Silicon-Derived Singlet Nucleophilic Carbene Reagents in Organic Synthesis

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\textit{Dedicated to Prof. Dr. Carsten Bolm on the occasion of his 60\textsuperscript{th} birthday.}

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\textbf{Abstract.} Over fifty years ago, the 1,2-rearrangement of acyl silanes was first described by Adrian Brook and co-workers. This rearrangement (now termed the Brook rearrangement) yields reactive silicon-based singlet nucleophilic carbene (SNC) intermediates that participate in a variety of chemical transformations including 1,2-carbonyl addition, 1,4-addition to electron-deficient unsaturated bonds and insertion into C-H and O-H bonds.

This review aims to cover the historical literature and recent advances with regards to these valuable silicon-based reagents and highlight additional aspects related to the intriguing reactivity of both the carbene and oxocarbenium intermediates.

\textbf{Keywords:} Organosilicon; Siloxy Carbene; Acyl Silane; Singlet Nucleophilic Carbene; Photochemistry

1.0 Introduction

Silicon containing molecules have unique and important physical properties that have been exploited in organic, medicinal and materials chemistry. In a medicinal chemistry setting, silicon has been employed as a bioisostere of carbon, affording access to analogues with enhanced physicochemical properties and novel intellectual property (IP) space.\cite{1} Comparatively, the silicon-carbon bond is almost 20\% longer than a carbon-carbon bond and silicon analogues are generally more lipophilic and have higher electropositivity than the corresponding carbon analogues.\cite{1a} In materials chemistry, silicon derivatives have been explored as an alternative to carbon based graphite anodes in batteries due to their extremely high theoretical specific capacity.\cite{2}

In addition to its important physical properties, silicon also plays a valuable role in organic synthesis.\cite{3} Silyl groups are employed as protecting groups to inhibit reaction at specific carbon or oxygen atoms or can be used to trap the enol tautomer of ketones to generate silyl enol ethers which act as nucleophilic reagents in processes such as the aldol reaction.\cite{4}

Organosilicon groups can also be transformed into a variety of other functional groups. For example, the Hiyama-Denmark coupling makes use of a silyl functional group as a handle for cross-coupling reactions.\cite{5} In the example shown in Scheme 1, a silyl-alkyne reagent facilitates incorporation of a silicon motif into an isoxazole, with this silyl group then taking part in the palladium-mediated cross-coupling process to afford 3,4,5-trisubstituted isoxazole heterocycles.\cite{6}
Scheme 1. Silicon functional groups can be employed in cross-coupling reactions

More recently, Mancheno and co-workers reported the use of silyl groups to access radical intermediates that underwent the Giese reaction with electron-deficient alkenes. The key radical intermediate is generated following oxidation of the carbon-silicon bond via a singlet electron transfer process facilitated by an acridinium photocatalyst (Scheme 2).

Scheme 2. Silicon reagents can be employed in photoredox catalysed transformations

To prepare silicon containing derivatives for application in organic or medicinal chemistry, suitable methods must exist to enable the efficient preparation of organosilicon compounds. To this end, Oestreich and co-workers have recently disclosed the discovery of new reactions that facilitate installation of silicon functionality into small molecules including cyclopropanes. (Scheme 3).

Scheme 3. Silicon-containing molecules can be accessed via a range of catalytic strategies.

One strategy to incorporate silicon into target molecules is the use of silyl-derived carbene reagents. Silicon-based electrophilic singlet carbene intermediates (see Scheme 4) accessed from α-silyl-α-diazoesters or α-silyl-α-diazo ketones have been employed to prepare a range of silicon-containing compounds. For example, Bolm and co-workers reported the rhodium-catalysed synthesis of silyl substituted α-amino acids, dioloxolanes and α-hydroxyacetic acids from α-silyl α-diazoacetates.

Silicon-based nucleophilic carbene intermediates (Scheme 4) can be accessed from the corresponding acyl or amidoyl silane via Brook rearrangement and react in a variety of transformations to form valuable silicon-containing molecules. To this end, it is the focus of this review to highlight the broad synthetic utility of silicon-based nucleophilic carbene reagents intermediates in chemical synthesis.

Scheme 4. Electrophilic and nucleophilic carbene intermediates have been employed in chemical synthesis

Since Dumas’ initial efforts to prepare methylidene in 1835, the concept of a divalent carbon reactive intermediate has captured the imagination of many chemists with decades of research culminating in the pioneering isolation of the first stable carbene by Bertrand in 1988 (Figure 1).

Carbene are neutral carbon species that contain six valence electrons. Four of the valence electrons occupy two low-energy sigma-bonding orbitals, and the other two electrons occupy either one or both non-bonding orbitals giving rise to four possible carbene electronic states (Figure 1). Carbene exist in the singlet state (paired non-bonding electrons) or triplet state (unpaired non-bonding electrons).

Figure 1. The various possible electrons configurations at the carbenic carbon.

A large variety of carbene species are now known. As early as the 1960s, Hines stated that for a reactive species to be defined as a carbene, there must exist a stable dimer or a four-coordinate adduct produced via carbene insertion into a σ-bond (for example H-OR). Traditional carbenes such as methylidene cannot be isolated and display reactivity that is typically electrophilic including insertion into C-H bonds and cyclopropanation reactions. On the other hand, N-heterocyclic carbenes (NHCs), for example imidazolidine or triazolylidine derivatives are highly nucleophilic and can be “bottled”.

For a divalent carbene of linear geometry, the two unbound valence electrons are typically distributed across degenerate orbitals affording a triplet ground state carbene. For the simplest possible carbene (i.e. H$_2$C:), the triplet ground state is favored over the singlet state by approximately 9 kcal/mol. To note, solvent interactions can also influence whether the carbene exists in its triplet or singlet ground state.

The reactivity of triplet carbenes often parallels that...
of radicals (e.g. abstraction reactions).\textsuperscript{[12c, 17]} Despite not being isolable, the application of triplet carbenes in synthesis has advanced significantly in recent years due to the efforts of Tomioka, Hirai and others.\textsuperscript{[12c]}

For singlet carbenes the non-bonding electrons on the carbene nucleus are paired. Singlet carbenes should be ambiphilic as they possess the characteristics of both a carbocation and a carbanion—an empty \( \pi \)-orbital and a carbon-centred lone pair. As such, substituents that stabilise a carbocation or carbanion relative to a radical can also stabilise a singlet carbene.\textsuperscript{[18]}

For stabilised singlet carbenes, at least one carbene substituent is typically a heteroatom capable of \( \pi \)-donation. Singlet electrophilic carbenes predominantly contain electron-withdrawing substituents such as an \( \alpha \)-ketone or \( \alpha \)-ester groups which accept electron density through \( \pi \)-effects or inductive withdrawing effects which stabilise the carbene intermediate.\textsuperscript{[19]} As the 2p-orbital remains vacant, these carbenes exhibit electrophilic reactivity. The most relevant stabilising interaction for a singlet nucleophilic carbene is electron donation to the unoccupied, non-bonding p-orbital from this adjacent heteroatom.\textsuperscript{[12b]}

Depending on the major form of stabilisation from carbene substituents, the terms donor (or push) and acceptor (or pull) have been used in varying combinations to classify carbenes (see Figure 2).\textsuperscript{[19]} Donation of electron density is considered a “push” (from substituents including \( \text{NR}_2 \) or \( \text{OSiMe}_3 \)) whereas “pull” indicates the presence of a carbene substituent with \( \pi \)-electron accepting or inductive withdrawing properties (e.g. CF\(_3\) or CO\(_2\)Et).\textsuperscript{[19,20]}

### Figure 2

Overview of the first stable carbenes to be isolated and common classifications of carbenes.

Extensive investigations have been conducted into the application of electrophilic singlet carbenes in chemical synthesis (for example the acceptor and donor-acceptor carbenes shown in Figure 2). Such carbenes readily participate in C-H insertion and cyclopropanation processes or react with heteroatoms to form ylides which themselves are useful intermediates for subsequent transformations.\textsuperscript{[17, 21]} Additional stabilisation of these carbenes is often achieved by generating the carbene intermediates from diazo compounds using an organometallic complex which affords a metal carbenoid species.\textsuperscript{[21a, 22]} Recently, the metal-free photochemical generation of electrophilic carbene intermediates has gained increasing interest in organic synthesis.\textsuperscript{[23]}

With regards to singlet nucleophilic carbenes (SNCs), the isolation of stable \( N \)-heterocyclic carbenes (NHCs), first achieved by Arduengo and co-workers in the early 1990s (Figure 2),\textsuperscript{[24]} has enabled significant advances to be realised with such carbenes now widely utilised as ligands in organometallic complexes that catalyse a range of transformations.\textsuperscript{[25]} More recently, cyclic alkyl amino carbenes have demonstrated significant potential in catalysis (Figure 2).\textsuperscript{[26]}

\( N \)-heterocyclic carbenes have also been exploited in organocatalysis, where chiral derivatives have been developed to catalyse a range of new chemical reactions with exceptional chemo- and enantio-selectivity (see example in Figure 2).\textsuperscript{[27]} The focus of this article is not however singlet nucleophilic carbene derivatives in their capacity as ligands or catalysts, rather with regards to their application as reagents and building blocks in organic synthesis.

### 2.0 Discussion

A variety of singlet nucleophilic carbene (SNC) reagents have been investigated and applied as reagents in chemical synthesis. Examples of such carbene derivatives include cyclic oxacarbenes, dimethoxycarbenes, aryl alkoxy carbenes, amino aryl carbenes and siloxy carbenes.

Oxacarbenes can be generated photochemically from cyclic ketones such as cyclopentanone and cyclobutanone.\textsuperscript{[20]} Ultraviolet irradiation of such ketones promotes homolysis to generate an alkyl acyl biradical that rearranges to form a cyclic oxacarbene that can undergo subsequent transformations such as O-H insertion in the presence of alcohols (Scheme 5).\textsuperscript{[28a]}

![Scheme 5](image)

\textbf{Scheme 5.} Photochemically generated oxacarbenes undergo O-H insertion processes

Another class of singlet nucleophilic carbenes is aryl alkoxy carbenes, for example phenyl methoxy carbene, generated photochemically from the corresponding diazirine. Moss and co-workers published a series of papers in the late 1980’s describing the unusual ambiphilic reactivity of these aryl alkoxy species when compared to the
cyclopropanation and dimerisation transformations expected of traditional carbenes (Scheme 6). \[29\]

Scheme 6. Aryl alkoxy carbenes, generated from diazirines, react with electron deficient alkenes

The synthetic utility of dimethoxycarbene has been investigated extensively by Warkentin and others who generated dimethoxycarbene thermally from the corresponding 2,5-dihydro-1,3,4-oxadiazoles and developed new chemical reactions utilising a range of substrates. \[30\] For example, Nair and co-workers developed the multicomponent reaction of dimethoxycarbene and DMAD with carbonyl substrates such as aldehydes (Scheme 7). \[31\]

Scheme 7: Multicomponent reaction of dimethoxycarbene intermediates.

In addition to their use as ligands and organocatalysts in chemical synthesis, aryl and alkyl substituted amino carbenes have also been explored as reagents. \[32\] For example, Bertrand and co-workers reported that aryl amino carbenes accessed via deprotonation of an iminium ion readily insert into C-H and O-H bonds (Schemes 8 and 9).

Scheme 8. Generation of amino aryl carbenes from iminium ions

Scheme 9. Aryl amino carbenes undergo C-H insertion with proximal tert-butyl groups

2.1 Siloxy Carbenes

Siloxy carbenes, first described by Brook and co-workers in the 1960s, \[33\] are accessed from the corresponding acyl silane via 1,2-Brook rearrangement of the silicon motif which can be initiated thermally or photochemically. \[34\] The siloxy carbene precursors, acyl silanes themselves possess unique properties due to the inductive release of electrons from the silicon atom to the carbonyl group. \[35\]

When acyl silanes are activated thermally or photochemically (using visible or near-UV irradiation), an n–π* transition occurs involving promotion of an electron from the non-bonding orbital of the oxygen atom to the anti-bonding orbital of the carbonyl π-system. This transition generates an acyl silane excited singlet state, from which intersystem crossing (ISC) to the acyl silane triplet state occurs. From the acyl silane excited triplet state, the 1,2-Brook rearrangement of the silicon atom to generate a carbene can take place or alternatively, homolysis of the carbon-silicon bond can occur (Scheme 10). \[36\]

Scheme 10. Overview of siloxy carbene formation

When homolysis occurs, Norrish-Yang and Paternò-Büchi reactivity has been observed analogous to that which takes place following the photochemical activation of ketones. \[37\] An example of chemistry arising from the homolysis process includes an intramolecular (2+2) cycloaddition of
acyl(allyl)silanes developed by Hammaecher and Portella. More recently, Capaldo and co-workers reported the use of a decatungstate photoredox catalyst to exclusively facilitate homolyses of acyl silanes to generate acyl radical species.

When the 1,2-Brook rearrangement takes place, a singlet nucleophilic carbene intermediate is generated (with stabilising contributions from the ylide resonance form). Since the first report of siloxy carbenes, a range of studies have been reported exploring the formation and reactivity profiles of these intriguing singlet carbene intermediates. In addition to hydride abstraction and insertion into polar bonds, siloxy carbenes undergo electrocyclications. 1,2-addition to carbonyl groups (benzoin-type reactivity) and 1,4-addition to electron deficient double bonds (Stetter-type reactivity).

As shown in Figure 3, a diverse array of structures can be accessed from siloxy carbene intermediates, the formation of which can often be attributed to the properties of the corresponding oxocarbenium intermediate (formed following carbene protonation or nucleophilic addition to an electrophile) rather than the properties of the parent carbene itself. Singlet nucleophilic carbenes are stabilised by electron donation to the vacant 2p-orbital via conjugation from the adjacent heteroatom. This is illustrated for siloxy carbenes as shown in Figure 4. Interaction of oxygen’s non-bonding valence electrons with the unoccupied 2p carbene orbital stabilises the carbene nucleus through a reduction in energy of the ns orbital energy. Due to this interaction, the energy of the unoccupied molecular orbital is shifted to a higher energy causing a net increase in ΔE_{mb} which leads to a greater preference for the singlet state and renders such carbenes nucleophilic. In general, all SNCs contain at least one heteroatom capable of π-donation into the carbene centre raising the energy of the LUMO and decreasing the electrophilicity of these substrates.

The silicon-derived carbene intermediates outlined herein contain either one or two heteroatom substituents (e.g. N or O) which affords nucleophilic (Lewis basic) carbene intermediates. Two approaches to provide insight into the nature of carbenes using DFT analysis have been developed involving determination of the ΔE_{ST} (singlet-triplet gap) and carbene stabilisation enthalpy (CSE). A positive ΔE_{ST} indicates a triplet carbene ground state whereas a negative ΔE_{ST} value indicates a singlet state carbene. Nearly all heteroatom substituted carbenes have significant CSE (singlet) values and moderate to low CSE (triplet) values, the net effect being a strong shift towards the singlet state characterised by large singlet-triplet gaps with preferences for the singlet carbene as high as 60 kcal/mol in some cases.

The outcomes of a study into the ΔE_{ST} and CSE of siloxy carbenes were recently published by the Priebbenow group which included calculation of the atomic orbital occupancy to determine the extent of the interaction of the oxygen lone pair with the vacant 2p carbene orbital. From this study, it was determined that the ΔE_{ST} for alkyl substituted siloxy carbenes ranged from -11 to -23 kcal/mol. Interestingly, the singlet-triplet gap for cyclic alkyl siloxy carbenes (ΔE_{ST} = -11 to -18 kcal/mol) was lower than that for the corresponding acyclic carbenes (ΔE_{ST} = -19 to -23 kcal/mol).

The calculated ΔE_{ST} for aryl substituted siloxy carbenes ranged from -11 to -19 kcal/mol. In addition, aryl siloxy carbenes were determined to be less hard and more electronegative overall than the alkyl siloxy carbene derivatives. For the amino siloxy carbenes investigated in this study, the ΔE_{ST} averaged -50 kcal/mol, with the presence of the secondary heteroatom adjacent to the carbene centre providing additional stabilisation compared to aryl and alkyl siloxy carbene variants.

Based on the additional understanding provided by this study, the literature regarding silicon-based nucleophilic carbenes is herein reviewed with the aim to provide new insight that enables these unique silicon-derived carbene intermediates to be further exploited in synthetic organic chemistry. Of significant advantage is that most transformations employing siloxy carbenes only require the use of...
light to drive the reaction, minimising the use of transition-metal or organocatalysts and additives.

Siloxy carbenes can react as either a Brønsted base or Lewis base, depending on the structure of the parent acyl silane and the solvent and reagents present. Several decades ago, Arduengo determined the proton affinity of what are now known as the Arduengo-type carbenes to be approximately 250 kcal/mol. Since that time, the Bronsted basicity of carbenes has emerged as an important topic of consideration in the design and development of catalysts and ligands. To this end, several groups have recently reported the outcomes of studies into carbene basicity and its impact on NHC catalysed transformations.

To explore the basicity of siloxy carbenes, $\Delta H_{\text{acid}}$ was calculated for alkyl, aryl and amino siloxy carbenes. The $\Delta H_{\text{acid}}$ value provides insight into the basicity of carbenes by determining the energy required to remove the proton from the corresponding protonated carbene. Compared to methylidene ($\Delta H_{\text{acid}} = 208$ kcal/mol), the siloxy carbenes returned much higher values ranging from 259-270 kcal/mol for the alkyl siloxy carbenes, 260-275 kcal/mol for the aryl siloxy carbenes and an average of 265 kcal/mol for the amino siloxy carbenes. To note, experimental measurements have shown that the protonated carbenium ion of carbenes containing at least one heteroatom substituent possess a pKa in the range of 15-23.

The proton affinity of carbenes gives rise to the common reactions observed for nucleophilic carbenes being 1,2-hydride shift or insertion into the O-H bond of weak proton donors such as water or an alcohol. Independent of whether the siloxy carbene reacts as a base or nucleophile, the structure of the final product formed is influenced by the properties of the corresponding oxocarbenium intermediate which is generated following the initial reaction of the carbene with a proton or electrophile (Figure 5).

![Figure 5](image-url)

**Figure 5.** Siloxy carbenes can react as Brønsted bases or as nucleophilic Lewis bases

For the cation formed following protonation or addition to an electrophile, the oxocarbenium resonance form is preferred over the carbonium ion as all atoms retain a full octet. The structure of the products formed from reaction of siloxy carbenes can be reconciled via analysis of the oxocarbenium ion intermediate which undergoes subsequent nucleophilic attack at one of two electrophilic sites (i) either the carbonyl carbon to form a silyl ether; or (ii) at the silicon atom which leads to cleavage of the oxygen-silicon bond and regeneration of the carbonyl system (Scheme 11). Consideration of the oxocarbenium ion is thus central to the discussion that follows.

![Scheme 11](image-url)

**Scheme 11.** The oxocarbenium ion has two reactive electrophilic sites

The enhanced proton affinity of siloxy carbenes accounts for the product formed from the 1,2-Brook rearrangement of isopropyl acyl silane whereby following siloxy carbene formation, a 1,2-hydride shift yields the corresponding silyl enol ether in high yield (Scheme 12).

An analogous intramolecular 1,2-proton shift was observed following the thermal activation of acetyl (dimethylphenyl)silane to afford the corresponding silyl enol ether in 98% yield (Scheme 13). Isobutyryltrimethylsilane was also reported to undergo a similar rearrangement process involving insertion of the carbene into the $\beta$-C-H bond.

![Scheme 12](image-url)

**Scheme 12.** 1,2-hydride shift of siloxy carbenes generates silyl enol ethers

![Scheme 13](image-url)

**Scheme 13.** Thermally generated siloxy carbene intermediates undergo 1,2-H shift to afford the corresponding silyl enol ether.
A similar transformation was observed by Hassner and Soderquist, who in 1980 reported that vapor phase pyrolysis of cyclic acylsilane at 550°C afforded the cyclic silyl enol ether product via a carbene intermediate (Scheme 14). To note, during the reaction some of the decarbonylated product was also formed through the radical pathway.

Scheme 14. 1,2-H shift occurs within cyclic siloxy carbene intermediates.

The formal insertion of carbenes into X-H bonds (where X is a heteroatom including O, N, S or Si) to form the corresponding mixed acetal (or analogous species) is the most common transformation reported for siloxy carbenes and variations on this process have been disclosed by several groups. Duff and Brook first reported on the Brønsted basicity of siloxy carbene intermediates formed from 1,2-Brook rearrangement of acyl silanes in 1973. They observed that the reagents that most effectively trapped the proposed siloxy carbene intermediate were, in general, quite acidic, generating a range of silyl derivatives (e.g. ROH, HOAc, HCN, HCl, and pyrrole – Schemes 15 and 16). Brook and co-workers also noted that acetonitrile (pKa ~25) failed to react with the basic carbene whereas malonitrile (pKa ~12) reacted, providing further evidence that it was the acidity of a substance rather than the availability of a site for electrophilic attack (i.e. CN group) that dictated the reaction outcome.

Scheme 15. Insertion of siloxy carbene intermediates into O-H bonds to form acetals.

Svarovsky and co-workers capitalised on the ability of siloxy carbenes to undergo O-H insertion to prepare a series of silicon-derived glycosides designed as potential pH-sensitised prodrugs for treating cancer (two examples shown in scheme 17). From this study, one glucose derivative reportedly exhibited moderate anti-cancer activity.

Scheme 17. Siloxy carbene intermediates undergo O-H insertion to produce siloxy acetal glycoside derivatives.

The light-mediated formal insertion of siloxy carbenes into Si-H bonds has also been described by Watanabe and co-workers. This process afforded a variety of aryl substrates containing both silane and siloxy functional groups (Scheme 18).

Scheme 18. Siloxy carbenes insert into Si-H bonds.

Recently, Glorius and co-workers reported the insertion of siloxy carbenes into the B-H bond of pinacolborane by irradiation of acyl silanes using 3W blue LEDS (λ_{max} = 420 nM). A range of both alkyl and aryl derived acyl silanes were applicable to this reaction process to afford a series of siloxy borane derivatives in quantitative yield (Scheme 19).

Scheme 19. Insertion of siloxy carbene intermediates into B-H bonds.
Glorius also showed that if light of a higher wavelength was used \( (\lambda_{\text{max}} = 455 \text{ nm}) \) carbone formation did not efficiently occur, however at this wavelength inclusion of a catalytic amount of the photosensitiser \( [\text{Ir}(dF(F\text{CF}_3)_{2}\text{ppy})(dttbpy)]PF_6 \) (commonly utilised to facilitate triplet-triplet energy transfer processes)\(^{[53]} \) was promoted reaction between the siloxy carbone and pinacol borane.\(^{[52]} \) Such an outcome infers that siloxy carbene intermediates are generated from the \( T_1 \) acyl silane excited state.

Whether the mechanistic pathway for the X-H insertion processes involving siloxy carbenes (Schemes 15–19) proceeds in a stepwise or concerted fashion has been an ongoing topic of discussion (Scheme 20). The stepwise ionic process involves a basic singlet carbone removing the acidic proton from a secondary substrate to generate the corresponding nucleophile (conjugate base) which then reacts with the oxocarbenium ion (equivalent to an activated aldehyde) to form the mixed acetal type products.

In their recent report, Glorius and co-workers proposed that the insertion of siloxy carbenes into the B-H bond of pinacol boranes likely proceeds in a concerted fashion,\(^{[52]} \) however a 1998 article from Steenken on the formation of carbenium ions from carbenes via protonation reports that several carbenes undergo O-H insertion into alcohols via a stepwise ionic pathway.\(^{[54]} \) Both processes are plausible and the actual pathway involved most likely depends on the solvent, basicity of the carbone and the acidity of the X-H bond in the reagent.\(^{[55]} \)

![Scheme 20. Insertion of siloxy carbenes into X-H bonds can occur in a stepwise or concerted fashion.](image)

Siloxy carbenes also insert into C-H bonds in an intramolecular fashion. For example, the carbone generated thermally from pivaloilsilane inserted into a C-H bond of a proximal methyl group to afford a dimethyl siloxy cyclopropane (Scheme 21).\(^{[57]} \)

![Scheme 21. Intramolecular insertion of siloxy carbene into C-H bond.](image)

In 2009, Dong & co-workers reported the thermal 1,2-Brook rearrangement of \textit{ortho}-benzyloxy substituted acyl silanes to generate a siloxy carbone that underwent C-H insertion to afford the corresponding dihydrofuran (Scheme 22).\(^{[56]} \) If heated for an extended period, subsequent elimination of the siloxy group occurred to yield the 2-aryl benzofuran. Interestingly, for the O-benzyl substrates, the \textit{cis}-isomer was formed predominantly, whereas for the S-benzyl derivative, the \textit{trans}-isomer was the major diastereomer formed.

![Scheme 22. Insertion of siloxy carbone into O-benzyl and S-benzyl C-H bonds](image)

In 2012, Wang & co-workers conducted computational studies into this reaction process and proposed that this transformation proceeded through an excited singlet carbone state, with proton abstraction without spin multiplicity change leading to formation of a diradical species, which underwent subsequent diradical coupling to afford the final product.\(^{[57]} \) Such abstraction-recombination pathways have been reported for other cyclisation reactions involving carbone intermediates.\(^{[56, 58]} \) Of interest, an analogous C-H insertion process was observed during pyrolysis of 2-(\textit{2-methoxyphenyl})-2-oxoacetic acid which presumably proceeds via the hydroxy carbone generated following decarboxylation (Scheme 23).\(^{[59]} \)

![Scheme 23. Insertion of carbene into O-methyl C-H bond](image)

In 2015, Becker and co-workers published a related study whereby silicon-derived \textit{N}-heterocyclic indoline products were formed from the corresponding \textit{ortho}-amino aroylsilanes (Scheme 24).\(^{[60]} \) Interestingly, it was observed that in the presence of the phenyl group (carbone generated thermally, Scheme 24, equation 1) the \textit{cis}-diastereoisomer was the major isomer formed whereas for the ester derivative (carbone generated photochemically, Scheme 24, equation 2), the \textit{trans}-isomer was predominantly formed.\(^{[60c]} \)
Shih and Swenton reported the thermal rearrangement of 2-methyl benzoyl silanes to generate silicon-derived benzaldehydes (Scheme 25).[60] A mechanism involving intramolecular C-H insertion followed by a ring opening process to generate an oxocarbenium ion was proposed to account for the 2-silylmethyl benzaldehyde product formed.

In addition to their ability to insert into X-H and C-H bonds, heteroatom-stabilised singlet carbenes are also excellent nucleophiles. This has been widely exploited in the case of highly stabilised N-heterocyclic carbenes as nucleophilic organocatalysts to catalyse a range of useful (asymmetric) synthetic transformations. The nucleophilicity of siloxy carbenes is discussed in the following section, and again it is the properties of the corresponding oxocarbenium ion which typically influences the structure of the final products formed.

A range of reports have described the activation of acyl silanes to yield siloxy carbene intermediates that undergo 1,4-conjugate addition to electron deficient alkenes and alkenes (Stetter-type reactions). The products formed from such processes include cyclopropanes, hexanones and functionalised ketones. Despite an array of possible mechanisms postulated throughout the literature including diradicals and cyclopropenes, the variation in reactivity can be more simply explained by the nucleophilic addition of a singlet carbene to an electron deficient olefin, with properties of the resultant oxocarbenium ion influencing product formation (compare Pathways A, B and C in Scheme 26).

The predominant pathway observed from the reaction of siloxy carbenes with electron-deficient alkenes and alkynes is Pathway A, whereby the carbanion generated following conjugate addition reacts with the proximal silicon group on the oxocarbenium ion to form a new carbon-silicon bond and regenerate the carbonyl group (refer to Scheme 11). The reactivity of siloxy carbenes through Pathway A has been reported in a series of publications by the Bolm group who have described the inter- and intramolecular silyl acylation of internal alkynes and alkenes.[40b-d]

For example, in 2013, Becker et al. described the intermolecular silyl acylation of electron-deficient alkynes to afford vinyl silanes (Scheme 27, equation 1).[40b] This process was initiated by the photochemical 1,2-Brook rearrangement to generate a nucleophilic singlet carbene which adds to the alkyn. The resultant carbanion then attacks the silyl group (cleaving the O-Si bond) through a 1,4-retro-Brook rearrangement to regenerate the carbonyl system and afford a vinyl silane. The use of more bulky silyl groups resulted in decreased yield, proposedly due to a less efficient Brook rearrangement. Of interest, for internal alkynes containing neutral substituents (e.g. diethyl or diphenyl acetylene), no reaction occurred.

In 2012, Zhang and co-workers reported the intramolecular version of this reaction (Scheme 27, equation 2), whereby the carbene generated photochemically added across the proximal alkyne to afford a series of silylated chroman-4-ones. Both alkyl and aryl substituents on the alkyne were tolerated for this process.[40d] Zhang et al. subsequently demonstrated that the silyl group could be used as a handle for cross-coupling with aryl halides in a copper-mediated arylation process.
In 2015, the Bolm group extended this work to the nitrogen analogues, prepared \textit{via} the \textit{ortho}-amidation of acyl silanes using iridium catalysis, exploiting the ability of the acyl silane group to act as a weakly coordinating directing group for C-H activation (Scheme 27, equation 3),\cite{40c} For these particular substrates, the photochemical method to generate the siloxy carbene did not lead to a clean reaction (proposedly due to photo-mediated isomerisation of the alkene in the product) and as such, thermal activation (210°C in a microwave reactor) was instead employed to successfully furnish a series of silicon-derived dihydroquinolinones in high yield with 100% atom economy.

To further explore the substrate scope, Becker and co-workers prepared a series of alkenyl substrates which reacted in a similar silyl acylation process to afford silyl indolinones \textit{via} Michael addition of the carbene (generated photochemically) to the tethered alkene followed by a 1,4-retro Brook rearrangement to afford the final product (Scheme 27, equation 4).\cite{40c}

While the stepwise process involving 1,4-nucleophilic addition followed by 1,4-retro Brook rearrangement detailed in pathway A (Scheme 26) above appears most common, products arising from Pathways B and C involving siloxy carbenes have been reported. Examples of Pathways B and C also exist in the literature for the reaction of ylides with electron-deficient alkenes.\cite{61}

The reaction of a cyclic acyl silane with diethyl fumarate afforded the \textit{trans}-cyclopropane adduct (Scheme 28).\cite{34d} While both a stepwise and concerted mechanism can be envisaged, the concerted [2+2]-cycloaddition process is most feasible here due to the \textit{trans}-isomer being formed exclusively.\cite{62} In the case of acetyl trimethylsilane, the carbene intermediate reacts with electron-deficient alkenes to afford the cyclopropane adduct (Scheme 29).\cite{63} For the reaction with fumarate, the \textit{trans}-cyclopropane was formed exclusively, however, the corresponding reaction with dimethyl maleate was non-stereospecific, affording a 3:2 mixture of \textit{trans/cis} cyclopropanes.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme27}
\caption{Siloxy carbenes react in intra- and intermolecular silyl acylation processes with alkenes and alkynes.}
\end{scheme}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme28}
\caption{Addition of cyclic siloxy carbenes to electron deficient alkenes generates cyclopropanes.}
\end{scheme}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme29}
\caption{Nucleophilic addition of alkyl siloxy carbenes to electron deficient alkenes generates cyclopropanes.}
\end{scheme}

Nucleophilic siloxy carbenes also undergo 1,2-carbonyl addition to aldehydes and ketones (benzoin-type processes). Again, multiple mechanistic pathways are possible and product formation appears to be governed by steric factors associated with the oxocarbenium ion intermediate (Scheme 30).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme30}
\caption{Siloxy carbenes undergo 1,2-carbonyl addition to form a range of products.}
\end{scheme}

In 2018, Kusama and co-workers reported the intermolecular 1,2-carbonyl addition of siloxy carbenes to aldehydes (benzoin reaction). For this process, siloxy carbenes were generated photochemically from acyl silanes and a range of Lewis acids were trialled to increase the reactivity of

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the aldehyde, with zinc(II) iodide (5 mol%) proving to be most effective (Scheme 31).140

This reaction process follows Pathway A as outlined in Scheme 30, with the oxyanion generated following 1,2-carbonyl addition of the nucleophilic carbene, reacting with the proximal silyl group of the oxocarbenium ion to generate a new oxygen-silicon bond and regenerate the carbonyl system. The authors demonstrated that this process can be applied to over 25 examples including both aryl and alkyl acyl silanes and aldehydes in yields ranging from 32-88%.140

[Scheme 31. Lewis acid mediated benzoin reaction of photochemically generated siloxy carbenes with aldehydes]

It has been observed that for alkyl acyl silanes, when exposed to light-irradiation to generate siloxy carbenes, Norrish type II fragmentations can occur leading to unwanted side reactions. To circumvent this during the benzoin reaction outlined above, Kusama and co-workers have demonstrated that the desired carbene intermediates can be accessed via triplet-triplet energy transfer using the photosensitiser [Ir(dF(CF₃)ppy)₂(dbbbpy)]PF₆ (which is commonly utilised to facilitate triplet-triplet energy transfer processes).64 This strategy enables irradiation at a higher wavelength to be employed which suppressed Norrish-type fragmentations of alkanoyl silanes and afforded the desired product in higher yield (Scheme 32).

[Scheme 32. Side reactions could be minimised in the benzoin reaction when the siloxy carbenes were generated via triplet-triplet energy transfer catalysis.]

In the case of cyclic acyl silanes, following initial 1,2-addition of the carbene to the aldehyde due to ring strain the oxyanion intermediate cannot “reach” the silyl motif of the oxocarbenium ion, and as such, reacts at the central carbon of the oxocarbenium ion to form the oxirane in 43% yield (Scheme 33).34d

Such a process can be considered similar to the Corey-Chaykovsky reaction utilised for the synthesis of oxiranes and cyclopropanes using sulfur ylides.65

For one case involving nucleophilic 1,2-carbonyl addition of a siloxy carbene to a ketone, steric factors gave rise to a third pathway whereby the resultant oxyanion intermediate deprotonates the beta-position of the silyl oxocarbenium ion to afford the cyclic silyl enol ether (Scheme 34).34d

[Scheme 33. Nucleophilic addition of cyclic siloxy carbenes to acetaldehyde afforded the oxirane product.]

[Scheme 34. Nucleophilic addition of siloxy carbenes to cyclohexanone afforded the silyl enol ether product.]

The nucleophilicity of siloxy carbenes has also been exploited in reaction with boronic esters (boronates). This process involves initial addition of the nucleophilic siloxy carbene to the boron atom to form the oxocarbenium ion, followed by migration of the phenyl group to afford intermediate I, from which either trans-acetalisation occurs to afford new heterocycle II, or acid-mediated hydrolysis takes place to generate the ketone product (Scheme 35).66

Again, Kusama and co-workers noted that Norrish-type fragmentations of alkanoyl silanes under direct excitation led to reduced efficiency in carbene formation during this reaction process and thus lower yields of the desired product. To overcome this, the use of the photosensitiser and higher wavelengths to form the carbene via a triplet-triplet energy transfer process was successfully able to suppress the unwanted side reactions (Scheme 36).

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Scheme 35. Nucleophilic addition of siloxy carbenes to boronates

Scheme 36. Addition of siloxy carbenes to boronates can be accomplished using a triplet-energy transfer catalyst to mitigate the formation of unwanted by-products.

The ability of siloxy carbenes (generated via 1,2-Brook rearrangement of acyl silanes) to undergo electrocyclisation processes has also been observed. Becker and co-workers reported a 6π-electrocyclisation of ortho-olefinated acyl silanes, prepared via rhodium(III)-mediated alkenylation of aromatic acyl silanes, employing acyl silanes as a weakly coordinating directing group for C-H activation. Following electrocyclisation, a 1,5-sigmatropic shift proposedly occurs to reform the aromatic system, affording a series of silyl enol ether indenes which could be readily hydrolysed to afford the corresponding indanones (Scheme 37).

Scheme 37. Light-mediated electrocyclisation of ortho-olefinated benzoyl silanes.

The electrocyclisation of siloxy carbene derivatives was also reported by Loh and co-workers, who prepared a series of 2-alkenyl indoles via C-H activation, coupling the indole-C2-position with acryloyl silanes. Exposure of these substrates to light facilitated formation of a siloxy carbene intermediate that underwent 6π-electrocyclisation to afford a new 5-membered carbocyclic ring (Scheme 38). Initial isomerisation of the double bond under photochemical conditions was required to enable this electrocyclisation to take place. Subsequent 1,3-retro Brook rearrangement followed by a 1,3-H shift proposedly occurred to afford a series of silicon containing 2,3-dihyrocyclopenta[b]indol-1(4H)-ones in moderate yields.

Scheme 38. Light-mediated electrocyclisation of indole-derived siloxy carbenes

2.2 Amino Siloxy Carbenes

The 1,2-Brook rearrangement of amidoyl or carbamoyl silanes generates the corresponding amino siloxy carbenes. Carbamoyl silanes are typically prepared via deprotonation of a formamide followed by reaction with a silyl chloride. Due to additional resonance contributions provided by the second heteroatom substituent (i.e. NR₂), these carbenes are more stable than the alkyl or aryl siloxy carbenes previously discussed.

Computational analysis of amino siloxy carbenes revealed a ΔEST (i.e. singlet-triplet gap) of approximately -50 kcal/mol and CSE of 88 kcal/mol for the singlet and 23 kcal/mol for the triplet. The enhanced stability of these intermediates is readily apparent by the ease at which these carbenes are generated thermally (typically 60-100°C compared to 210-250°C required for alkyl or aryl substituted acyl silanes). The reactivity of carbamoylsilanes and the corresponding amino siloxy carbenes is discussed in the following section.

In comparison to the alkyl and aryl silanes discussed previously, for a number of processes involving amino siloxy carbenes, the silicon functionality is not incorporated into the final product, however the silyl group is critical for generation of the carbene intermediate and a range of
interesting products can be generated using these silicon reagents.

Chen and co-workers observed that the carbene generated from the 1,2-Brook rearrangement of carbamoyl silanes could insert into the C-H bond of highly electron deficient aromatic systems (Scheme 39). A series of hemi-aminol or amidoyl functionalised aryl and heteroaryl substrates were prepared using this method. Interestingly, in the presence of reactive carbonyl and isocyanate groups, C-H insertion proceeds exclusively over nucleophilic addition to these electrophilic motifs.

Cunico also discovered that the insertion of a carbene derived from carbamoyl silane into the C-H bond of the terminal alkyne methyl propiolate. The carbene readily inserts into the acidic alkynyl C-H bond to afford the siloxy hemi-aminol (Scheme 40, equation 1).

Table 1. Products resulting from 1,4-Michael addition (Stetter type reaction) of amino siloxy carbenes with electron-deficient alkenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Si</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS</td>
<td>Me₂N=S(RMe₂O)₂CO₂Et</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>TBS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>TMS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>TBS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>TMS</td>
<td>Me₂N=S(RMe₂O₂Et)</td>
<td>84</td>
</tr>
</tbody>
</table>

Pathway C as outlined in Scheme 26 has been observed for amino siloxy carbenes where following 1,4-conjugate addition to an electron deficient alkene, the resultant negative charge is further stabilised through resonance forms involving the electron-withdrawing group on the alkene. In these cases, the carboxylate or nitrate intermediates react with the silyl group of the oxocarbenium ion, cleaving the silicon-oxygen bond and regenerating the carbonyl motif (Scheme 41).

Exploiting this unique mechanistic pathway, a range of silicon containing amide derivatives were prepared (Scheme 42).
The carbenes generated from carbamoyl silanes have also been reported to undergo 1,2-addition to ketones, keto-esters, isatins, acid chlorides, imines and iminium ions. For example, Cunico observed the formation of α-siloxyamides following the reaction of amino siloxy carbenes with alkyl or aryl substituted aldehydes and ketones (Scheme 43).[72]

Chen and co-workers described the 1,2-addition of amino siloxy carbenes generated thermally from carbamoyl silanes to α-ketoesters (Scheme 44).[73]

Chen and Cunico also developed a protocol involving addition of nucleophilic carbenes derived from carbamoyl silanes to iminium salts to form the corresponding α-(dimethylamino)amides (Scheme 46, equation 1).[75]

In 2015, Chen and co-workers disclosed two reports describing the addition of carbenes derived thermochemically from either N,N-dimethyl or N-methyl-N-methyl methoxy carbamoyl silane to N-sulfonylimines (Scheme 46, equation 2).[76] Of utility, the methoxymethyl protecting group could be subsequently hydrolysed under acidic conditions to afford the corresponding methyl amide.

The Chen research group have also reported the addition of nucleophilic carbenes generated thermally from carbamoyl silanes with alkyl or aryl substituted N-Boc imines to afford a series of α-aminoamides (Scheme 46, equation 3).[77] Interestingly, the electronic properties of the imine appear to have little effect on the success of the transformation with similar yields obtained regardless of whether an electron donating or withdrawing substituent was present.

The reaction of nucleophilic amino siloxy carbenes with acyl chloride electrophiles was also developed to afford a series of secondary α-ketoamides (Scheme 47, equation 1).[78] More recently this work was extended to include reaction with α-oxo acid. 

Scheme 42. 1,4-addition of amino siloxy carbenes to electron-deficient alkenes followed by silyl abstraction. TBS = tert-butyldimethylsilyl

Scheme 43. Benzoin reaction of amino siloxy carbenes with ketones and aldehydes

Scheme 44. Benzoin reaction of amino siloxy carbenes with ketoesters

Scheme 45. Benzoin reaction of amino siloxy carbene with functionalised isatins

Scheme 46. Aza-benzoin reaction of amino siloxy carbenes with iminium ions and imines
chlorides to afford vicinal tricarbonyl amide derivatives (Scheme 47, equations 2 and 3).

Scheme 47. Reaction of amino siloxy carbenes with acyl chlorides

In 2005, Chen, Pandey and Cunico described their investigations into the diastereoselective formation of \( \alpha \)-aminoamides from carbamoyl silanes possessing a chiral auxiliary (Scheme 48). Moderate yields were typical for this process, however for some substrates a diastereomeric ratio (d.r.) as high as 1:16 was obtained. Further investigations revealed that the diastereoselectivity of this process was enhanced when chiral substituents were present in both the carbamoyl silane and imino substrates, with the best d.r. values obtained when complementary sets of \((S)\)-imines and \((R)\)-carbamoyl silanes were utilized. Overall, with regards to selectivity, the \( N\)-[1-(1-naphthylethyl) derived imines performed better than the \( N\)-(1-phenylethyl) derivatives.

Scheme 48. Diastereoselective addition of amino siloxy carbenes to imines.

The enhanced stability of the amino siloxy carbenes generated from the 1,2-Brook rearrangement of carbamoyl silanes has also been exploited in palladium- and nickel-catalysed coupling reactions with aryl halides, alkyl halides, alkenyl halides and imino chlorides. This type of reactivity correlates with the known ability of \( N\)-heterocyclic carbenes to stabilise metal complexes. The intermediates proposed by Cunico for the palladium-mediated processes are outlined in Scheme 49.

Scheme 49. Proposed intermediates involved in the palladium-catalysed coupling of amino siloxy carbenes

The palladium-catalysed reaction of the carbenes obtained thermochemically from carbamoyl silanes with imidoyl chlorides to afford \( \alpha \)-iminoamides has also been described (Scheme 50, equation 1). Of interest, the reaction requires no additive or base and proceeds readily in THF at 60°C. Cunico and Pandey also reported the palladium-mediated reaction of carbamoyl silanes with alkyl and benzyl halides to afford a series of amide derivatives (Scheme 50, equation 2). Of interest, the authors also described attempts to form analogous benzyllamides using pseudo halides such as benzyl trifluoroacetates (in place of benzyl halides) in the presence of a palladium catalyst however the only product formed was a result of nucleophilic 1,2-carbonyl addition of the carbene to the carbonyl of the trifluoroacetate group (Scheme 51).

Scheme 50. Palladium-mediated coupling of amino siloxy carbenes

Scheme 51. Attempted cross-coupling of amino siloxy carbenes with pseudohalides resulted in 1,2-carbonyl addition of carbene to the ester.

Chen and co-workers discovered a nickel-catalysed aminocarbonylation of aryl halides using carbamoyl silanes as an amide source (Scheme 52). Using tetrakistriphenylphosphine nickel (0) in toluene at
elevated temperatures, a large series of benzamide derivatives were accessed.

[Chemical structure image]

Scheme 52. Nickel-mediated coupling of amino siloxy carbenes with aryl halides

A related reaction with aryl bromides and aryl chlorides was also developed by Chen employing a palladium (0) catalyst in toluene at 100°C (Scheme 53, equation 1). Under these conditions, for some substrates hydrolysis of the methoxymethyl ether group took place to afford the methylimide adduct.[83] Cunico and Maity also demonstrated that alkenyl and alkynyl halides were suitable coupling partners for the palladium-mediated amidation process with carbamoyl silanes, with selected examples outlined in Scheme 53, equations 2 and 3.[81]

[Chemical structure image]

Scheme 53. Palladium-mediated coupling of amino siloxy carbenes with aryl, alkenyl and alkynyl halides

3.0 Conclusion

Acyl and amidoyl silanes undergo photochemical or thermally initiated 1,2-Brook rearrangement to generate basic and nucleophilic siloxy carbone intermediates. Siloxy carbenes display unique reactivity including the ability to insert into C-H bonds, undergo 1,2-carbonyl and 1,4-conjugate addition and participate in transition-metal mediated cross-coupling reactions.

Siloxy carbone intermediates offer significant value by enabling access a wide variety of substrates that contain useful silyl functionality. These carbone reagents also represent useful model substrates to explore the reactivity and properties of singlet nucleophilic carbenes. Furthermore, reaction processes involving siloxy carbone intermediates typically only require the use of light to activate the substrates, eliminating the need for additional catalysts or additives.

It is hoped that this review draws attention to the synthetic utility and potential of silicon-derived carbone reagents in organic synthesis and inspires other research groups to explore these intriguing reactive intermediates.

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References

REVIEW

Silicon-Derived Singlet Nucleophilic Carbene Reagents in Organic Synthesis


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where Si = -SiR₃ or -OSiR₃
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