Review

From Alkynes to Heterocycles through Metal-Promoted Silylformylation and Silylcarbocyclization Reactions

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Abstract: Oxygen and nitrogen heterocyclic systems are present in a large number of natural and synthetic compounds. In particular, oxo- and aza-silacyclic, tetrahydrofuran, benzofuran, cycloheptadifuranone, cycloheptadipyrrrole, pyrrolidine, lactone, lactam, phthalan, isochromanone, tetrahydroisquinolinone, benzoindolizidinone, indoline and indolizidine scaffolds are present in many classes of biologically active molecules. Most of these contain a C=O moiety which can be easily introduced using carbonylative reaction conditions. In this field, intramolecular silylformylation and silylcarbocyclization reactions may afford heterocyclic compounds containing a carbonyl functional group together with a vinylsilane moiety which can be further transformed. Considering these two aspects, in this review a detailed analysis of the literature data regarding the application of silylformylation and silylcarbocyclization reactions to the synthesis of several heterocyclic derivatives is reported.

Keywords: silylformylation; silylcarbocyclization; alkynes; N-heterocycles; O-heterocycles

1. Introduction

The silylformylation reaction of terminal acetylenic compounds [1–5] consists of the simultaneous introduction of a trialkysilylgroup and a formyl moiety into a carbon–carbon multiple bond (Scheme 1). The reaction takes place with total regio- and stereoselectivity, -CHO and -SiR₃ being added syn to the triple bond with the formyl group bonded to the carbon atom connected to the alkyl chain.

Scheme 1. General scheme of silylformylation reaction.

This reaction represents an extension of the well-known hydroformylation process [6–15], where the H₂ molecule is replaced by a hydrosilane. Since the first study of Matsuda et al. that appeared in 1989 [16], the silylformylation of triple bonds has been extensively studied as it provides a direct route to the synthesis of β-silylalkenals. Many different rhodium catalysts have been found to be effective in the alkynes silylformylation. Rh₄(CO)₁₂ is the most widely used species [16–19], but also Rh(I) [20,21], Rh(II) [22–24] and bimetallic Rh-Co [25–29] complexes were employed. Moreover, Doyle investigated the catalytic activity of Rh₂(pfb)₄ (perfluorobutyrrate) [30,31] in the silylformylation of terminal alkynes, Alper developed a zwitterionic species, (η⁶-C₆H₆BPh₃)⁺Rh⁺(1,5-COD) (Rh⁺sw) [32–34] and Aronica et al. [35] showed that rhodium nanocluster, obtained by Metal Vapor Synthesis (MVS)

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technique could be able to catalyze the silylfomylation of linear and branched acetylenes. It is worth noting that silylfomylation of alkyynes is generally tolerant of many functionalities such as ethers, esters, alcohols, ketones, aldehydes, amines, nitriles, chlorines, bromines and double bonds [18,26,30,33,36,37].

Many applications of the silylfomylation of terminal acetylenes have been carried out. In organic synthesis, this process represents an ideal route to many organic compounds because of its high regio and stereoselectivity. It provides β-silylalkenals, which can be easily transformed into silylsubstituted dienes, dienones, α,β-unsaturated ketones and alcohols [35–42], and can be important precursors for the synthesis of more complicated molecules via Peterson olefination [43] or Nazarov-type annulation [44,45]. Finally, fluoride promoted aromatic ring migration from the dimethylarylsilyl moiety to the adjacent carbon atom of the β-silylalkenal yields 2-(arylmethyl)alkanals (Scheme 2) [18,19,46].

Scheme 2. Fluoride-promoted aryl rearrangement of β-silylalkenals: synthesis of 2-(arylmethyl)alkanals.

The “cyclic” version of silylfomylation reaction may occur into two different ways: (1) intramolecular silylfomylation of ω-silylacetylenes, giving the corresponding silacyclocalkanes; (2) silylcarbocyclization reactions (SiCaC) of suitable alkenynes, involving the formation of cyclic compounds together with the insertion of a silane and a -CHO functional groups. Therefore, the content of this review will be divided into two sections: the first is dedicated to giving a detailed description of intramolecular silylfomylation reactions, while the second is centered on the silylcarbocyclization of functionalized acetylenes. In each section we will give particular emphasis to the heterocycles which can be obtained as well as a special look to the used metal catalysts.

2. Heterocycles Synthesis via Metal-Catalyzed Intramolecular Silylfomylation of Alkyynes

2.1. The Intramolecular Silylfomylation of ω-Silylalkynes: Synthesis of Silacyclocanes

The first example of intramolecular silylfomylation reaction of acetylenes was reported by Alper and Matsuda in 1995 [47]. Pent-4-ynylnmethylphenylsilane (Scheme 3, n = 1, R1 = Me, R2 = Ph, R3 = H) was initially treated with triethylamine (1.0 equiv.), a catalytic amount of a rhodium catalyst under CO atmosphere (20 atm) and quite mild experimental conditions (40 °C, 24 h). Both the zwitterionic complexes (η⁶-C₆H₆BPh₃)⁺Rh⁺(1,5-COD) (Rh₃) and Rh₃(CO)₁₂ were effective, giving the corresponding aldehyde in good yields. According to Baldwin’s rules [48,49], only the exo-dig cyclization occurred, generating 2-(formylmethylene)-1-silacyclocalkanes with complete regio and stereoselectivity. None of the products derived from an endo-dig-mode cyclization or an intermolecular silylfomylation were produced.

Scheme 3. First example of intramolecular silylfomylation reaction of acetylenes reported by Alper and Matsuda.
The same trend was observed in the case of hexynylsilanes (Scheme 3, n = 2), which afforded the corresponding six ring silacycloalkanes. The yield of aldehyde was affected by the nature of R1R2HSi-group connected to the alkyl chain: higher product amounts were isolated when alkynylmethylphenylsilanes (Scheme 3, R1 = Me, R2 = Ph) were reacted rather than alkynylidiphenylsilanes. The intramolecular silylformylation proceeded smoothly also for internal alkynylsilanes (Scheme 3, R1 = Et, n-Bu, Ph) regardless of the alkyl and aryl substituent. Thus, this method provides a vehicle for complete regio- and stereoselective formylation of acetylenic bonds.

The general mechanism proposed by the authors (Scheme 4, X = CH2) involved initially an oxidative addition of Si-H to the rhodium catalyst, cis addition of the Rh-Si species to the triple bond followed by CO insertion into the Rh—C bond and reductive elimination with regeneration of the catalyst and formation of the -CHO group.

![Scheme 4. General mechanism for intramolecular silylformylation reactions.](image)

A few years later, Aronica and co-workers investigated the reactivity of both linear and C3-branched 6-(methylphenylsilyl)-1-hexynes [50]. Linear substrate was first tested in the intramolecular silylformylation reaction, promoted by both zwitterionic Rhsw and covalent complexes such as Rh(acac)(CO)2 and Rh4(CO)12. In all cases, pure aldehyde was obtained in good yields with complete regioselectivity, i.e., exclusive addition of the -CHO moiety to terminal sp-carbon atom (Scheme 5).

![Scheme 5. Intramolecular silylformylation reaction of linear ω-silylacetylenes.](image)

As a consequence, the air-stable Rhsw species was used in subsequent reactions of C3-branched acetylenes. As is evident from Scheme 6, the presence of an -R group did not influence the regioselectivity of the process, which afforded exocyclic isomers exclusively. On the other hand, when a bulky substituent, such as a tert-butyl group, was bonded to the alkyl chain, higher CO pressure (50 atm) and longer reaction times (48 h) were required to improve the yield of the silacyclane. One of the most interesting features of these reactions concerns the stereoselectivity: the presence of two chiral centers (i.e., Si* and C*-R) involved the possible formation of two different diastereomers, cis and trans. Unexpectedly, if a mixture of both isomers was obtained for the intramolecular silylformylation of 3-methyl-6-(methylphenylsilyl)-1-hexyne (Scheme 6, R = Me), the cyclization involving the tert-butyl derivative (Scheme 6, R = t-Bu) afforded the trans product exclusively.
with that of conventional organometallic compounds, high regio and diasteroselectivity being observed also in this case. Silacycloalkanes have been investigated as new and promising pharmaceutical substances [54]. Some of them have been tested as agents acting on the nervous system and showed activity as antitremorine compounds and gave promising results in the treatment of depression. Moreover, silicon derivatives were also proposed for the treatment or prevention of psoriasis and panic disorder. Some silacyclic derivatives exhibited high cytotoxicity and a broad spectrum of fungicidal activity. Finally, silacyclane compounds have been investigated as odorants since they showed quite different olfactory properties with respect to their carbon analogs, thus opening new possibilities for the fragrance industry.

2.2. The Intramolecular Silylformylation of \( \omega \)-Bis(Dimethylsilylamo)alkynes: Synthesis of Azasilacyclanes

The only example of intramolecular silylformylation of dimethylsilylamoacetylenes was reported by Ojima and Vidal [55]. As a model reaction they reacted 1-bis(dimethylsilylamo)-3-octyne with CO in the presence of three different Rh-Co catalysts (Scheme 7). Unfortunately, the obtained azasilacyclopentane was highly unstable. Nevertheless, the authors observed that a stable product was generated by removing the silyl group connected to the nitrogen atom with NaBH\(_4\) with contemporary reduction of the -CHO moiety.

\[
\begin{align*}
\ce{C≡C-Bu & 60°C, CO & [Rh] \rightarrow & BuN-SiMe_2H_2 & [Rh] = Rh(acac)(CO)_2, (t-BuNC)_2RhCo(CO)_4, Rh_2Co_2(CO)_12} \\
\end{align*}
\]

Scheme 7. Intramolecular silylformylation/desilylation of 1-bis(dimethylsilylamo)-3-octyne.

Thus coupling the silylformylation together with the reduction/desilylation step, azasilacyclopentane and cyclohexane were obtained in high yields, as depicted in Scheme 8.

\[
\begin{align*}
\text{R} & \quad (52\%-80\%) \\
\text{n} & \quad (1) \ 60°C, \text{CO} \ 50 \text{ atm, [Rh]} \\
\text{n} & \quad (2) \ \text{NaBH}_4 \\
\ce{C≡C-R & R = Bu, Ph \rightarrow & R-SiMe_2HNCH_2OH & \[Rh] = Rh(acac)(CO)_2, (t-BuNC)_2RhCo(CO)_4, Rh_2Co_2(CO)_12} \\
\end{align*}
\]

Scheme 8. Intramolecular silylformylation/desilylation reaction of bis(silyl)amino-alkynes.
Similar experimental conditions (60 °C, 10 atm CO, 14 h, Rh(acac)(CO)$_2$(t-BuNC)$_4$R(CO)$_4$ or Rh$_2$Co$_2$(CO)$_{12}$, then NaBH$_4$) were also applied to the intramolecular silylformylation/desilylation of (dimethylsilylamino)hexynylcyclohexane and cyclopentane derivatives which, after treatment with NaBH$_4$, gave the corresponding azasilabicycloalkanes (Scheme 9).

![Scheme 9](image)

**Scheme 9.** Intramolecular silylformylation reaction of (dimethylsilylamino)hexynylcycloalkanes.

Surprisingly, when a dimethylsilyl group was replaced by a diphenylsilyl group, intramolecular silylformylation afforded the corresponding silapiperidine product in 63% isolated yield (Scheme 10).

![Scheme 10](image)

**Scheme 10.** Synthesis of 1,1-diphenyl-2-silyl-6-(1-formyl-1-benzylidene)azasilacyclohexane via intramolecular silylformylation reaction.

### 2.3. The Intramolecular Silylformylation of ω-Silyloxyalkynes: Synthesis of Oxasilacyclanes

In 1995, Ojima and co-workers described the first case of intramolecular silylformylation of terminal and internal alkynes featured by a dimethylsiloxy moiety as a directing group [56]. In agreement with the intramolecular silylformylation of ω-silylacetylenes, complete regio- and stereoselectivity was observed. Cyclization reactions of ω-(dimethylsiloxy)-alkynes were carried out in the presence of (t-BuNC)$_4$RhCo(CO)$_4$, Rh$_2$Co$_2$(CO)$_{12}$ or Rh(acac)(CO)$_2$ as catalyst, in toluene at 60–70 °C for 3–14 h to give the corresponding 3-exo-(1-formylalkylidene)oxasilacycloalkanes (Scheme 11). Both oxa-silacyclopentanes (Scheme 11, n = 1) and oxa-silacyclohexanes (Scheme 11, n = 2) were achieved in good yields regardless of the nature of the catalyst.

![Scheme 11](image)

**Scheme 11.** First example of intramolecular silylformylation reaction of ω-(dimethylsiloxy)alkynes.

The intramolecular silylformylation was applicable also to cyclic systems. Indeed, the same authors tested the reactivity of O-(dimethylsilyl)-2-ethynyl and 2-propynyl derivatives depicted in...
Scheme 12 [56]. All reactions proceeded smoothly at 65 °C and 10 atm CO, with (t-BuNC)RhCo(CO)4 as the best catalyst.

Scheme 12. Intramolecular silylformylation of cyclic O-(dimethylsilyl)-2-ethynyl and propynyl derivatives.

As solvated metal atoms prepared according to the MVS technique had revealed high reactivity and selectivity in silylformylation reactions [35], it was interesting to verify the catalytic activity of these species in the intramolecular processes of 2-(dimethylsiloxy)-4-nonyne derived from a homopropargyl alcohol. Complete regio/stereoselectivity was observed: 3-[(1′-formylpentylidene)-1-oxa-2-silacyclopentane was obtained in high yield (86%) (Scheme 13) [57].

Scheme 13. Intramolecular silylformylation of 2-(dimethylsiloxy)-4-nonyne promoted by a Rh/mesitylene obtained via the Metal Vapor Synthesis (MVS) technique.

A few years later, starting from dimethylsiloxyalkadiynes, Bonafoux and Ojima developed a process of desymmetrization based on a single intramolecular silylformylation reaction [58]. As described in Scheme 14, Rh(acac)(CO)2 was effective in promoting the reactions of terminal and internal alkynes at room temperature and under 10 atm of carbon monoxide. Both cyclizations took place smoothly but 5-exo(formylmethylene)oxacyclopentane (Scheme 14, R = H) could not be purified as it decomposed when subjected to silica gel chromatography. Reduction of the formyl moiety with NaBH4 afforded the corresponding alcohol, isolated in good yield (70%). The highly functionalized cyclic products thus obtained represent useful synthetic intermediates, since they can be manipulated at the unreacted acetylene moiety as well as at the -CHO or -CH₂OH functional groups.

Scheme 14. Desymmetrization of dimethylsiloxyalkadiynes based on intramolecular silylformylation reaction.

The same authors also described a three-steps protocol for the synthesis of 5-(2-acetoxyalkyl)-2-oxa-1-silacyclopentenes [59]. The sequence started with the intramolecular silylformylation of ω-(dimethylsiloxy) alkynes, followed by reduction of the corresponding aldehyde to give 5-exo-(hydroxyethylene)-2-oxa-1-silacyclopentanes. Subsequent DMAP-catalyzed treatment of the obtained alcohols with acetic anhydride involved a skeletal rearrangement which afforded the corresponding oxasilacyclopentenes exclusively (Scheme 15).
Moreover, the authors observed that when O-dimethylsilylethynlycyclohexanol was submitted to the same transformations, 2-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-3-yl)cyclohexyl acetate was isolated in 76% yield (Scheme 16). The rearrangement products containing an acylated moiety together with an oxasilacyclopentene nucleus could be employed as useful polyfunctionalized intermediates in organic chemistry.

Another interesting application of oxa-silacyclopentanes was reported in 2003 by Denmark and Kobayashi [60]. First, intramolecular silylformylation of alkynyloxyhydrosilanes was carried out under CO pressure (10 atm) at 70 °C. (t-BuNC)₄RhCo(CO)₄ showed the best catalytic efficiency, affording the five-membered cyclic silyl ethers in 72% yield. (Scheme 17, step 1). With the (1-formylalkylidene)oxasilacycloalkanes in hands, authors investigated the possible cross-coupling of heterocyclic compounds. Initially, a deep investigation on the experimental conditions was performed: DMF resulted as the best solvent, the combination of [(allyl)PdCl₂] and CuI the optimal catalytic species and KF was chosen as a fluoride source. Then, oxa-silacyclopentanes were reacted with several aromatic iodides affording the corresponding α,β-unsaturated aldehydes (Scheme 17, step 2). Electrophiles with electron donating groups reacted more slowly than those bearing electron-withdrawing moieties, and the reaction of the cyclic silyl ether possessing a methyl group on the alkene was slower than the reaction of the terminal derivative. Nevertheless, cross-coupling products were achieved in good to excellent yields (57–93%).

Finally, Leighton and co-workers developed several sequential approaches to polyol derivatives via oxa-silacyclanes intermediates, which were generated in situ and then converted into polyketides fragments by means of Tamao oxidations (Scheme 18) [61–67].
3. Heterocycles Synthesis via Metal-Catalyzed Silylcyclocyclization of Alkynes

As well shown in the previous section, intramolecular hydrosilylation and silylformylation reactions of alkynes represent a valid route to several types of highly functionalized silcycles. Silylcyclocyclization (SiCAC) protocols are instead a different synthetic approach to heterocyclic compounds: these transition metal-catalyzed tandem addition/cyclization reactions of alkynes with hydrosilanes, often performed under carbonylative atmosphere, are very useful for obtaining highly functionalized heterocycles bearing exocyclic silyl moieties, sometimes amenable for further one-pot synthetic transformations.

The first silylcyclocyclization was serendipitously discovered by Ojima et al. in 1991: during their studies on the silylformylation of 1-hexyne with triethylsilane, carried out in the presence of Co$_2$Rh$_2$(CO)$_{12}$ as catalyst, in addition to the usual hydrosilylation and silylformylation products they observed a small amount of 2,4-dibutyl-3-(triethylsilyl)-cyclopent-2-en-1-one (Scheme 19) [25]. However, only mechanistic studies performed in a following paper better clarified the origin of this cyclic product: a metal-promoted silylformylation of 1-hexyne gave the β-silylacryloyl-metal intermediate (II), which in turn then provided a carbometalation on a second 1-hexyne molecule to generate (III); after the following carbocyclization and β-hydride elimination steps, a highly regioselective reduction of intermediate (IV) took place at the less sterically hindered double bond; finally, a hydrogen-metal exchange between species (V) and a further triethylsilane molecule gave the final cyclopentenone product (Scheme 19) [26].

Several synthetic applications of silylcyclocyclization reactions have been previously treated as part of more general reviews, focused on the transition metal-promoted cyclizations [68–70] or on the chemistry of hydrosilanes with alkynes [27]; however, a complete and up-to-date overview of SiCAC protocols for the preparation of heterocycles is still missing. Therefore, in the second part of the present review we shall try to provide an exhaustive and critical account of this literature, giving special emphasis on the adopted catalytic systems.

Silylcyclocyclization reactions applied to the synthesis of heterocyclic compounds can be divided into three main groups, depending on the starting alkynes: (i) standard silylcyclocyclizations, mainly involving allyl proparyl and dipropargyl ethers/amines, which gave in most cases tetrahydrofuran and pyrrolidine derivatives (Scheme 20, path a); (ii) cascade silylcyclocyclizations, involving instead enediyne and triynes with a suitable chemical structure, which led to the formation of fused tricyclic structures (Scheme 20, path b); (iii) heteroatom-promoted silylcyclocyclizations, involving ethynyl alcohols and amines, where lactones and lactames were obtained (Scheme 20, path c). The literature will be organized below following this systematic approach.
Silylcarbocyclizations of alkynes represent the most common synthetic approach to heterocycles based on SiCAC protocols and involve two main classes of substrates: enynes (i.e., allyl propargyl ethers and amines) and diynes (i.e., dipropargyl ethers/amines). In particular, SiCAC of allyl propargyl ethers and amines allow the formation of (triorganosilyl)methylene)pyrrolidine scaffolds, respectively; instead, SiCAC of dipropargyl ethers/amines leads to the formation of fused tricyclic structures.

Scheme 19. First example of silylcarbocyclization reaction reported by Ojima and co-workers (a) and related reaction mechanism (b).

Scheme 20. Classification of SiCAC reactions: (a) standard silylcarbocyclizations, involving allyl propargyl and dipropargyl ethers/amines (Section 3.1); (b) cascade silylcarbocyclizations, involving enediynes and triynes (Section 3.2); (c) heteroatom-promoted silylcarbocyclizations, involving ethynyl alcohols/amines (Section 3.3).

3.1. Synthesis of Heterocycles via Metal-Catalyzed Standard Silylcarbocyclizations of Alkynes

Transition metal-catalyzed standard silylcarbocyclizations of alkynes represent the most common synthetic approach to heterocycles based on SiCAC protocols and involve two main classes of substrates: enynes (i.e., allyl propargyl ethers/amines) and diynes (i.e., dipropargyl ethers/amines). In particular, SiCAC of allyl propargyl ethers and amines allow the formation...
of 3-(triorganosilylmethylene)tetrahydrofuran and 3-(triorganosilylmethylene)pyrrolidine scaffolds, respectively; instead, SiCAC of dipropargyl ethers and amines often lead to more complicated cyclopentafuranone and cyclopentapyrrolone derivatives, although in some cases functionalized tetrahydrofurans/pyrrolidines or piperidinones were also obtained. In general, standard SiCACs proceed successfully with both alkyl and aryl silanes, often performed under CO (at atmospheric or high pressure) and using rhodium or rhodium-cobalt complexes as catalysts.

### 3.1.1. Standard Silylcyclobicyclizations of Allyl Propargyl Ethers/Amines

The first investigation on standard silylcyclobicyclization of allyl propargyl ethers and amines was reported in 1992 by Ojima and co-workers [71]. They described the reaction of allyl propargyl ether with dimethylphenylsilane, performed in toluene at 70 °C and under CO pressure (1 atm), in the presence of Rh$_4$(CO)$_{12}$ as catalyst: 3-(silylmethylene)-4-methyltetrahydrofuran was obtained in 61% yield after 18 h. Interestingly, the same product was obtained in higher yields (85%) using Rh(acac)(CO)$_2$ as the catalytic system and under N$_2$ atmosphere, thus demonstrating that standard SiCAC reactions do not strictly require carbon monoxide. A three-step mechanism was hypothesized for this transformation, consisting of silylmethylation of the triple bond, cyclocyclization and H-shift (Scheme 21). In the same paper, the authors also described a similar SiCAC reaction for diallyl propargyl amine with PhMe$_2$SiH (Rh(acac)(CO)$_2$, CO 1 atm, 70 °C), which gave the corresponding pyrrolidine as the only product in almost quantitative yield.

**Scheme 21.** SiCAC of allyl propargyl ether with Me$_2$PhSiH: 3-(silylmethylene)-4-methyltetrahydrofuran was obtained through a three-steps mechanism, i.e., silylmethylation, cyclocyclization and H-shift.

In a following paper, the same group extended standard SiCAC to a more structurally complex allyl propargyl ether [72]. Working under the same conditions of their previous work (1.0 equiv. of Me$_2$PhSiH, 1 mol% of Rh(acac)(CO)$_2$, 1 atm of CO, at 50 °C in toluene), the expected SiCAC product was recovered as a mixture with the corresponding carbonylative SiCAC (namely, CO-SiCAC) derivative, arising from a carbon monoxide insertion between the cyclocyclization and H-shift steps. Interestingly, a fine tuning of the experimental conditions may influence the product selectivity: when the reaction was run in n-hexane 1 M under 1 atm of CO, the only SiCAC product was isolated in 60% yield; instead, in THF 0.07 M with 2.6 atm of CO, the CO-SiCAC product was found the most predominant compound in 95% yield (Scheme 22).

In 2002 Ojima et al. reported a more detailed investigation on Rh-catalyzed SiCAC of enynes, with special focus on allyl propargyl amines for the synthesis of pyrrolidine derivatives [73]. Analogous to their previous work on hepta-1,6-dien-4-yl propargyl ether [72], the selectivity toward SiCAC or CO-SiCAC products can be controlled depending on the experimental conditions, while always working with 0.5 mol% of Rh$_4$(CO)$_{12}$ as catalyst: with an excess (1.5 equiv.) of hydrosilane at 0.4 M concentration in n-hexane, at 22 °C under atmospheric pressure of CO, the corresponding SiCAC products were surprisingly obtained in less than 1 min (yields: 74–89%).
The exclusive formation of CO-SiCAC pyrrolidines (56–85% yields) was instead found by using an almost equimolar amount of silane (1.05 equiv.) at 0.02 M concentration in 1,4-dioxane, under 20 atm of CO at 105 °C, in the presence of 10 mol% of P(OEt)$_3$ as ligand (Scheme 23). Since high reactants dilution is not advantageous in organic synthesis, authors also investigated a further optimization of the protocol for obtaining CO-SiCAC products: the amine solution in 1,4-dioxane was cooled before the addition of Rh$_4$(CO)$_{12}$, hydrosilane and P(OEt)$_3$; then, the frozen reaction mixture was placed in autoclave and pressurized with CO (20 atm). This “freeze and CO” protocol was able to block the SiCaC reaction by freezing the reaction to start until the whole system is under high carbon monoxide pressure, thus favoring the formation of the CO-SiCaC product.

Matsuda et al. also reported an interesting study on rhodium-catalyzed standard silylcarbocyclization of 1,6-enynes, including allyl propargyl ethers and amines, working under the same conditions of their previous work (1.0 equiv. of Me$_2$PhSiH) [72,73]. Interestingly, the same product was obtained in higher yields (85%) using Rh(acac)(CO)$_2$ as catalyst: with an excess (1.5 equiv.) of hydrosilane at 0.4 M concentration in n-hexane, performed in toluene at 70 °C and under CO pressure (20 kg/cm$^2$). In the same paper, working with Rh$_4$(CO)$_{12}$ or Rh(acac)(CO)$_2$ catalysts under high CO pressure (20 kg/cm$^2$) they usually obtained the selective formation of the CO-SiCaC product; however, in the case of allyl propargyl benzylamine the SiCaC pyrrolidine compound was obtained as the sole product under the same experimental conditions. Although the authors did not provide any explanation for this result, they believe that the role of benzyl substituent on the nitrogen atom is crucial for explaining this different reactivity.

In 2003, Chung and collaborators proposed the first application of a supported and recoverable catalyst in silylcarbocyclization reactions, i.e., bimetallic Co/Rh nanoparticles immobilized on charcoal [75]. The supported catalyst was very easily prepared by refluxing Co$_2$Rh$_2$(CO)$_{12}$ with charcoal in THF, giving the final material with a fixed 2:2 cobalt-rhodium stoichiometry. It was then successfully employed in the standard SiCaC of a large family of 1,6-enynes, including allyl propargyl ethers bearing internal acetylene and/or alkene moieties: in particular, working with a large excess (5.0 equiv.) of hydrosilane at 105 °C in 1,4-dioxane under atmospheric pressure of CO, the corresponding CO-SiCaC products were obtained (23–87% yields) after 12 h; instead, SiCaC THF derivatives were recovered in satisfactory yields after only 2 h by using the same excess of hydrosilane, in n-hexane as solvent at 22 °C and without carbon monoxide atmosphere (Scheme 24). Therefore,
the present standard silylcarbocyclization protocol appears quite interesting, both for milder reaction conditions of CO-SiCAC pathways (often requiring high CO pressure and reagents concentration) and for catalyst recyclability.

In 2007, Denmark et al. developed a sequential Rh-catalyzed silylcarbocyclization protocol for the synthesis of more complex heterocyclic compounds, including biologically active products. In 2006, Murai et al. reported an extended investigation on the synthesis of 1,2,3-trisubstituted pyrrolidines and piperidines through the reaction of thioiminium salts (derived from the addition of lithium acetylides to \( \gamma \) - and \( \delta \) -thio lactams) with proper Grignard reagents [76]. In order to show the synthetic applicability of the obtained compounds, \( \gamma \)-allyl-2-ethyl-1H-pyrazines and octahydroindolizines were then also subjected to standard silylcarbocyclization: reactions were performed with \( \text{Rh}_2(\text{CO})_{12} \) (0.5 mol\%) as catalyst and \( \text{Me}_2\text{PPhSiH} \) (1.5 equiv.) as silane, in \( n \)-hexane under CO atmosphere and at room temperature. In the case of pyrrolidines, SiCAC afforded 1,2,7a-trisubstituted hexahydro-1H-pyrazolines as a mixture of four diastereomers, the stereochemistry of which was identified by NOESY spectroscopy; instead, standard SiCAC of piperidine reagents gave 1,2,8a-trisubstituted octahydroindolizines as a mixture of only two diastereomers (Scheme 25).

In 2007, Denmark et al. developed a sequential Rh-catalyzed silylcarbocyclization/Pd-catalyzed Hiyama cross-coupling protocol for the synthesis of highly functionalized tetrahydrofuran and pyrrolidine derivatives [77]. The first step was applied to 1,6-enynes, including allyl propargyl ethers and amines, under typical SiCAC conditions: \( \text{Rh}_2(\text{CO})_{12} \) (0.5–5 mol\%) as catalyst, an excess

Scheme 24. Standard silylcarbocyclization of allyl propargyl ethers bearing internal acetylene and/or alkene moi eties, catalyzed by Co/Rh nanoparticles immobilized on charcoal.

Scheme 25. Standard silylcarbocyclization of \( N \)-allyl-2-ethynyl-2-substituted pyrrolidines and piperidines: synthesis of hexahydro-1H-pyrazolines and octahydroindolizines.
with well-recognized properties as neuroexcitatory agents [78, 79].

In 1992, they reported the first attempt of SiCAC on allyldipropargylamine as starting substrate [71]. The reaction was performed with HSiEt$_3$ (0.25 mol%) as catalyst, in toluene at 65 °C and 50 atm of carbon monoxide: after 48 h, a bicyclic compound incorporating two CO units was obtained as a predominant product (62% yield), together with a small amount (<2% yield) of a piperidone derivative arising from a single CO incorporation. Interestingly, when the same reaction was performed with the more common Rh$_2$(dba)$_3$ catalyst and under atmospheric CO, the same piperidone was found as the sole product in good yields (81%). The proposed mechanism involved the silylmetalation of an alkynyl moiety of starting allyldipropargylamine, followed by CO insertion and carbocyclization steps; the obtained intermediate may then follow two different pathways: (i) second CO insertion and carbocyclization steps, followed by β-hydride elimination of [M]H, regioselective addition of [M]H and regeneration of Et$_3$Si[M], affording a final bicyclic SiCAC product; (ii) hydrosilylation of a second molecule of silane, followed by Et$_3$Si[M] regeneration to give the final piperidone derivative (Scheme 27).

In a following paper, authors used very similar experimental conditions for the (t-BuNC)$_4$RhCo(CO)$_3$ catalyzed Hiyama cross-coupling of allyl propargyl ethers and amines.

### 3.1.2. Standard Silylcarbocyclizations of Dipropargyl Ethers/Amines

Mostly investigated by the Ojima’s group, standard silylcarbocyclizations of dipropargyl ethers and amines represent a useful and rapid tool for obtaining O- and N-containing bicyclic compounds (especially cyclopentafuranone and cyclopentapyrrolone derivatives).

In 1992, they reported the first attempt of SiCAC on allyldipropargylamine as starting substrate [71]. The reaction was performed with HSiEt$_3$ (3.0 equiv.) in the presence of bimetallic (t-BuNC)$_4$RhCo(CO)$_3$ (0.25 mol%) as catalyst, in toluene at 65 °C and 50 atm of carbon monoxide: after 48 h, a bicyclic compound incorporating two CO units was obtained as a predominant product (62% yield), together with a small amount (<2% yield) of a piperidone derivative arising from a single CO incorporation. Interestingly, when the same reaction was performed with the more common Rh$_4$(CO)$_{12}$ catalyst and under atmospheric CO, the same piperidone was found as the sole product in good yields (81%). The proposed mechanism involved the silylmetalation of an alkynyl moiety of starting allyldipropargylamine, followed by CO insertion and carbocyclization steps; the obtained intermediate may then follow two different pathways: (i) second CO insertion and carbocyclization steps, followed by β-hydride elimination of [M]H, regioselective addition of [M]H and regeneration of Et$_3$Si[M], affording a final bicyclic SiCAC product; (ii) hydrosilylation of a second molecule of silane, followed by Et$_3$Si[M] regeneration to give the final piperidone derivative (Scheme 27).

In a following paper, authors used very similar experimental conditions for the (t-BuNC)$_4$RhCo(CO)$_3$ or Co$_2$Rh$_2$(CO)$_{12}$ catalyzed SiCAC of benzylidipropargylamine with t-butylidimethylsilane [80]: surprisingly, 7-azabicyclo[3.3.0]oct-1-ene was found (60% yield), together with small amounts of its Δ$^{1,5}$-isomer, which can be easily converted into 7-azabicyclo[3.3.0]oct-1-ene by in situ treatment with RhCl$_3$·3 H$_2$O at 50 °C. A plausible mechanism involved the starting silylmetalation of a triple bond with t-BuMe$_2$SiH, followed by a sequence of carbocyclization, CO insertion and carbocyclization to give the bicyclic intermediate $\mathbf{A}$, from which both final products can be obtained: (i) through a sequential β-hydride elimination, regioselective hydrometallation and β-hydride elimination, 7-azabicyclo[3.3.0]oct-1-ene was obtained; (ii) its Δ$^{5}$-isomer was instead obtained with a 1,3-[M] shift step, followed by the regeneration of Et$_3$Si[M] (Scheme 28) [81].
Scheme 27. First report of standard SiCAC of dipropargyl amines: two different mechanistic pathways afforded a bicyclic compound incorporating two CO units (i) or a piperidone derivative incorporating a single CO unit (ii).

Scheme 28. Standard silylcyclocyclization of benzyldipropargylamine with t-butyldimethylsilane and proposed reaction mechanism.
However, a more extensive and detailed investigation on standard SiCAC of dipropargyl ether and amines was reported in 1998 by the same research group, performed by testing different substrates, Rh catalysts and experimental conditions [82]. Interestingly, they found that carbon monoxide pressure is a very critical parameter: working under high CO pressure (15–50 atm), SiCAC reactions proceeded as previously described [80,81] to afford heterobicyclo[3.3.0]octenones in good yields; instead, under ambient carbon monoxide pressure reactions occurred in a different way, affording tetrahydrofuran or pyrrolidine derivatives as final products (Scheme 29). In this last case, the CO insertion does not occur after the silylmetallation and carbocyclization steps, therefore a hydride shift and a subsequent 1,2- and/or 1,4-hydrosilylation can give final heterocyclic products.

![Scheme 29. Ojima's investigation on standard SiCAC of dipropargyl ether and amines.](image)

In addition to the extensive studies performed by the Ojima’s research group, standard SiCAC of dipropargyl ethers/amines were also investigated by Matsuda et al. [83]: reactions were performed with 0.5 mol% of Rh₄(CO)₁₂ as catalyst and tBuMe₂SiH (2.0 equiv.) as silane, under high CO pressure (20 atm) at 95 °C and using benzene or CH₃CN as solvent, to give the corresponding heterobicyclo[3.3.0]octenones as a mixture of regioisomers.

To conclude this section on standard silylcyclizations, it is worth spending a few words on allenynes, showing a reactivity very similar to diynes. In 2004, Shibata and co-workers studied rhodium catalyzed SiCAC of propargyl homoallenyl ethers and amines under atmospheric CO pressure, providing cyclic (tetrahydrofuran or pyrrolidine) 1,4-dienes [84]. Reactions proceeded smoothly on a wide range of substrates, with both trialkylsilanes and trialkoxysilanes, using Rh(acac)CO₂ complex (5 mol%) as the most efficient catalyst (Scheme 30). The proposed mechanism, supported by deuterium labeling experiment, involved a regioselective silylmetallation on the double bond of the allene moiety closer to the heteroatom, followed by carbometallation on the alkynyl group to give the corresponding cyclic vinyl rhodium complex; finally, reductive elimination provided the heterocyclic product with regeneration of the Rh catalyst.

3.2. Synthesis of Heterocycles via Metal-Catalyzed Cascade Silylcyclizations of Alkynes

Transition metal-catalyzed cascade silylcyclizations of alkynes have been less studied than standard SiCAC as they involved more complex substrates, i.e., enediynes and triynes with a suitable chemical structure. However, cascade SiCAC represent very elegant synthetic protocols for the selective synthesis of fused tricyclic structures: heteroatom congeners of hexahydro-1H-cyclopenta[e]azulen-5(6H)-one and hexahydro-as-indacene using, respectively, enediynes and triynes as starting alkynes. If standard SiCAC can be performed under atmospheric or high CO pressure (in few cases even without CO), all the reported cascade SiCAC protocols always used 1 atm of carbon monoxide. Concerning catalysts, rhodium or rhodium-cobalt complexes have been successfully tested also for these reactions.
3.2.1. Cascade Silylcarbocyclizations of Enediynes

The first study on cascade silylcarbocyclization reactions of enediynes was reported in 2000 by Ojima’s research group [85]. Starting from the excellent results of their previous investigations on standard SiCAC of enynes and diynes, they tried to extend a similar protocol to enediynes. Interestingly, when dodec-11-ene-1,6-diyn was treated with PhMe2SiH (2.0 equiv.) in the presence of Rh(acac)(CO)2 (1 mol%), at 70 °C in toluene as solvent and under atmospheric CO, hexahydro-1H-cyclopenta[e]azulen-5(6H)-one was obtained as the main product after only 1 h, together with small amounts of two bis(cyclopentylidene) derivatives. However, a fine tuning of the experimental conditions allowed to improve selectivity: in fact, hexahydro-1H-cyclopenta[e]azulen-5(6H)-one was obtained as the only product when SiCAC reaction was performed in THF at lower reagents concentration and at room temperature. This optimized protocol was then applied to other enediynes, including their oxygen or nitrogen congeners, to give the corresponding O- or N-containing fused tricyclic structures. The proposed reaction mechanism provides three sequential carbocyclization steps (hence the name “cascade SiCAC”: after starting silylmatalation of the terminal alkyne moiety, the first carbocyclization took place; because of the steric hindrance between vinylsilane and vinyl-rhodium moieties in the resulting intermediate, it was then subjected to an isomerization via the “Ojima-Crabtree mechanism”, followed by the second carbocyclization step; the subsequent CO insertion step gave an acyl-rhodium intermediate, which was then subjected to the last carbocyclization, and a β-silyl elimination step afforded the final tricyclic product (Scheme 31).

More recently, Ojima and co-workers extended their studies on the scope and limitation of cascade SiCAC to 1-substituted dodec-11-ene-1,6-diynes and their heteroatom congeners [86]. When 1-methyl substituted dodec-11-ene-1,6-diyn was treated with PhMe2SiH (0.5 equiv.) in the presence of [Rh(COD)Cl]2 or Rh(acac)(CO)2 as catalyst (1 mol%), at 70 °C in toluene and under atmospheric CO pressure, they did not find the expected hexahydro-1H-cyclopenta[e]azulen-5(6H)-one but the corresponding 5-6-5 fused tricyclic compound (i.e., incorporating no CO unit) as the only product (70% yield in the case of [Rh(COD)Cl]2; 96% yield by using Rh(acac)(CO)2). However, the authors serendipitously discovered that working under similar conditions but in the absence of hydrosilane, the hexahydro-1H-cyclopenta[e]azulen-5(6H)-one was instead obtained in good yield (Scheme 32). This last Rh-catalyzed reaction in the absence of hydrosilane is actually an intramolecular [2 + 2 + 2 + 1] cycloaddition, occurring through a mechanism totally different from cascade SiCAC, although the same type of products is formed. We will not take into account this reaction, which is beyond the scope of the present review, but it is worth emphasizing that it has been successfully applied to several 1-substituted dodec-11-ene-1,6-diynes, including their oxygen and nitrogen congeners [87].
More recently, Ojima and co-workers extended their studies on the cascade SiCAC of enediynes. In 1999, Ojima and collaborators treated dodec-1,6,11-triynes and their heteroatom congeners. Although less investigated than diynes, also triynes were successfully tested as starting substrates for cascade silylcarbocyclization reactions. In 1999, Ojima and collaborators treated dodec-1,6,11-triynes and some oxygen- and nitrogen-containing analogs with several hydrosilanes (1.0–2.0 equiv.), in toluene under atmospheric carbon monoxide pressure, using different Rh complexes (0.1–2.0 mol%) as catalyst, including Rh₂(CO)₁₂, Rh(acac)(CO)₁₂, [Rh(COD)Cl]₂ and [Rh(NBD)Cl]₂. SiCAC reactions afforded 1,3,6,8-tetrahydrobenzo[1,2-c;3,4-c']difurans or 1,2,3,6,7,8-hexahydropyrrolo[3,4-e]isoindoles as a mixture of two products: the 4-triorganosilyl-substituted compound and the corresponding desilylated product (Scheme 33) [88].

**Scheme 31.** First investigation of cascade SiCAC of enediynes: the proposed reaction mechanism involved three sequential carbocyclization steps, hence the name “cascade SiCAC”.

**Scheme 32.** Rhodium-catalyzed cascade SiCAC vs. intramolecular [2 + 2 + 2 + 1] cycloaddition of 1-substituted dodec-11-ene-1,6-diynes and their heteroatom congeners.

### 3.2.2. Cascade Silylcarbocyclizations of Triynes

Although less investigated than diynes, also triynes were successfully tested as starting substrates for cascade silylcarbocyclization reactions. In 1999, Ojima and collaborators treated dodec-1,6,11-triynes and some oxygen- and nitrogen-containing analogs with several hydrosilanes (1.0–2.0 equiv.), in toluene under atmospheric carbon monoxide pressure, using different Rh complexes (0.5–1.0 mol%) as catalyst, including Rh₂(CO)₁₂, Rh(acac)(CO)₁₂, [Rh(COD)Cl]₂ and [Rh(NBD)Cl]₂. SiCAC reactions afforded 1,3,6,8-tetrahydrobenzo[1,2-c;3,4-c']difurans or 1,2,3,6,7,8-hexahydropyrrolo[3,4-e]isoindoles as a mixture of two products: the 4-triorganosilyl-substituted compound and the corresponding desilylated product (Scheme 33) [88].
The most plausible mechanism starts with a silicon-initiated cascade carbometalation to give a 3,3'-bifuranylidene/3,3'-bipyrolylidene intermediate, which can then follow two different pathways: (a) carbocyclization followed by β-hydride elimination, affording the 4-triorganosilyl-substituted product; (b) a Z-E isomerization favored by high temperatures, followed by a similar carbocyclization step and subsequent β-silyl elimination, giving the corresponding desilylated product.

3.3. Synthesis of Heterocycles Via Metal-Catalyzed Heteroatom-Promoted Silylcarbocyclizations of Alkynes

As already stressed, carbocyclizations of alkynes are extremely important reactions in the synthesis of numerous carbonyl and heterocyclic compounds of pharmaceutical and theoretical interest.

During the studies on the mechanism and the synthetic potential of silylformylation reactions of acetylenes, new and interesting reactions of heteroatom-promoted silylcarbocyclization were discovered [89, 90]. Reactions of propargyl alcohols or amides with a hydrosilane, catalyzed by Rh₄(CO)₁₂, and in the presence of a base (e.g., Et₃N, DBU) provided as main products (triorganosilyl)methylene- β-lactones and β-lactams respectively, which are important scaffolds present in many natural compounds.

3.3.1. Heteroatom-Promoted Silylcarbocyclizations of Ethynyl Alcohols

The first example of heteroatom-promoted silylcarbocyclizations of propargyl alcohols was described by Matsuda and co-workers in 1990 [89]. Based on a previous study on the silylformylation reactions of functionalized alkynes [16], they decided to investigate the possible cyclization of acetylenic alcohols under the silylformylation reactions conditions (R₂SiH, Et₃N, CO, 100 °C, Rh₄(CO)₁₂) (Scheme 34). Linear and branched alcohols were tested in the presence of different silanes (Me₂PhSiH, t-BuMe₂SiH, Et₃SiH, (i-Pr)₃SiH) and bases (Et₃N, DBU, pyridine, DABCO, DBU). Chemoselectivity of the reaction (i.e., β-lactone vs. aldehyde) depended strongly on the steric hindrance of silane and on the strength of the base. Indeed, while the reaction between 2-propynol (Scheme 34, R¹, R² = H) and Me₂PhSiH in the presence of Et₃N and Rh₄(CO)₁₂ gave exclusively the corresponding alkenal, the use of t-BuMe₂SiH and DBU afforded the expected methylene-β-lactones in very high yields (79–86%) and selectivity.

The formation of two different products, the alkenal and β-lactones ring, was explained by Matsuda and co-workers with the hypothesis of a Rh-acyl species (Figure 1), which could be the common intermediate to give both products. Indeed, an experiment performed under carbonylation conditions of the alkenal did not afford the corresponding lactone derivatives, thus suggesting that the two products are formed competitively.
The most plausible mechanism starts with a silicon-initiated cascade, which required DBU as the base (Scheme 35) to generate the desired compounds in good yields (68–86%) [89,91].

Heteroatom-promoted SiCAC was then applied to the synthesis of spiro-type β-lactones, which required DBU as the base (Scheme 35) to generate the desired compounds in good yields (68–86%) [89,91].

Moreover, the same SiCAC reaction was also extended to butynol and pentynols derivatives, affording the corresponding γ- and δ-lactones in very high yields (84–90%) even if Et₃N was used, thus indicating that the formation of both five- and six-membered heterocyclic compounds is extremely favored (Scheme 36) [89].

Similarly, complete chemoselectivity towards the lactone formation was observed by the same research group in the silylcarbocyclization reactions of cyclohexanol containing a propargyl or butynyl group connected to alcohol carbon atom (Scheme 37) [4]. Once more, the use of DBU together with t-BuMe₂SiH and Rh₄(CO)₁₂ yielded the corresponding γ- and δ-spirolactones, selectively.
A few years later, Aronica and co-workers reported a detailed study on the **heteroatom-promoted** SiCAC reaction of several propargyl alcohols characterized by different steric and electronic requirements [92]. All reactions were performed in CH$_2$Cl$_2$ at 100 °C, under 30 atm of CO, with 0.1 mol% of Rh$_4$(CO)$_{12}$ as catalyst and DBU as base. As previously observed by Matsuda, the chemoselectivity of the process was clearly influenced by steric hindrance: the presence of a tert-butyl, ethyl or cyclohexyl group on the propargyl carbon atom determined a nearly total chemoselectivity towards β-lactones, while the reaction involving 3-propynol generated the corresponding β-silylalkenal predominantly (Scheme 39).

In order to improve the formation of the lactone ring, arylsilanes containing a hindered substituent (MePh$_2$SiH, Ph$_3$SiH, o-CH$_3$-(C$_6$H$_4$)Me$_2$SiH, p-Ph-(C$_6$H$_4$)Me$_2$SiH) were tested in the **heteroatom-promoted** silylcarbocyclization of 1-hexynol performed with Rh$_4$(CO)$_{12}$ as catalyst (Scheme 40) [92].
The obtained results clearly indicated that the choice of hydrosilane plays a crucial role. Indeed, the best chemo-selectivity was observed in the reaction with o-tolylidimethylsilane and diphenyldimethylsilane; on the contrary, Ph$_3$SiH and (t-Bu)$_2$PhSiH were totally inactive. Finally moving from dichloromethane to toluene as solvent and operating at lower temperature (70 °C), a significant improvement of the lactone selectivity was detected. The same results were obtained when two homopropargyl alcohols were considered. In these cases, the cyclization process was definitely favored (Scheme 41). All (dimethylphenylsilyl)methylene β- and γ-lactones can be submitted to a TBAF-promoted phenyl migration without a ring opening, affording useful building blocks for the synthesis of pharmaceutical compounds.

The same authors then investigated the heteroatom-promoted silylcyclization of propargyl alcohols promoted by different catalytic species [93]. Initially, a preliminary study on Rh/mesitylene co-condensate, prepared according to the MVS technique [35,51–53] and consisting of small rhodium nanoclusters, was carried out. With respect to commercial Rh$_4$(CO)$_{12}$, Rh/mesitylene catalyst showed excellent performance in the SiCAC process of 1-hexyn-3-ol with t-BuMe$_2$SiH, in CH$_2$Cl$_2$ and DBU, at 100 °C and under 30 atm of carbon monoxide. The β-lactone ring was obtained with 87% of selectivity (Scheme 42).

When the same rhodium co-condensate was deposited on several matrices (charcoal, γ-alumina, Fe$_2$O$_3$ and polybenzimidazole), supported Rh/C, Rh/γ-Al$_2$O$_3$, Rh/Fe$_2$O$_3$ and Rh/PBI were prepared and tested in the heteroatom-promoted silylcyclization reactions [93]. Among them, Rh/C showed the best results in terms of conversion (87%) and selectivity (92%), even compared with a commercial Rh/C species. As a consequence, Rh/C (MVS) was used in the SiCAC processes of 3-dialkylpropargyl alcohols with Me$_2$PhSiH, in CH$_2$Cl$_2$ as solvent and DBU as base (Scheme 43): the reactions afforded β-lactone derivatives with almost complete chemo- and even homoselectivity (92–97%). High resolution transmission electron microscopy (HR-TEM) analysis of Rh/C (MVS) indicated the presence of very small Rh nanoparticles (2.4 nm mean diameter) on the support, which could be the reason of its high catalytic activity. Unfortunately, preliminary investigations evidenced a relevant metal leaching into solution during the reactions, thus indicating that Rh/C (MVS) acted as a reservoir of soluble active nanoparticles.

Scheme 40. Heteroatom-promoted SiCAC protocol applied to 1-hexyn-3-ol involving arylsilanes with a hindered substituent.

Scheme 41. Heteroatom-promoted SiCAC of homopropargyl alcohols: synthesis of γ-lactones.

Scheme 42. Heteroatom-promoted SiCAC reaction of 1-hexyn-3-ol promoted by different catalytic species.
probably due to the formation of hydrogen during the SiCAC reaction [89]. Only a slight improvement was observed when (η⁶-C₆H₆BPh₃)⁺Rh⁺(1,5-COD) (Rhsw) catalyst was employed instead of Rh₄(CO)₁₂:

![Scheme 43. Heteroatom-promoted SiCAC of 3-dialkylpropargyl alcohols catalyzed by Rh/C (MVS).](image)

In 2017, the Aronica’s research group developed a new protocol for the synthesis of 3-isochromanone derivatives based on heteroatom-promoted silylcycarbocyclization reactions of 2-ethynylbenzyl alcohol [94]. Initially, the SiCAC process was performed with Me₂PhSiH as hydrosilane and Rh₄(CO)₁₂ as catalyst, in CH₂Cl₂ as solvent and DBU as base, under 30 atm of CO at 100 °C. Surprisingly, together with the expected product, relevant amounts of the corresponding hydrogenated by-product were obtained, regardless of catalyst loading, temperature and CO pressure (Scheme 44), probably due to the formation of hydrogen during the SiCAC reaction [89]. Only a slight improvement in chemoselectivity (33% isochromanone) was observed when (η⁶-C₆H₆BPh₃)⁺Rh⁺(1,5-COD) (Rhsw) catalyst was employed instead of Rh₄(CO)₁₂:

![Scheme 44. Heteroatom-promoted SiCAC of 2-ethynylbenzyl alcohol with Me₂PhSiH for the synthesis of 3-isochromanone derivatives.](image)

Unexpectedly, working without DBU, the selectivity towards methyleneisochromanone increased. As a consequence, the optimized experimental conditions (Rhsw 0.1–0.2 mol%, 100 °C, 30–50 atm of CO, 2–6 h), were used for the SiCAC reactions of ethynylbenzyl alcohol with different aryldimethylsilanes. All reactions afforded the expected products with good yields and total stereoselectivity, since only (Z) isochromanones were formed (Scheme 45):

![Scheme 45. Heteroatom-promoted SiCAC of 2-ethynylbenzyl alcohol with different aryldimethylsilanes for the synthesis of (Z)-isochromanones.](image)

### 3.3.2. Heteroatom-Promoted Silylcycarbocyclizations of Ethynyl Amines

The β-lactam moiety is the key of one of the most widely employed class of antibiotics [95–97], i.e., β-lactam antibiotics such as penicillins and cephalosporins, which are distinguished by good tolerance and therapeutic safety. In particular, the α-methylene-β-lactam unit is a very common structural feature included in potent β-lactamase inhibitors [98], such as asparenomycins [99,100] and penicillanic acids [101,102]. Therefore, the synthesis of α-methylene-β-lactams (3-methylene-2-azetidinones) has received great attention in the literature [103–106].

In 1991, Matsuda et al. described the first example of heteroatom-promoted SiCAC reactions of ethynyl amines, applied to the formation of α-silylmethylene-β-lactams [90]. On the base of the results previously obtained in the silylcycarbocyclizations of propargyl alcohols, they started their investigation with the reaction of N-(1-ethynylcyclohexyl)-p-toluensulfonamide with RM₂SiH (R = Ph or t-Bu), Rh₄(CO)₁₂, a suitable base, at 100 °C and under 20 atm of CO. In particular, the best result (81% lactam)
was obtained by the combined use of a bulky silane (t-BuMe₂SiH) and DBU as the base (Scheme 46). Under the same experimental conditions, other sulfonamides afforded the corresponding β-lactams with good selectivity; instead, the less hindered toluensulfonamide and N-propargylcarbamates generated the corresponding silylformylation product predominantly.

Scheme 46. First example of heteroatom-promoted silylcyclization of propargyl amides: synthesis of α-silylmethylene-β-lactams.

Better results were described by the same research group when alkynylbenzylamines were used as substrates for heteroatom-promoted silylcyclizations, which generated the corresponding γ- and δ-lactams [4]. The reactions were carried out with Rh₄(CO)₁₂ (0.25 mol%), DBU, 20 atm of CO, 100 °C and t-BuMe₂SiH, which was fundamental for the cyclization reaction to occur (Scheme 47).

Scheme 47. Heteroatom-promoted SiAC of benzylamines applied to the synthesis of γ- and δ-lactams.

Ethynylpiperidine derivatives were also tested in the heteroatom-promoted SiAC reaction under the same experimental conditions, affording the corresponding ring-fused lactam compounds in good yields (Scheme 48) [4].

Scheme 48. Heteroatom-promoted SiAC reactions of ethynylpiperidines.

Isoquinoline-based substrates were deeply investigated in heteroatom-promoted silylcyclizations. Matsuda et al. worked under the above-mentioned optimized conditions (i.e., t-BuMe₂SiH, Rh₄(CO)₁₂
0.25 mol%, DBU, CO 20 atm, 100 °C), affording selectively the corresponding benzoindolizidinone as the Z-isomer (Scheme 49, path A) [4].

**Scheme 49.** Heteroatom-promoted SiCAC reactions applied to the synthesis of benzoindolizidinones.

Ojima and co-workers used different conditions: PhMe₂SiH, Rh(acac)(CO)₂ 1 mol%, in toluene under 50 atm of carbon monoxide, at 60 °C but without DBU. In this case, SiCAC took place with different stereoselectivity, giving the E-isomer of benzoindolizidinone in poor yield (21%), probably due to the absence of the base (Scheme 49, path B) [107]. The authors suggested that the isomerization of silylvinyl group took place during the reaction (Scheme 50), after the addition of H[Rh]SiMe₂Ph to the triple bond, according to what was previously observed in the hydrosilylation reaction of 1-alkynes [108].

**Scheme 50.** Mechanism hypothesized by Ojima and co-workers for their heteroatom-promoted SiCAC protocol of isoquinoline-based substrates.

Prompted from this result, the same group investigated the formation of an indolizidine skeleton by means of heteroatom-promoted SiCAC of butynylpyrrolidine and hydrosilanes [107]. Both Rh(acac)(CO)₂ and Rh₂CO₂(CO)₁₂ (2 mol%) were an effective catalyst for the silylcarbocyclization reaction, which was found to be very sensitive to the nature of the silane (Scheme 51).
were achieved with 90–100% selectivity after 4 h, at 100 °C. The presence of DBU and a quaternary α-carbon on the substrate were essential for the SiCAC reaction to occur with complete chemoselectivity towards the β-lactam ring, regardless the steric and electronic requirements of the silanes. Moreover, (Z)-stereoisomers were exclusively obtained (Scheme 53).

More recently, Aronica et al. applied the heteroatom-promoted SiCAC transformation to some propargyl tosylamides, using Rh₄(CO)₁₂ (0.1 mol%) as catalyst, DBU as base, under CO pressure (30 atm), at 100 °C [36]. The presence of DBU and a quaternary α-carbon on the substrate were essential for the SiCAC reaction to occur with complete chemoselectivity towards the β-lactam ring, regardless the steric and electronic requirements of the silanes. Moreover, (Z)-stereoisomers were exclusively obtained (Scheme 53).

Taking into account the same tosylamides, Aronica and co-workers tested different supported Rh catalysts prepared according to the MVS technique in the SiCAC reactions [93]. As already observed for the reactions performed with propargyl alcohols, among MVS Rh/C, Rh/γ-Al₂O₃, Rh/Fe₂O₃ and Rh/PBI, the first species showed a specific activity even higher than homogeneous Rh₄(CO)₁₂ used as a reference catalyst. When Rh/C was used in the heteroatom-promoted SiCAC, the expected β-lactams were achieved with 90–100% selectivity after 4 h, at 100 °C and 30 atm CO (Scheme 54). Moreover, the same batch of Rh/C could be reused without loss of activity.

In 2019, Albano and co-workers described the first synthesis of indolines and tetrahydroisoquinolines via heteroatom-promoted SiCAC of suitable tosylamides [109]. The (2-ethylphenyl)-4-tosylamide was first tested in the reaction with dimethylphenylsilane, promoted by Rh⁴⁺ (0.3 mol%), under 30 atm of CO, at 30 °C (Scheme 55). The formation of the corresponding five-membered heterocyclic compound took place without the need of a base as previously observed in the silylcarbocyclization applied to the
The synthesis of isochromanones [94]. Together with tosylindolinone, the corresponding hydrogenated derivative tosylindolinol was surprisingly generated too. In order to improve the chemoselectivity of the SiCAC process, reactions at higher temperature (50–100 °C) were performed. However, tosylindolynol was obtained as the sole product.

Scheme 55. Synthesis of tosylindolinol via heteroatom-promoted SiCAC of (2-ethynylphenyl)-4-tosylamide.

The silylcarbocyclization was then extended to the synthesis of tetrahydroisoquinolines but, again, tosyltetrahydroisoquinolins were selectively obtained regardless the temperature employed and the nature of the catalyst (i.e., Rh\textsuperscript{sw}, Rh(acac)(CO), Rh\textsubscript{6}(CO))\textsubscript{16}, as depicted in Scheme 56 [109]. The formation of the reduced compounds was ascribed to the presence of molecular H\textsubscript{2}, which is formed as a by-product in the reaction vessel.

Scheme 56. Heteroatom-promoted SiCAC applied to the synthesis of tosyltetrahydroisoquinolins.

With the optimal reaction conditions in hand, the authors investigated the reactivity of hydrosilanes possessing different steric requirements with both tosylamides. The optimized SiCAC procedure afforded the corresponding products in very good yields (51–75%) [109]. Moreover, the ring formation took place with complete stereoselectivity of the exocyclic double bond (Z isomer exclusively), not only in reactions involving aryl silanes but also for benzyl derivative (Scheme 57). The obtained silylated tosylindolinols and tosyltetrahydroisoquinolins could be easily desilylated by means of TBAF, which promoted aryl rearrangements from silicon to the adjacent carbon atom, generating new polyfunctionalized N-heterocycles.

Scheme 57. Synthesis of tosylindolinols and tosyltetrahydroisoquinolins via heteroatom-promoted SiCAC with several ArMe\textsubscript{2}SiH.

4. Conclusions

In summary, intramolecular silylformylation and silylcarbocyclization processes provide efficient and versatile methods for the construction of monocyclic, bicyclic and polycyclic heterocycles.

We really hope that the present review may stimulate further research in the field of silylformylation and silylcarbocyclization reactions, and in particular for the preparation of new biologically relevant O-
and N-heterocycles, as a valid alternative to the most common cycloaddition [110–112] or cross-coupling reactions [113–116]. Moreover, the recent studies on CO surrogates [117–119] may be a strong stimulus for innovative and safer development of new silylcarbonylation processes.

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