be built into lead series early in the drug discovery process.

5. CONCLUSION

The key findings in this study are (1) the development of multi-gram-scale syntheses of unsubstituted azasiline heterocycles based on tetrahydroquinoline and tetrahydroisoquinoline cores, (2) the identification of accessible intermediates and their reactivities, (3) the functionalization of the azasiline cores with an array of electrophiles and nucleophiles to prepare novel silicon-containing heterocycles in good to excellent yields, (4) the optimization of well-established reactions to accommodate the inherent physical and electronic properties of silicon, and (5) the description of biological and pharmacokinetic parameters to sketch potential outcomes of silicon incorporation in drug discovery. Furthermore, the building block strategy presented allows for the rapid assembly of diverse structures from a small pool of inexpensive and readily available reagents and starting materials (Table 10).

Azasiline **1** was amenable to the broadest array of N-functionalization reactions among the five cores and was easily functionalized at C(4) with electrophiles to produce useful compounds, including a diversifiable amino acid. The related 1,3-azasilin-4-one **2** could be widely elaborated at C(4) as well, with weak nucleophiles, to prepare a number of nitrile, allyl, and amidine-containing structures. The 2,4-azasiline **3** was equally susceptible to diversification, and the C(3) carbon was found to perform variably as either a nucleophile (organolithium) or an electrophile (carbamoyl iminium ion). The 1,4-azasiline **4** was amenable to a variety of transformations and was quite stable when N-substituted, although silicon effected resistance to C-functionalization. The fifth and final core, the 1,4-azasilin-3-one **5**, originally envisioned as an extension of the 1,4-azasiline, proved to be surprisingly unstable.

Most importantly, the discovered reactivities of these molecules—including unexpected chemistry—provide guidelines for the preparation of new cyclic silicon-containing compounds beyond those reported herein. Critical features of N-functionalizations are as follows: aprotic, non-coordinating solvents are superior in general, and simple deoxygenation of the reaction media allows for N-substitution of heterocycles containing silicon α to nitrogen. For C-functionalizations, organolithium intermediates can be prepared with superb site selectivity with the appropriate base, and the reactions of carbamoyl iminium ions represent the mildest and perhaps broadest means of appending useful functionality in a manner compatible with silicon.

Finally, to facilitate the informed implementation of silicon in early drug discovery, direct comparisons of the biological properties of select azasilines and their carbon analogues were evaluated. These studies showed that silicon did not pose a metabolic, efflux, or DDI liability, and in fact improved oral bioavailability in a rat pharmacokinetic model, highlighting the value of the early application of silicon in the drug discovery process rather than the relatively late point at which the carbon−silicon switch tactic is typically employed. To better understand the geometrical and conformational impact of silicon substitution on reactivity, current studies are dedicated to the correlation of structure to chemical properties from X-ray diffraction data. Syntheses of analogous oxygen-containing silaheterocycles are also underway. These works will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b03187.

General experimental information, detailed experimental procedures, characterization data, NMR spectra, computational data, biological protocols, additional figures, schemes, and tables (PDF)

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Notes

The authors declare no competing financial interest.

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