catalysts

Review

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

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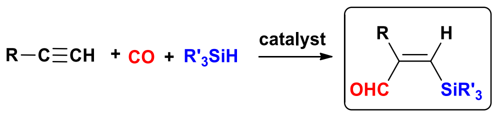
Abstract: Oxygen and nitrogen heterocyclic systems are present in a large number of natural and synthetic compounds. In particular, oxa- and aza-silacyclane, tetrahydrofuran, benzofuran, cycloheptadifuranone, cycloheptadipyrrolone, pyrrolidine, lactone, lactam, phthalan, isochromanone, tetrahydroisoquinolinone, 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

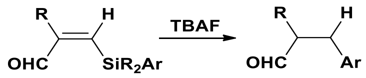
The silylformylation reaction of terminal acetylenic compounds [1–5] consists of the simultaneous introduction of a trialkylsilylgroup and a formyl moiety into a carbon–carbon multiple bond (Scheme 1). The reaction takes place with total regio- and stereoselectivity, -CHO and -SiR_3 being added *syn* 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 H_2 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. $Rh_4(CO)_{12}$ 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 $Rh_2(pfb)_4$ (perfluorobutyrrate) [30,31] in the silylformylation of terminal alkynes, Alper developed a zwitterionic species, $(\eta^6\text{-}C_6H_6BPh_3)^-Rh^+$(1,5-COD) ($Rh^{sw}$) [32–34] and Aronica et al. [35] showed that rhodium nanocluster, obtained by Metal Vapor Synthesis (MVS) technique could be able to catalyze the silylformylation of linear and branched acetylenes. It is worth noting that silylformylation of alkynes is generally tolerant of many functionalities such as ethers, esters, alcohols, ketones, aldehydes, amines, nitrile, chlorine, bromine and double bonds [18,26,30,33,36,37].

Many applications of the silylformylation 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].



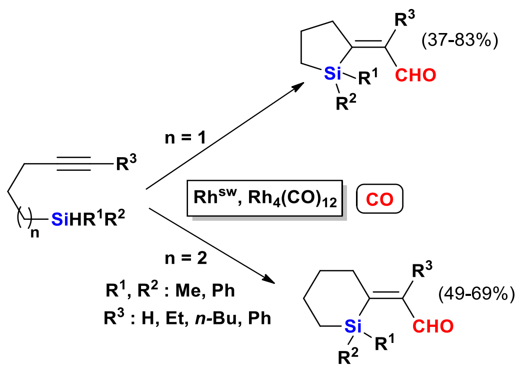
Scheme 2. Fluoride-promoted aryl rearrangement of β-silylalkenals: synthesis of 2-(arylmethyl)alkanals.

The "cyclic" version of silylformylation reaction may occur into two different ways: (1) *intramolecular silylformylation* of ω-silylacetylenes, giving the corresponding silacycloalkanes; (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 silylformylation 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 Silylformylation of Alkynes

2.1. The Intramolecular Silylformylation of ω-Silylalkynes: Synthesis of Silacyclanes

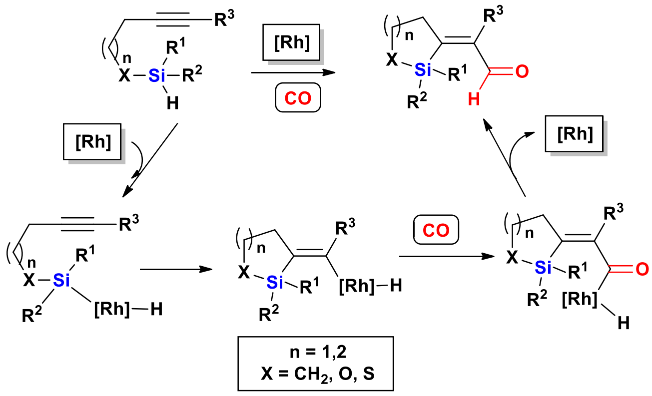
The first example of intramolecular silylformylation reaction of acetylenes was reported by Alper and Matsuda in 1995 [47]. Pent-4-ynylmethylphenylsilane (Scheme 3, n = 1, R^1 = Me, R^2 = Ph, R^3 = H) was initially treated with triethylamine (1.0 equiv.), a catalytic amount of a rhodium catalyst under CO atmosphere (20 atm) and quite mild experimental conditions (40 °C, 24 h). Both the zwitterionic complexes $(\eta^6\text{-}C_6H_6BPh_3)^-Rh^+(1,5\text{-COD})$ (Rh^{sw}) and $Rh_4(CO)_{12}$ 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-silacycloalkanes with complete regio and stereoselectivity. None of the products derived from an *endo-dig*-mode cyclization or an intermolecular silylformylation were produced.



Scheme 3. First example of intramolecular silylformylation reaction of acetylenes reported by Alper and Matsuda.

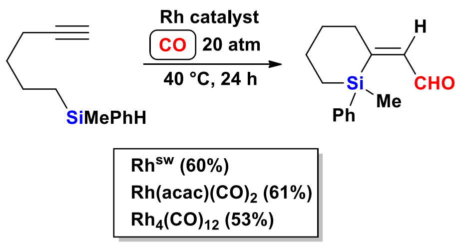
The same trend was observed in the case of hexynylsilanes (Scheme 3, n = 2), which afforded the corresponding six ring silacycloalkanes. The yield of aldehyde was affected by the nature of R^1R^2HSi- group connected to the alkyl chain: higher product amounts were isolated when alkynylmethylphenylsilanes (Scheme 3, R^1 = Me, R^2 = Ph) were reacted rather than alkynyldiphenylsilanes. The intramolecular silylformylation proceeded smoothly also for internal alkynylsilanes (Scheme 3, R^3 = 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 = CH_2) 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.



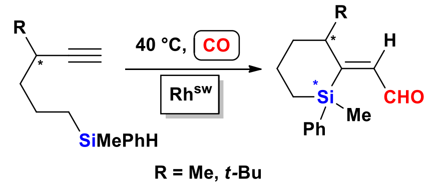
Scheme 4. General mechanism for intramolecular silylformylation reactions.

A few years later, Aronica and co-workers investigated the reactivity of both linear and C_3-branched 6-(methylphenylsilyl)-1-hexynes [50]. Linear substrate was first tested in the intramolecular silylformylation reaction, promoted by both zwitterionic Rh^{sw} and covalent complexes such as $Rh(acac)(CO)_2$ and $Rh_4(CO)_{12}$. 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.

As a consequence, the air-stable Rh^{sw} species was used in subsequent reactions of C_3-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.



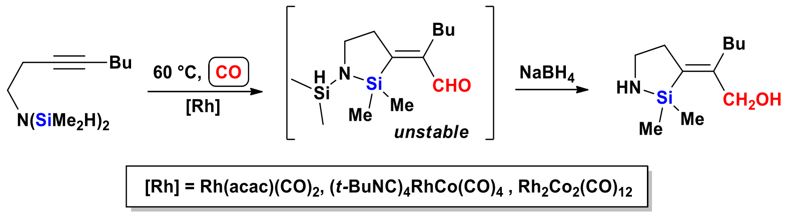
Scheme 6. Intramolecular silylformylation reaction of branched ω-silylacetylenes.

The same result was obtained [50] performing the reaction with a different catalyst, the co-condensate Rh/mesitylene, prepared according to the MVS technique [35,51–53] and consisting in a solution of small Rh metal clusters. The MVS species revealed a catalytic activity comparable with that of conventional organometallic compounds, high regio and disterostereoselectivity 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.

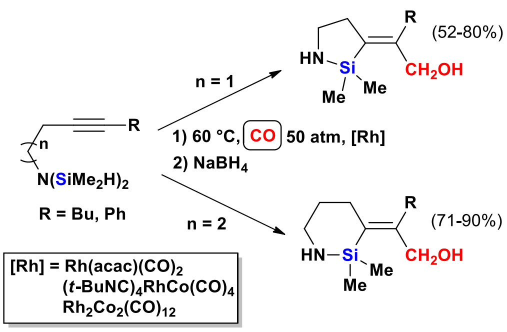
2.2. The Intramolecular Silylformylation of ω-Bis(Dimethylsilylamino)Alkynes: Synthesis of Azasilacyclanes

The only example of intramolecular silylformylation of dimethylsilylaminoacetylenes was reported by Ojima and Vidal [55]. As a model reaction they reacted 1-bis(dimethylsilylamino)-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.



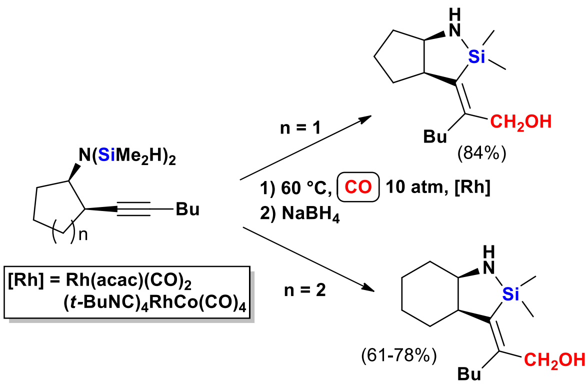
Scheme 7. Intramolecular silylformylation/desilylation of 1-bis(dimethylsilylamino)-3-octyne.

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



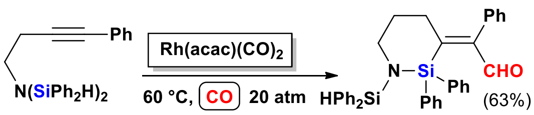
Scheme 8. Intramolecular silylformylation/desilylation reaction of *bis*(silyl)amino-alkynes.

Similar experimental conditions (60 °C, 10 atm CO, 14 h, $Rh(acac)(CO)_2$, $(t\text{-}BuNC)_4RhCo(CO)_4$ or $Rh_2Co_2(CO)_{12}$, 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 azasilabicycloalkenes (Scheme 9).



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

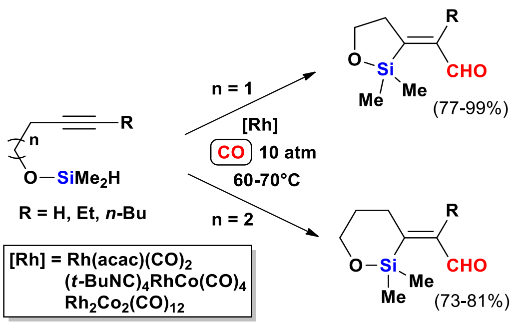
Surprisingly, when a dimethylsilyl group was replaced by a diphenylsilyl group, intramolecular silylformylation afforded the corresponding silapiperidine product in 63% isolated yield (Scheme 10).



Scheme 10. 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*

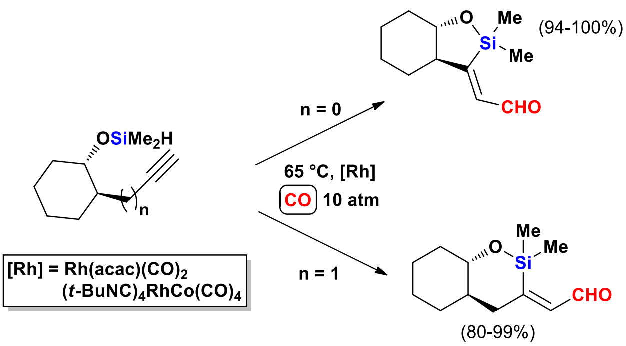
In 1995, Ojima and co-workers described the first case of intramolecular silylformylation of terminal and internal alkynes featured by a dimethylsiloxy moiety as a directing group [56]. In agreement with the intramolecular silylformylation of ω-silylacetylenes, complete regio- and stereoselectivity was observed. Cyclization reactions of ω-(dimethylsiloxy)-alkynes were carried out in the presence of $(t\text{-}BuNC)_4RhCo(CO)_4$, $Rh_2Co_2(CO)_{12}$ 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. First example of intramolecular silylformylation reaction of ω-(dimethylsiloxy)alkynes.

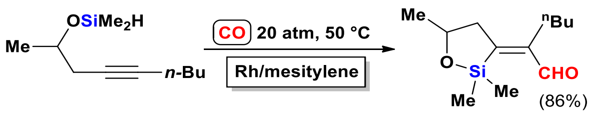
The intramolecular silylformylation was applicable also to cyclic systems. Indeed, the same authors tested the reactivity of *O*-(dimethylsilyl)-2-ethynyl and 2-propynyl derivatives depicted in

Scheme 12 [56]. All reactions proceeded smoothly at 65 °C and 10 atm CO, with (*t*-BuNC)$_4$RhCo(CO)$_4$ as the best catalyst.



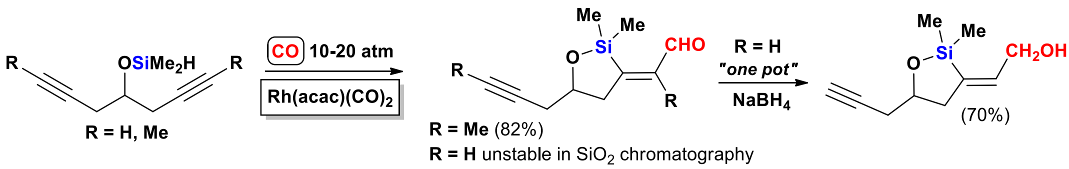
Scheme 12. Intramolecular silylformylation of cyclic *O*-(dimethylsilyl)-2-ethynyl and propynyl derivatives.

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].



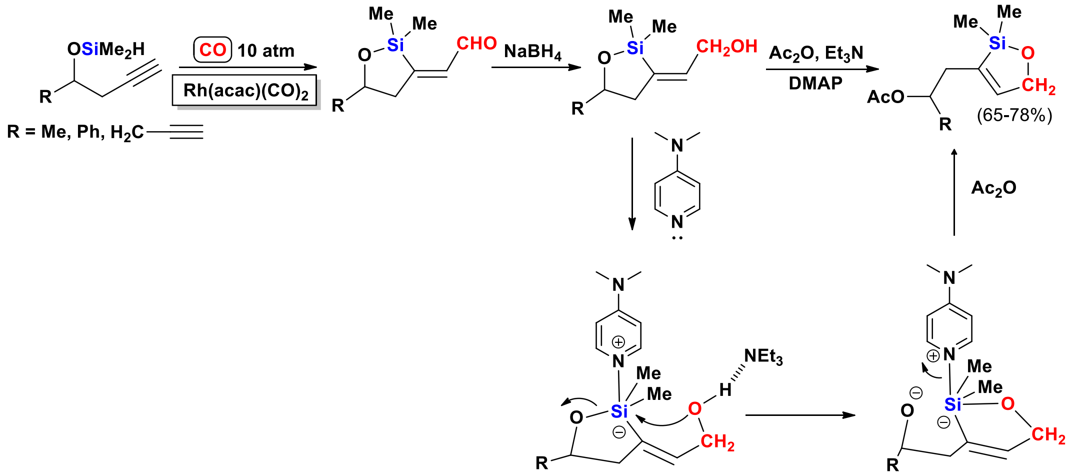
Scheme 13. Intramolecular silylformylation of 2-(dimethylsiloxy)-4-nonyne promoted by a Rh/mesitylene obtained via the Metal Vapor Synthesis (MVS) technique.

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 NaBH$_4$ 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 -CH$_2$OH functional groups.



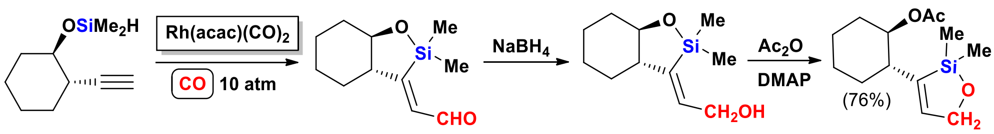
Scheme 14. Desymmetrization of dimethylsiloxyalkadiynes based on intramolecular silylformylation reaction.

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).



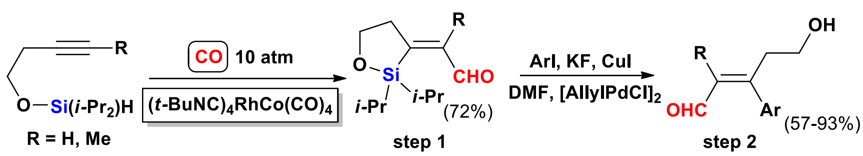
Scheme 15. Three-steps protocol for the synthesis of 5-(2-acetoxyalkyl)-2-oxa-1-silacyclopentenes.

Moreover, the authors observed that when *O*-dimethylsilylethynylcyclohexanol 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.



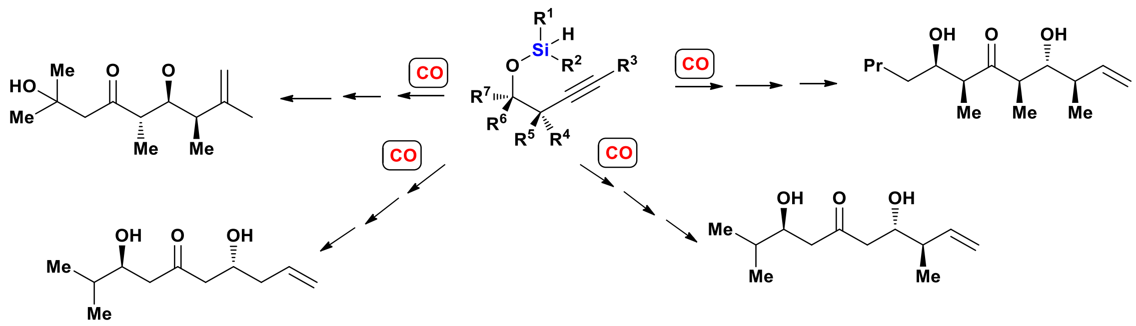
Scheme 16. Skeletal rearrangement of *O*-dimethylsilylethynylcyclohexanol.

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)$_4$RhCo(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)oxa-silacycloalkanes 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)PdCl]$_2$ 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 silylether 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%).



Scheme 17. Tandem intramolecular silylformylation/cross-coupling reactions of alkynyloxyhydrosilanes.

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].



Scheme 18. Tandem intramolecular silylformylation/crotylsilylation reactions.

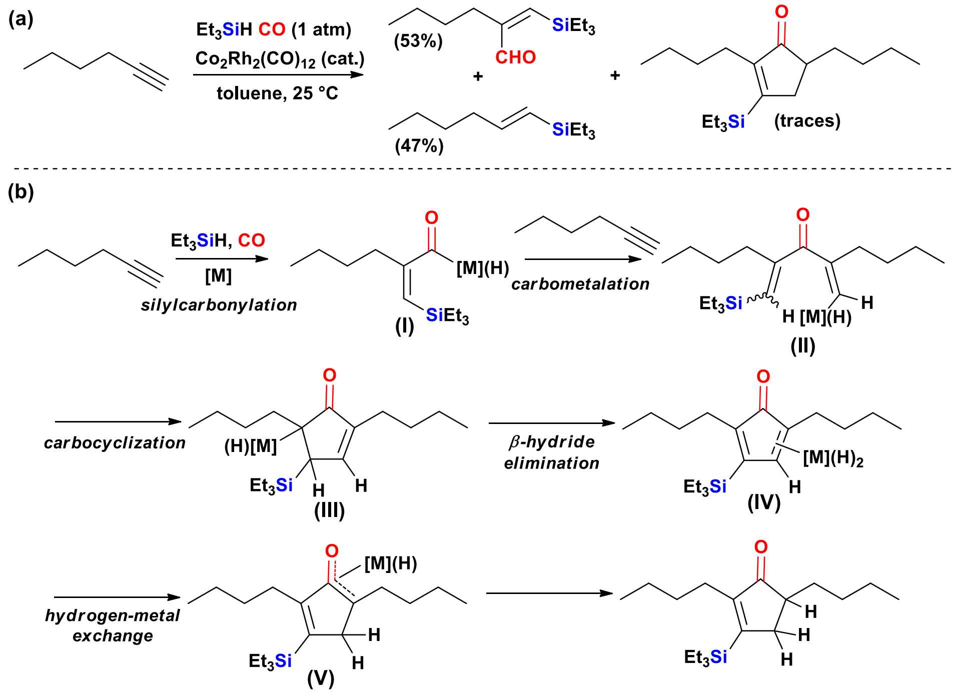
3. Heterocycles Synthesis via Metal-Catalyzed Silylcarbocyclization of Alkynes

As well shown in the previous section, intramolecular hydrosilylation and silylformylation reactions of alkynes represent a valid route to several types of highly functionalized silacycles. Silylcarbocyclization (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.

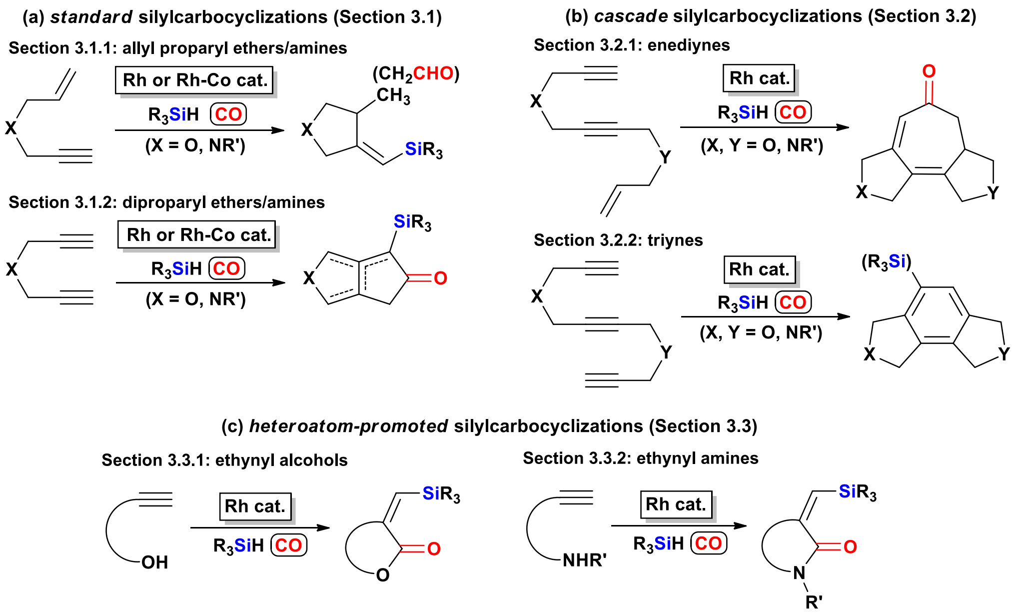
The first silylcarbocyclization was serendipitously discovered by Ojima et al. in 1991: during their studies on the silylformylation of 1-hexyne with triethylsilane, carried out in the presence of $Co_2Rh_2(CO)_{12}$ as catalyst, in addition to the usual hydrosilylation and silylformylation products 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 silylcarbonylation of 1-hexyne gave the β-silylacryloyl-metal intermediate (**I**), which in turn then provided a carbometalation on a second 1-hexyne molecule to generate (**II**); 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 silylcarbocyclization 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.

Silylcarbocyclization reactions applied to the synthesis of heterocyclic compounds can be divided into three main groups, depending on the starting alkynes: (i) *standard* silylcarbocyclizations, mainly involving allyl proparyl and dipropargyl ethers/amines, which gave in most cases tetrahydrofuran and pyrrolidine derivatives (Scheme 20, path a); (ii) *cascade* silylcarbocyclizations, involving instead enediynes and triynes with a suitable chemical structure, which led to the formation of fused tricyclic structures (Scheme 20, path b); (iii) *heteroatom-promoted* silylcarbocyclizations, 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.



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



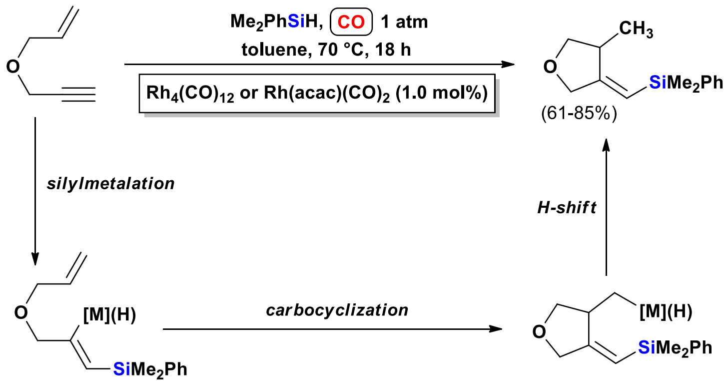
Scheme 20. Classification of SiCAC reactions: (**a**) *standard* silylcarbocyclizations, involving allyl propargyl and dipropargyl ethers/amines (Section 3.1); (**b**) *cascade* silylcarbocyclizations, involving enediynes and triynes (Section 3.2); (**c**) *heteroatom-promoted* silylcarbocyclizations, 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-((triorganosilyl)methylene)tetrahydrofuran and 3-((triorganosilyl)methylene)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 Silylcarbocyclizations of Allyl Propargyl Ethers/Amines

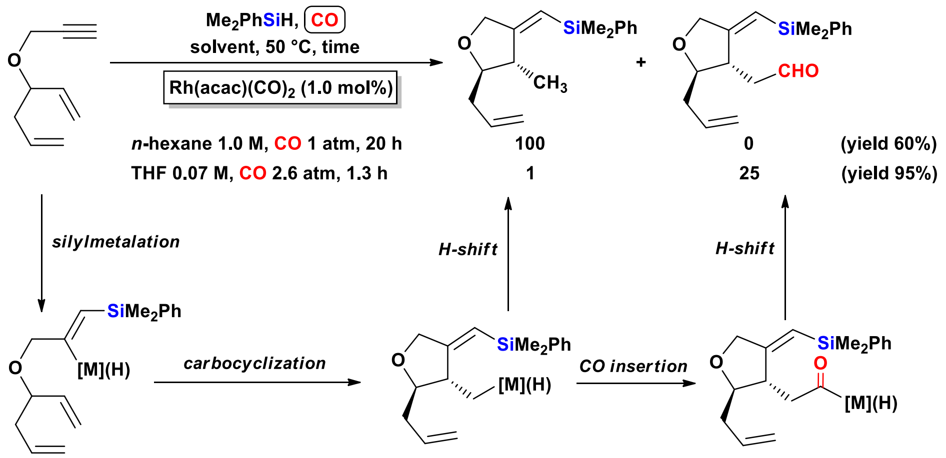
The first investigation on *standard* silylcarbocyclization of allyl propargyl ethers and amines was reported in 1992 by Ojima and co-workers [71]. They described the reaction of allyl propargyl ether with dimethylphenylsilane, performed in toluene at 70 °C and under CO pressure (1 atm), in the presence 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 silylmetalation of the triple bond, carbocyclization and H-shift (Scheme 21). In the same paper, the authors also described a similar SiCAC reaction for diallyl propargyl amine with $PhMe_2SiH$ ($Rh(acac)(CO)_2$, 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_2PhSiH: 3-(silylmethylene)-4- ethyltetrahydrofuran was obtained through a three-steps mechanism, i.e., silylmetalation, carbocyclization and H-shift.

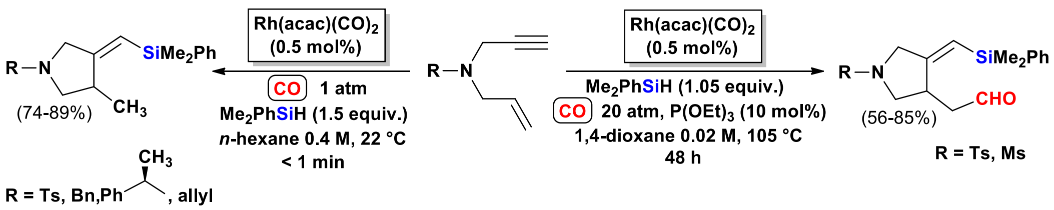
In a following paper, the same group extended *standard* SiCAC to a more structurally complex allyl propargyl ether [72]. Working under the same conditions of their previous work (1.0 equiv. of Me_2PhSiH, 1 mol% of $Rh(acac)(CO)_2$, 1 atm of CO, at 50 °C in toluene), the expected SiCAC product was recovered as a mixture with the corresponding carbonylative SiCAC (namely, CO-SiCAC) derivative, arising from a carbon monoxide insertion between the carbocyclization 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%).



Scheme 22. *Standard* silylcarbocyclization of hepta-1,6-dien-4-yl propargyl ether with Me_2PhSiH.

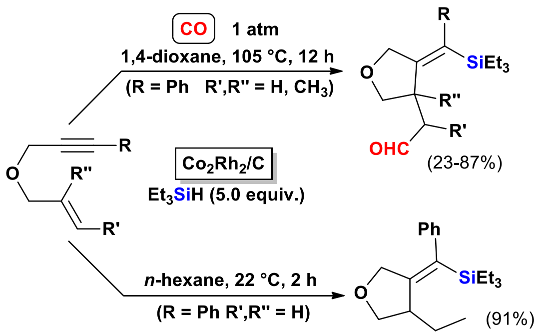
The exclusive formation of CO-SiCAC pyrrolidines (56–85% yields) was instead found by using an almost equimolar amount of silane (1.05 equiv.) at 0.02 M concentration in 1,4-dioxane, under 20 atm of CO at 105 °C, in the presence of 10 mol% of $P(OEt)_3$ as ligand (Scheme 23). Since high reactants dilution 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.



Scheme 23. Synthesis of pyrrolidine derivatives via *standard* silylcarbocyclization of allyl propargyl amines.

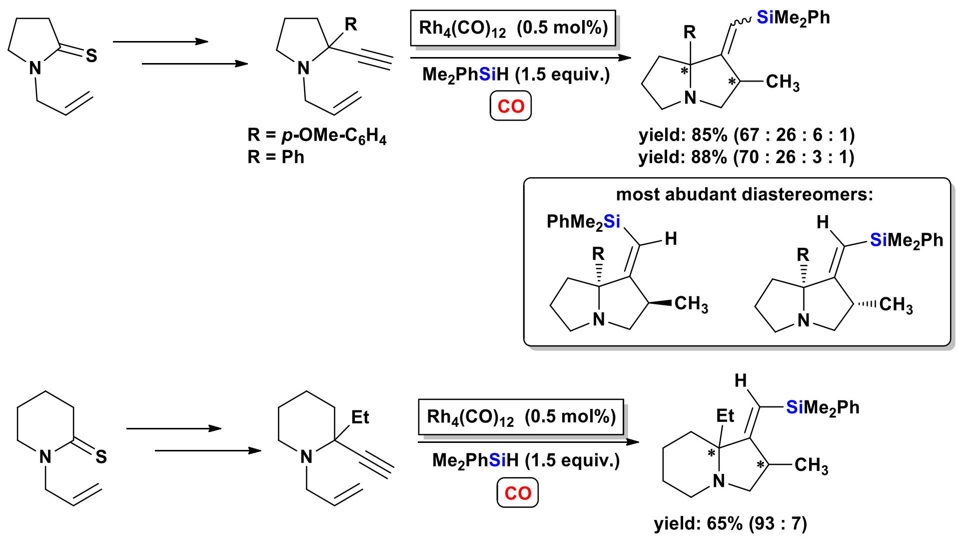
Matsuda et al. also reported an interesting study on rhodium-catalyzed *standard* silylcarbocyclization of 1,6-enynes derivatives, including allyl propargyl ethers and amines [74]. As previously observed by Ojima and coll. [72,73], working with $Rh_4(CO)_{12}$ or $Rh(acac)(CO)_2$ catalysts under high 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 $Co_2Rh_2(CO)_{12}$ 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.



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

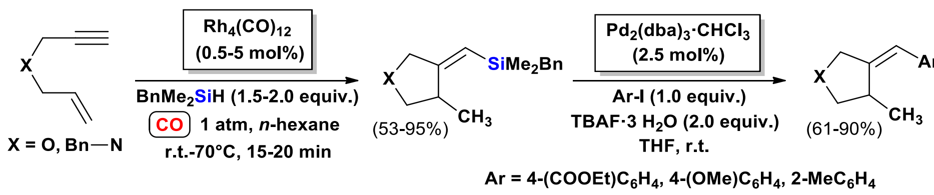
In the last fifteen years, *standard* silylcarbocyclization protocols have been mostly applied as a key step for the synthesis of more complex heterocyclic compounds, including biologically active products. In 2006, Murai et al. reported an extended investigation on the synthesis of 1,2,2′-trisubstituted pyrrolidines and piperidines through the reaction of thioiminium salts (derived from the addition of lithium acetylides to γ-and δ-thiolactams) with proper Grignard reagents [76]. In order to show the synthetic applicability of the obtained compounds, *N*-allyl-2-ethynyl-2-substituted pyrrolidines and piperidines were then also subjected to *standard* silylcarbocyclization: reactions were performed with $Rh_4(CO)_{12}$ (0.5 mol%) as catalyst and Me_2PhSiH (1.5 equiv.) as silane, in *n*-hexane under CO atmosphere and at room temperature. In the case of pyrrolidines, SiCAC afforded 1,2,7*a*-trisubstituted hexahydro-1*H*-pyrrolizines as a mixture of four diastereomers, the stereochemistry of which was identified by NOESY spectroscopy; instead, *standard* SiCAC of piperidine reagents gave 1,2,8*a*-trisubstituted octahydroindolizines as a mixture of only two diastereomers (Scheme 25).



Scheme 25. *Standard* silylcarbocyclization of *N*-allyl-2-ethynyl-2-substituted pyrrolidines and piperidines: synthesis of hexahydro-1*H*-pyrrolizines and octahydroindolizines.

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: $Rh_4(CO)_{12}$ (0.5–5 mol%) as catalyst, an excess

(1.5–2.0 equiv.) of silane, under atmospheric CO pressure at the selected temperature. Interestingly, the triorganosilyl moiety of the corresponding heterocyclic products can be then subjected to a Hiyama cross-coupling reaction with aryl iodides in the presence of a suitable palladium catalyst. The best performance was observed with 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 2.0 equiv. of TBAF·3 H_2O as additive, in THF at room temperature: both electron rich and electron poor aryl iodides gave the coupling products in good yields (Scheme 26). More recently, the same research group applied *standard* silylcarbocyclization to a highly functionalized allyl propargyl amine, i.e., *N*-tosyl-*N*-methylpropargyl-(*L*)-vinylglycine methyl ester, as a key step for the total synthesis of isodomoic acids G and H, two kainoid amino acid derivatives isolated from red alga *Chondria armata* with well recognized properties as neuroexcitatory agents [78,79].



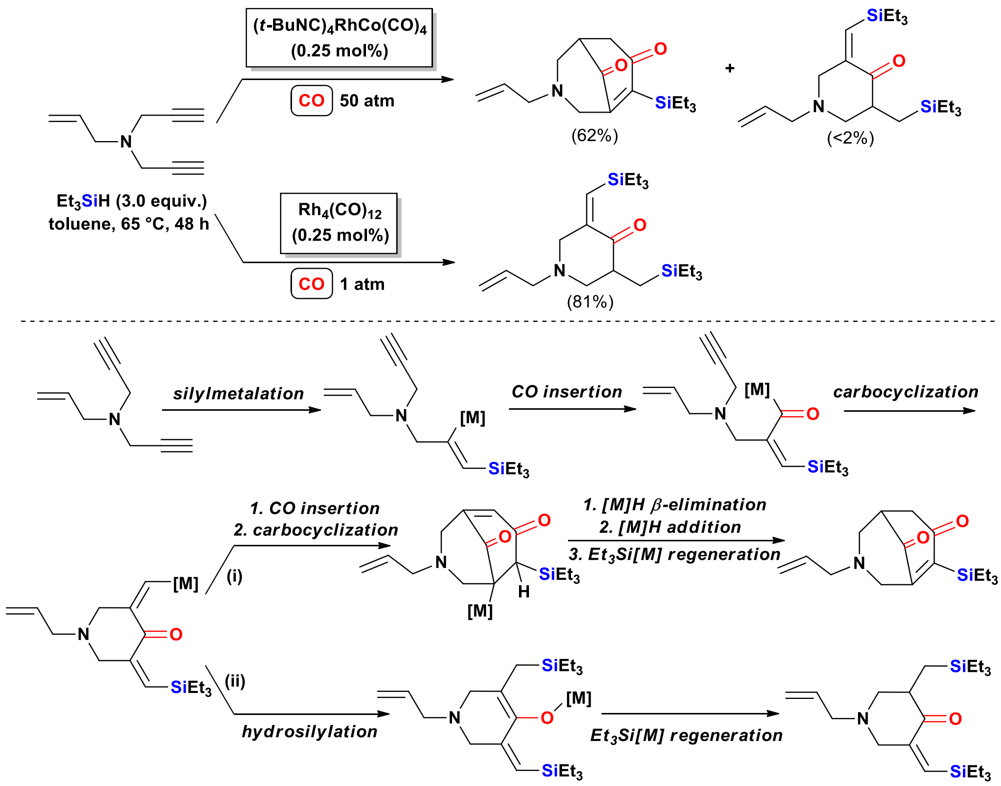
Scheme 26. Sequential Rh-catalyzed *standard* silylcarbocyclization/Pd-catalyzed Hiyama cross-coupling of allyl propargyl ethers and amines.

3.1.2. Standard Silylcarbocyclizations of Dipropargyl Ethers/Amines

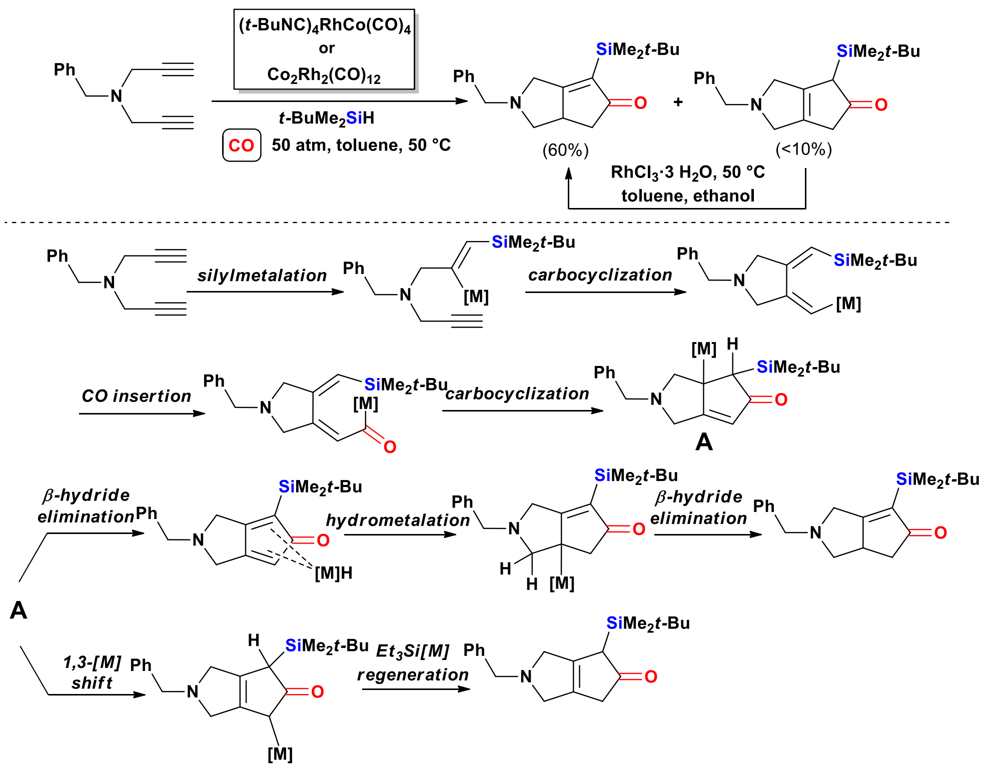
Mostly investigated by the Ojima's group, *standard* silylcarbocyclizations of dipropargyl ethers and amines represent a useful and rapid tool for obtaining *O*- and *N*-containing bicyclic compounds (especially cyclopentafuranone and cyclopentapyrrolone derivatives).

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 $(t\text{-BuNC})_4RhCo(CO)_4$ (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_3Si[M], affording a final bicyclic SiCAC product; (ii) hydrosilylation of a second molecule of silane, followed by Et_3Si[M] regeneration to give the final piperidone derivative (Scheme 27).

In a following paper, authors used very similar experimental conditions for the $(t\text{-BuNC})_4RhCo(CO)_4$ or $Co_2Rh_2(CO)_{12}$ catalyzed SiCAC of benzyldipropargylamine with *t*-butyldimethylsilane [80]: surprisingly, 7-azabicyclo[3.3.0]oct-1-ene was found (60% yield), together with small amounts of its $\Delta^{1,5}$-isomer, which can be easily converted into 7-azabicyclo[3.3.0]oct-1-ene by in situ treatment with $RhCl_3{\cdot}3\ H_2O$ at 50 °C. A plausible mechanism involved the starting silylmetalation of a triple bond with *t*-$BuMe_2SiH$, followed by a sequence of carbocyclization, CO insertion and carbocyclization to give the bicyclic intermediate **A**, from which both final products can be obtained: (i) though a sequential β-hydride elimination, regioselective hydrometalation and β-hydride elimination, 7-azabicyclo[3.3.0]oct-1-ene was obtained; (ii) its $\Delta^{,5}$-isomer was instead obtained with a 1,3-[M] shift step, followed by the regeneration of Et3Si[M] (Scheme 28) [81].

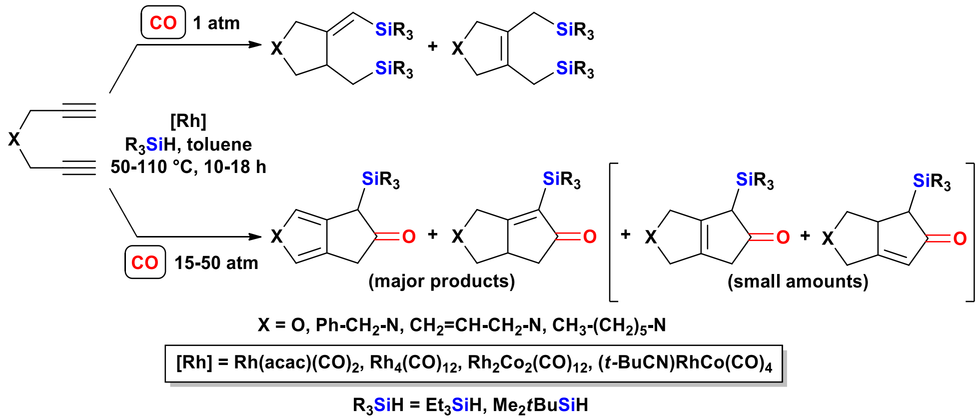


Scheme 27. First report of *standard* SiCAC of dipropargyl amines: two different mechanicistic pathways afforded a bicyclic compound incorporating two CO units (i) or a piperidone derivative incorporating a single CO unit (ii).



Scheme 28. *Standard* silylcarbocyclization 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 silylmetalation and carbocyclization steps, therefore a hydride shift and a subsequent 1,2- and/or 1,4-hydrosilylation can give final heterocyclic products.



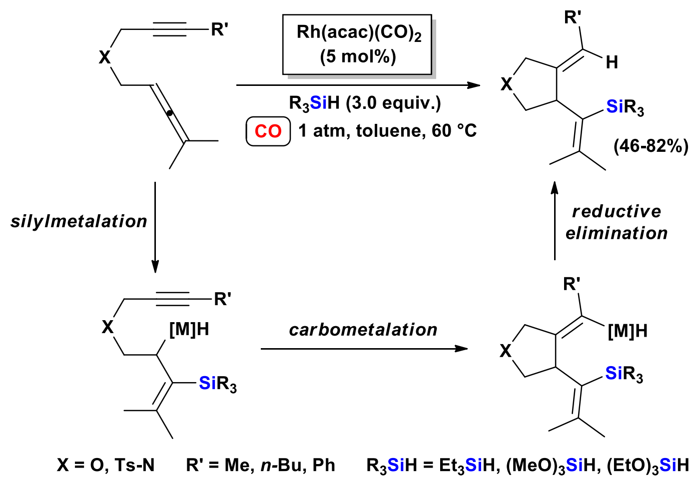
Scheme 29. Ojima's investigation on *standard* SiCAC of dipropargyl ether and amines.

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 $Rh_4(CO)_{12}$ as catalyst and tBuMe$_2$SiH (2.0 equiv.) as silane, under high CO pressure (20 atm) at 95 °C and using benzene or CH_3CN as solvent, to give the corresponding heterobicyclo[3.3.0]octenones as a mixture of regioisomers.

To conclude this section on *standard* silylcarbocyclizations, 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)CO_2 complex (5 mol%) as the most efficient catalyst (Scheme 30). The proposed mechanism, supported by deuterium labeling experiment, involved a regioselective silylmetalation on the double bond of the allene moiety closer to the heteroatom, followed by carbometalation 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 Silylcarbocyclizations of Alkynes

Transition metal-catalyzed *cascade* silylcarbocyclizations 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-1*H*-cyclopenta[*e*]azulen-5(6*H*)-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.

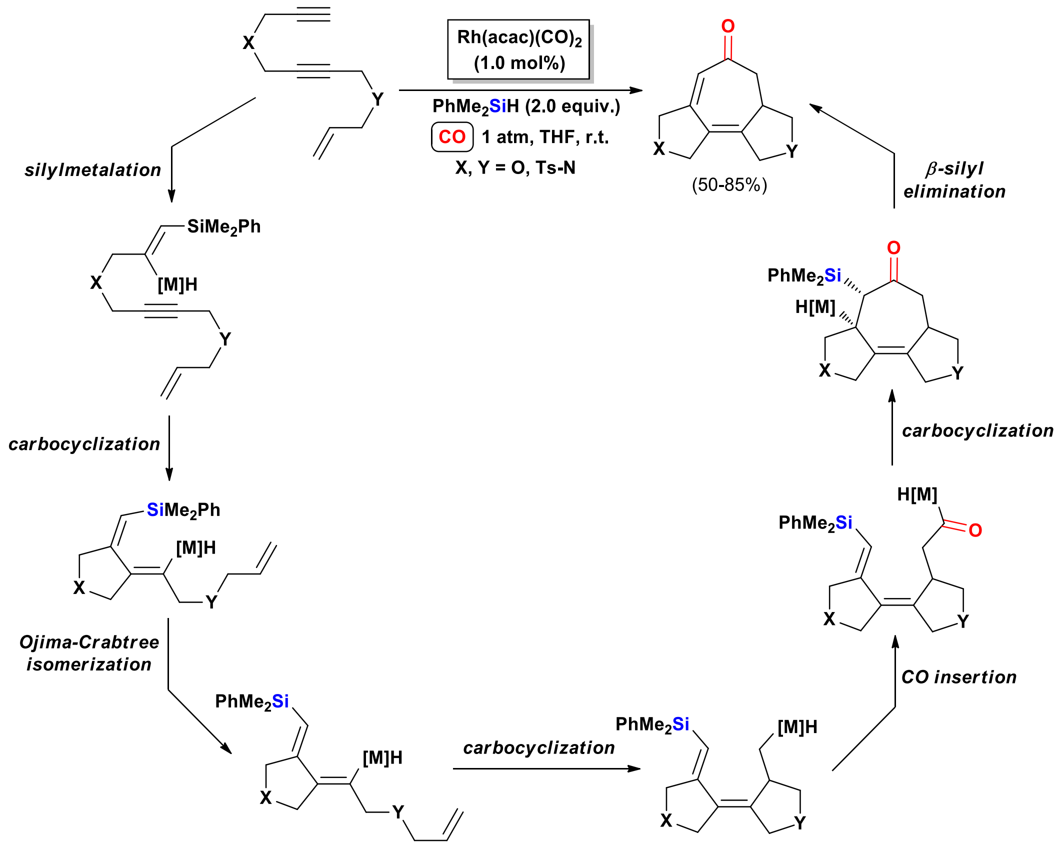


Scheme 30. *Standard* SiCAC of proparyl homoallenyl ethers and amines under atmospheric CO pressure: synthesis of cyclic (tetrahydrofuran or pyrrolidine) 1,4-dienes.

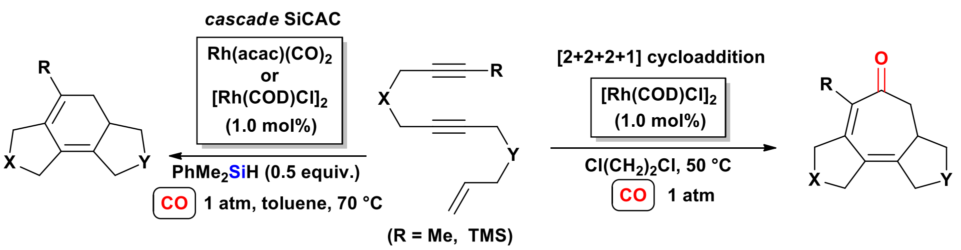
3.2.1. Cascade Silylcarbocyclizations of Enediynes

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-diyne was treated with $PhMe_2SiH$ (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-1*H*-cyclopenta[*e*]azulen-5(6*H*)-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-1*H*-cyclopenta[*e*]azulen-5(6*H*)-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 silylmetalation 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-diyne was treated with $PhMe_2SiH$ (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-1*H*-cyclopenta[*e*]azulen-5(6*H*)-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-1*H*-cyclopenta[*e*]azulen-5(6*H*)-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].



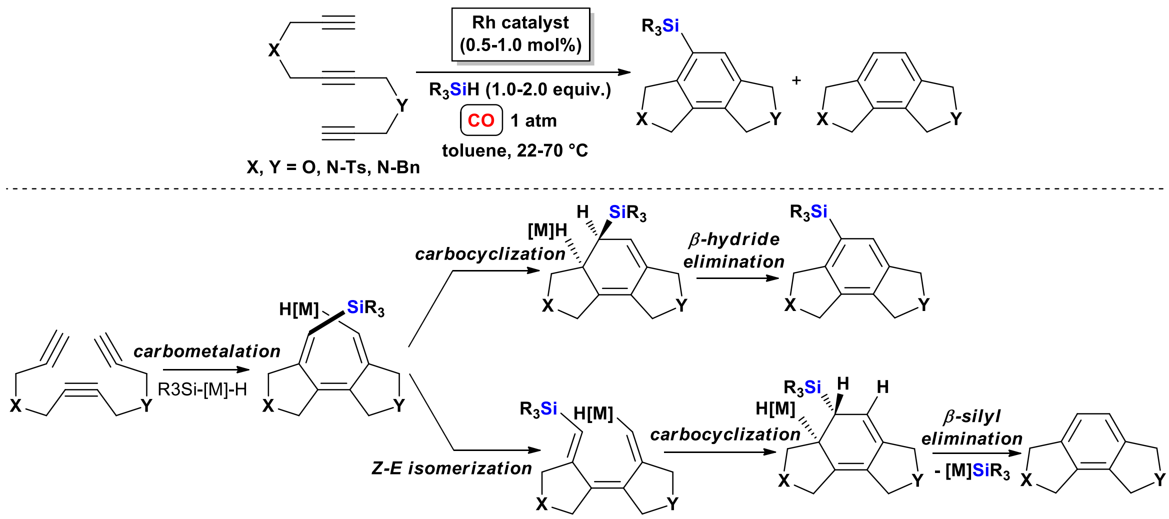
Scheme 31. First investigation of *cascade* SiCAC of enediynes: the proposed reaction mechanism involved three sequential carbocyclization steps, hence the name "cascade SiCAC".



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 $Rh_4(CO)_{12}$, $Rh(acac)(CO)_2$, $[Rh(COD)Cl]_2$ 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 33. Rh-catalyzed *cascade* SiCAC of oxygen- and nitrogen-containing analogs of dodec-1,6,11-triynes: synthesis of 1,3,6,8-tetrahydrobenzo[1,2-*c*:3,4-*c′*]difurans and 1,2,3,6,7,8-hexahydropyrrolo[3,4-*e*]isoindoles.

The most plausible mechanism starts with a silicon-initiated cascade carbometalation to give a 3,3′-bifuranylidene/3,3′-bipyrrolylidene 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*

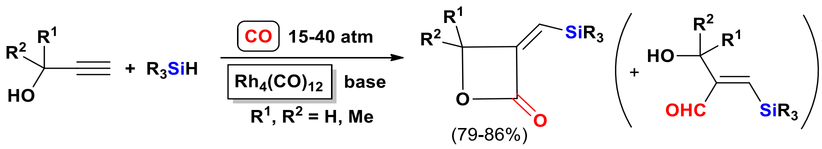
As already stressed, carbocyclizations of alkynes are extremely important reactions in the synthesis of numerous carbonyl and heterocyclic compounds of pharmaceutical and theoretical interest.

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 $Rh_4(CO)_{12}$, and in the presence of a base (e.g., Et_3N, 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 (R_3SiH, Et_3N, CO, 100 °C, $Rh_4(CO)_{12}$) (Scheme 34). Linear and branched alcohols were tested in the presence of different silanes (Me_2PhSiH, *t*-$BuMe_2SiH$, Et_3SiH, (*i*-Pr)$_3$SiH) and bases (Et_3N, 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, R^1, R^2 = H) and Me_2PhSiH in the presence of Et_3N and $Rh_4(CO)_{12}$ gave exclusively the corresponding alkenal, the use of *t*-$BuMe_2SiH$ 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.



Scheme 34. First example of *heteroatom-promoted* silylcarbocyclization of ethynyl alcohols.

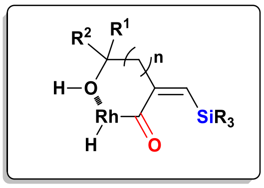
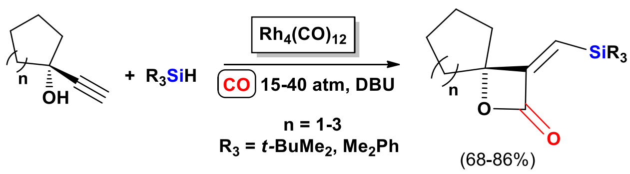


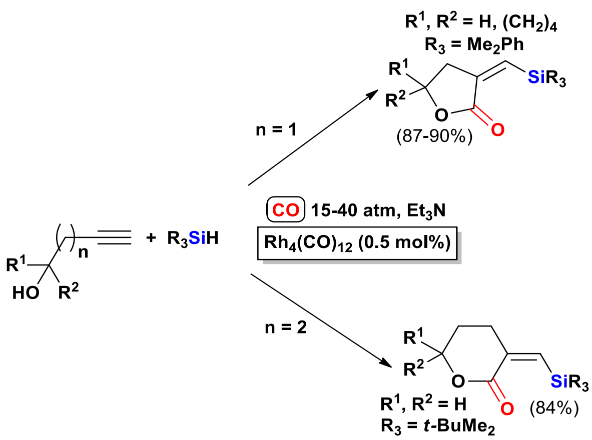
Figure 1. Rhodium-acyl intermediate hypothesized by Matsuda and co-workers in the *heteroatom-promoted* SiCAC of propargyl alcohols.

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].



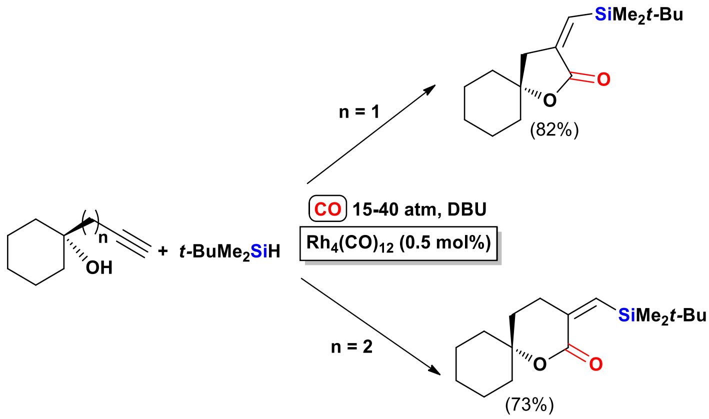
Scheme 35. Synthesis of spiro-type β-lactones via *heteroatom-promoted* SiCAC of ethynylcycloalkanols.

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 Et_3N was used, thus indicating that the formation of both five- and six-membered heterocyclic compounds is extremely favored (Scheme 36) [89].



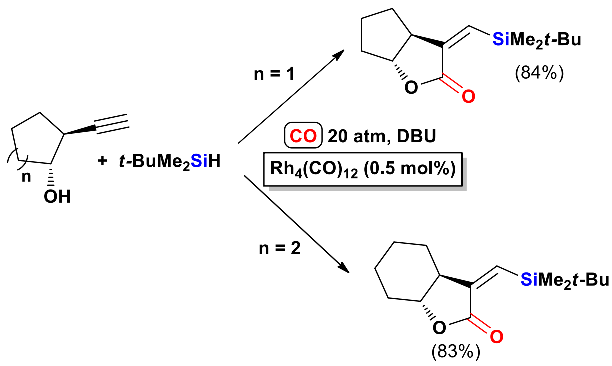
Scheme 36. Synthesis of γ- and δ-lactones via *heteroatom-promoted* SiCAC reactions.

Similarly, complete chemoselectivity towards the lactone formation was observed by the same research group in the silylcarbocyclization reactions of cyclohexanol containing a propynyl or butynyl group connected to alcohol carbon atom (Scheme 37) [4]. Once more, the use of DBU together with t-$BuMe_2SiH$ and $Rh_4(CO)_{12}$ yielded the corresponding γ- and δ-spirolactones, selectively.



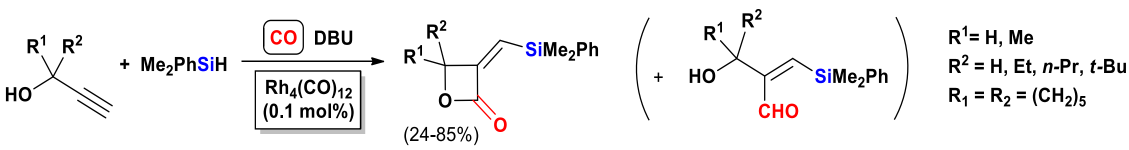
Scheme 37. Synthesis of γ- and δ-spirolactones via *heteroatom-promoted* SiCAC reactions.

However, γ-lactones can also be obtained via SiCAC reaction of *trans*-2-ethynylcyclopentanol and cyclohexanol, as depicted in Scheme 38 [4]. DBU and *t*-BuMe$_2$SiH, together with Rh$_4$(CO)$_{12}$ as catalyst, resulted in being the best reagents for the selective formation of the lactone nucleus fused to a cyclopentane and cyclohexane ring in high yields (83–84%).



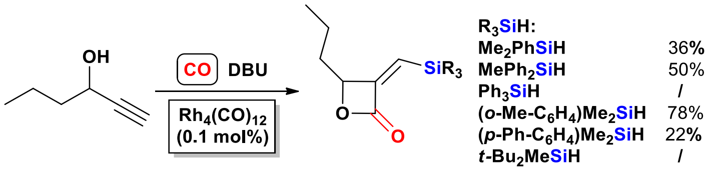
Scheme 38. *Heteroatom-promoted* SiCAC reaction applied to the synthesis of γ-lactones.

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).



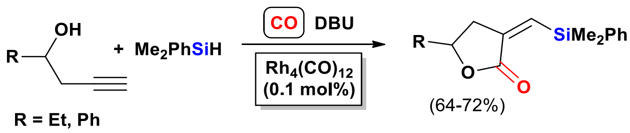
Scheme 39. *Heteroatom-promoted* SiCAC of propargyl alcohols.

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].



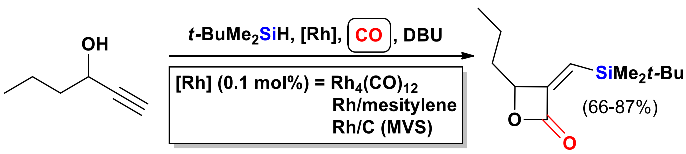
Scheme 40. *Heteroatom-promoted* SiCAC protocol applied to 1-hexyn-3-ol involving arylsilanes with a hindered substituent.

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*-tolyldimethylsilane and diphenylmethylsilane; on the contrary, Ph_3SiH 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.



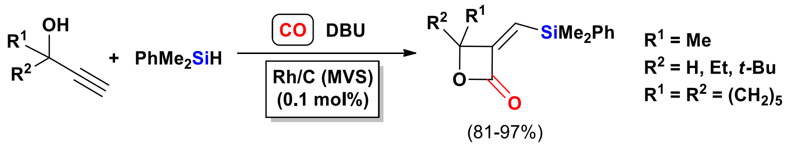
Scheme 41. *Heteroatom-promoted* SiCAC of homopropargyl alcohols: synthesis of γ-lactones.

The same authors then investigated the *heteroatom-promoted* silylcarbocyclization 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_2Cl_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).



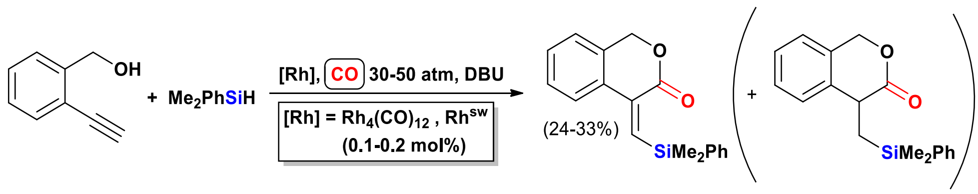
Scheme 42. *Heteroatom-promoted* SiCAC reaction of 1-hexyn-3-ol promoted by different catalytic species.

When the same rhodium co-condensate was deposited on several matrices (charcoal, γ-alumina, Fe_2O_3 and polybenzoimidazole), supported Rh/C, Rh/γ-Al_2O_3, Rh/Fe_2O_3 and Rh/PBI were prepared and tested in the *heteroatom-promoted* silylcarbocyclization 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_2PhSiH, in CH_2Cl_2 as solvent and DBU as base (Scheme 43): the reactions afforded β-lactone derivatives with almost complete chemoselectivity (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.



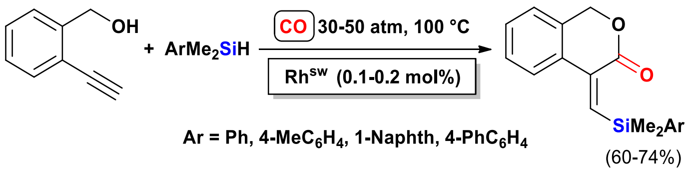
Scheme 43. *Heteroatom-promoted* SiCAC of 3-dialkylpropargyl alcohols catalyzed by Rh/C (MVS).

In 2017, the Aronica's research group developed a new protocol for the synthesis of 3-isochromanone derivatives based on *heteroatom-promoted* silylcarbocyclization reactions of 2-ethynylbenzyl alcohol [94]. Initially, the SiCAC process was performed with Me_2PhSiH as hydrosilane and $Rh_4(CO)_{12}$ as catalyst, in CH_2Cl_2 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 $(\eta^6\text{-}C_6H_6BPh_3)^-Rh^+$(1,5-COD) ($Rh^{sw}$) catalyst was employed instead of $Rh_4(CO)_{12}$.



Scheme 44. *Heteroatom-promoted* SiCAC of 2-ethynylbenzyl alcohol with Me_2PhSiH for the synthesis of 3-isochromanone derivatives.

Unexpectedly, working without DBU, the selectivity towards methyleneisochromanone increased. As a consequence, the optimized experimental conditions (Rh^{sw} 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).

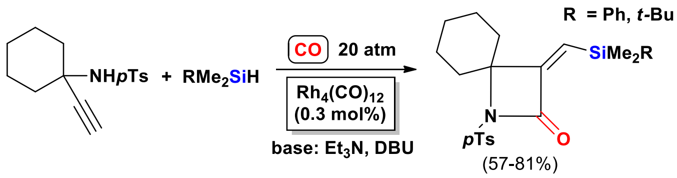


Scheme 45. *Heteroatom-promoted* SiCAC of 2-ethynylbenzyl alcohol with different aryldimethylsilanes for the synthesis of (*Z*)-isochromanones.

3.3.2. Heteroatom-Promoted Silylcarbocyclizations of Ethynyl Amines

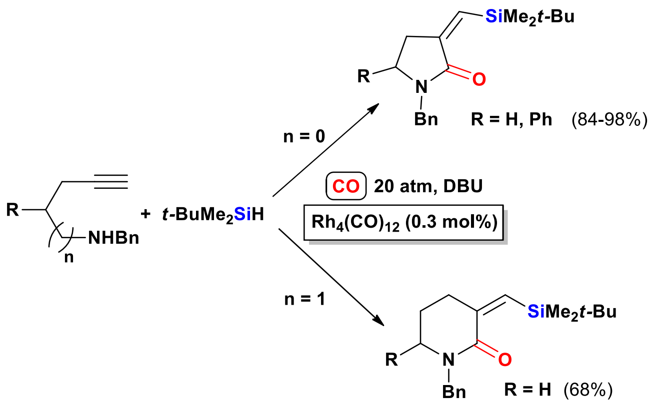
The β-lactam moiety is the key of one of the most widely employed class of antibiotics [95–97], i.e., β-lactam antibiotics such as penicillins and cephalosporins, which are distinguished by good tolerance and therapeutic safety. In particular, the α-methylene-β-lactam unit is a very common structural 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 silylcarbocyclizations of propargyl alcohols, they started their investigation with the reaction of *N*-(1-ethynylcyclohexyl)-*p*-toluensulfonamide with RMe_2SiH (R = Ph or *t*-Bu), $Rh_4(CO)_{12}$, 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-BuMe$_2$SiH) 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.



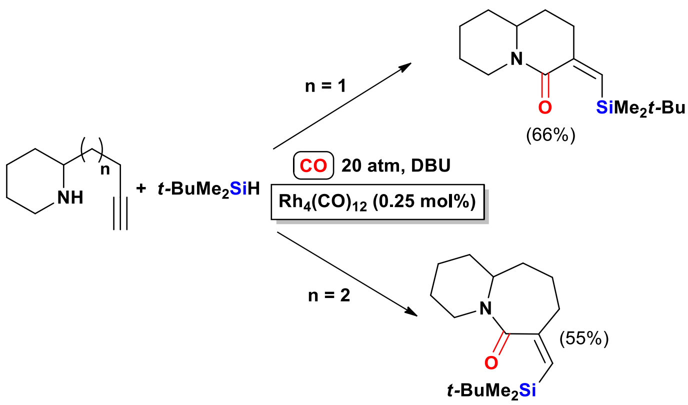
Scheme 46. First example of *heteroatom-promoted* silylcarbocyclization of propargyl amides: synthesis of α-silylmethylene-β-lactams.

Better results were described by the same research group when alkynylbenzylamines were used as substrates for *heteroatom-promoted* silylcarbocyclizations, which generated the corresponding γ- and δ-lactams [4]. The reactions were carried out with $Rh_4(CO)_{12}$ (0.25 mol%), DBU, 20 atm of CO, 100 °C and t-BuMe$_2$SiH, which was fundamental for the cyclization reaction to occur (Scheme 47).



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

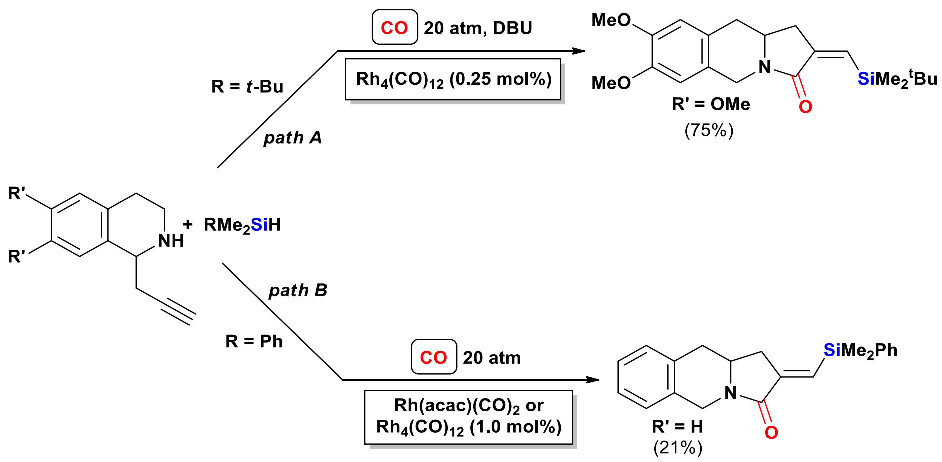
Ethynylpiperidine derivatives were also tested in the *heteroatom-promoted* SiCAC reaction under the same experimental conditions, affording the corresponding ring-fused lactam compounds in good yields (Scheme 48) [4].



Scheme 48. *Heteroatom-promoted* SiCAC reactions of ethynylpiperidines.

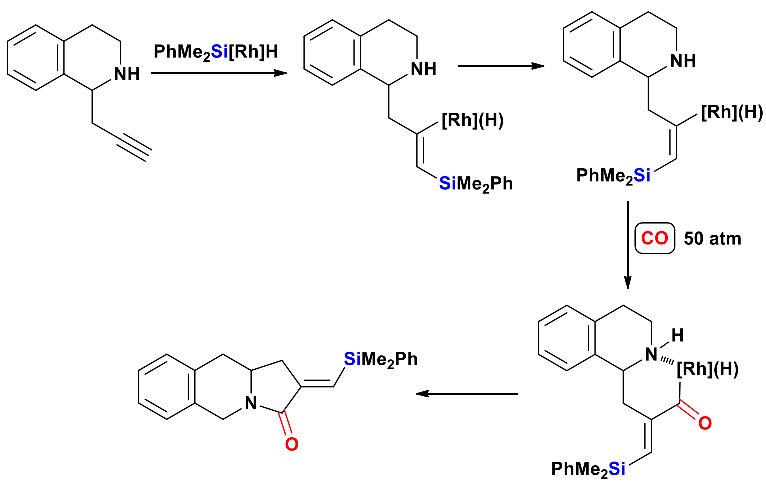
Isoquinoline-based substrates were deeply investigated in *heteroatom-promoted* silylcarbocyclizations. Matsuda et al. worked under the above-mentioned optimized conditions (i.e., t-BuMe$_2$SiH, $Rh_4(CO)_{12}$

0.25 mol%, DBU, CO 20 atm, 100 °C), affording selectively the corresponding benzoindolizidinone as the *Z*-isomer (Scheme 49, path A) [4].



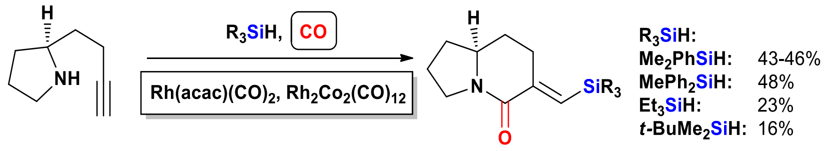
Scheme 49. *Heteroatom-promoted* SiCAC reactions applied to the synthesis of benzoindolizidinones.

Ojima and co-workers used different conditions: $PhMe_2SiH$, $Rh(acac)(CO)_2$ 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 $H[Rh]SiMe_2Ph$ to the triple bond, according to what was previously observed in the hydrosilylation reaction of 1-alkynes [108].



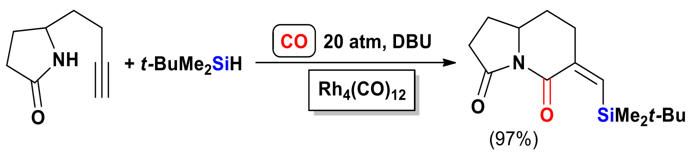
Scheme 50. Mechanism hypothesized by Ojima and co-workers for their *heteroatom-promoted* SiCAC protocol of isoquinoline-based substrates.

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 $Rh_2Co_2(CO)_{12}$ (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).



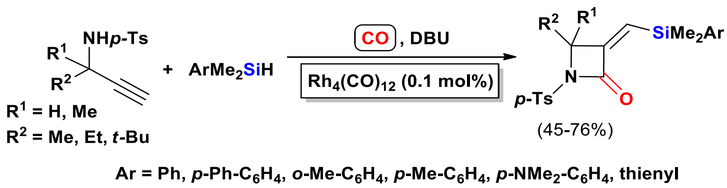
Scheme 51. *Heteroatom-promoted* SiCAC reactions applied to the synthesis of indolizidinones.

On the contrary, when Matsuda et al. investigated the reactivity of 5-(prop-2-yn-1-yl)pyrrolidin-2-one in silylcarbocyclization reaction, the corresponding *Z*-pyrrolizine-3,5(2*H*,6*H*)-dione was exclusively found, thus confirming again the central role of the base (Scheme 52).



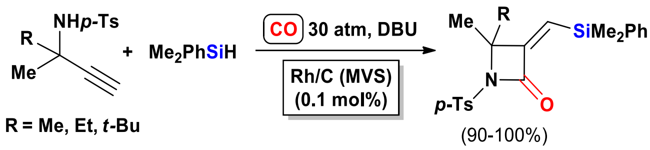
Scheme 52. *Heteroatom-promoted* SiCAC applied to the synthesis of pyrrolizine-3,5(2*H*,6*H*)-dione.

More recently, Aronica et al. applied the *heteroatom-promoted* SiCAC transformation to some propargyl tosylamides, using $Rh_4(CO)_{12}$ (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).



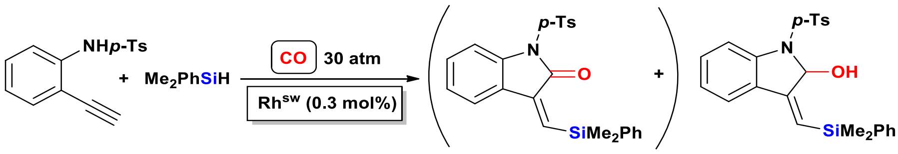
Scheme 53. *Heteroatom-promoted* SiCAC of propargyl tosylamides for the synthesis of β-lactams.

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-Al_2O_3, Rh/ Fe_2O_3 and Rh/PBI, the first species showed a specific activity even higher than homogeneous $Rh_4(CO)_{12}$ 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.



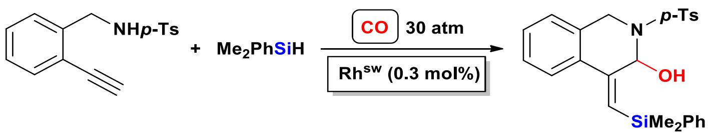
Scheme 54. Synthesis of β-lactams through *heteroatom-promoted* SiCAC reactions of propargyl tosylamides catalyzed by Rh/C (MVS).

In 2019, Albano and co-workers described the first synthesis of indolines and tetrahydroisoquinolines via *heteroatom-promoted* SiCAC of suitable tosylamides [109]. The (2-ethynylphenyl)-4-tosylamide was first tested in the reaction with dimethylphenylsilane, promoted by Rh^{sw} (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 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.



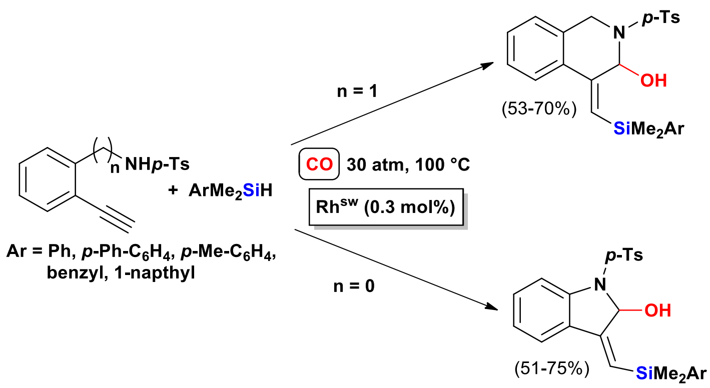
Scheme 55. Synthesis of tosylindolinol via *heteroatom-promoted* SiCAC of (2-ethynylphenyl)-4-tosylamide.

The silylcarbocyclization was then extended to the synthesis of tetrahydroisoquinolines but, again, tosyltetrahydroisoquinolinols were selectively obtained regardless the temperature employed and the nature of the catalyst (i.e., Rh^{sw}, $Rh(acac)(CO)_2$, $Rh_6(CO)_{16}$), as depicted in Scheme 56 [109]. The formation of the reduced compounds was ascribed to the presence of molecular H_2, which is formed as a by-product in the reaction vessel.



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

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 tosyltetrahydroisoquinolinols 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 tosyltetrahydroisoquinolinols via *heteroatom-promoted* SiCAC with several $ArMe_2SiH$.

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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