MICROREVIEW

Synthesis and reactivity of silylformylation products derived form alkynes

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The silylformylation reaction of unsaturated compounds consists of the rhodium catalysed addition of a R_3Si and a CHO moiety into a carbon-carbon multiple bond. The silylformylation process is applicable to both terminal and internal alkynes and is tolerant of several functional groups. Many factors can influence the chemoselectivity of the reaction that generally affords β-silylalkenals with high yields and regioselectivity. The β-silylalkenals are polyfunctionalised substrates that can be submitted to several chemical transformations and in particular can undergo fluoride-promoted (TBAF) aryl migration from an aryldimethylsilyl group to the adjacent carbon atom thus generating 2-(arylmethyl)aldehydes, important industrial precursors of perfumes. This silylformylation-aryl migration two-steps sequence can be applied to functionalised alkyne precursors and chemo-, regio- and stereoselectivity of the products can be modulated according to the nature and the position of the functional group. When a good leaving group is present in the ω position of the aliphatic chain of the alkyne cyclisation products are obtained, while α,β-unsaturated aldehydes are generated from propargyl~~ic~~ tosylamides, acetates and benzoates. α-Silylmethylen-β-lactams, prepared from ~~propargyl~~ *p*-tosylamides according to silylcarbocyclisation reaction, can be transformed into the corresponding arylmethyl-β-lactams by means of TBAF induced rearrangement that takes place without involving the lactam ring. A plausible mechanism of the rearrangement reaction is reported that suggests the addition of the fluoride ion to the arylsilicon moiety and the consequent migration of the aryl group to the adjacent carbon atom. Both aryl and heteroaryl substituents can migrate without any loss of configuration further enhancing the high synthetic value of this protocol.

1. Introduction

Silicon has received the attention of chemists for many years because of its low cost, abundance and non toxic properties. In particular, the use of organosilicon compounds in organic synthesis and large scale applications has been growing intensively, due to their relatively high stability and their ability to induce chemo-, regio- and stereoselective transformation when combined with appropriate catalysts.[1] For instance, the transition metal mediated hydrosilylation[2] and, more recently, the rhodium catalysed silylformylation reactions are among the most suitable methods used to functionalised carbon-carbon multiple bonds. While hydrosilylation has been known from nearly 50 years, the first example of silylformylation was reported by Murai and coworkers in 1977.[3] When cycloolefins were reacted with diethylmethylsilane and carbon monoxide in the presence of $Co_2(CO)_8$ enol silyl ethers were obtained. No compounds derived by direct formylation (i.e. β-silylaldehyde or acylsilane) were detected (Scheme 1).

On the contrary, treatment of a terminal triple bond with CO and a hydrosilane (silylformylation process) resulted in the carbonylation of the internal carbon of the unsaturated moiety affording (*Z*)-β-silylalkenals in high yields and with high degree of regio and stereochemical control (Scheme 2). [4]

The silylformylation of alkynes is generally tolerant of many functional groups such as ethers, esters, alcohols, aldehydes, halogens, nitriles and double bonds. As a consequence the silylformylation reaction of alkynes is considered a very useful experimental procedure to obtain polyfunctionalised compounds. The synthetic usefulness of the β-silylalkenals becomes particularly evident if the reactivity of vinylsilanes towards electrophiles[5] is considered together with the well known transformations of the α,β-unsaturated carbonyl moiety (Scheme 3).[6]

Indeed, β-silylalkenals can be converted into functionalised dienes,[7] dienones,[8] α,β-unsaturated alcohols, ester and ketones,[9] and can be important precursors for the synthesis of more complicated molecules via Peterson olefination,[10] Nazarov type cyclopentenone anulation[11] or Trost type cyclopentane anulation.[12]

Recently, taking advantage of the high chemical affinity between silicon and fluorine, we were able to transform β-arylsilylalkenals into the corresponding 2-methylaryl aldehydes by means of a fluoride induced aryl migration from the silicon to the adjacent carbon atom (Scheme 4). [13]

The reactivity of β-silylalkenals just described clearly enhances the importance of the silylformylation process as synthetic pathway to molecules of high added value.

At the beginning of this review a detailed survey on the metal catalysed silylformylation process and related reactions is reported. The influence of the alkyne and silane structures, of the rhodium species employed and in general of the experimental conditions on the chemo- and regioselectivity of the reaction is described. In the second part the reactivity and in particular the fluoride-induced transformation of the silylated products is deeply analysed.

2. Silylformylation Reactions

2.1 Silylformylation of alkynes

The silylformylation reaction can be considered as a hydrosilylation process performed under carbon monoxide atmosphere. The reaction generally results highly chemoselective but by-products of hydrosilylation of both the acetylenes and the β-silylalkenals have been observed sometimes (Scheme 5). In particular the extent of such side reactions is connected to the steric and electronic requirements of the alkyne and the silane. Generally speaking, non hindered reagents involve clean silylformylation processes with low or any by-products amounts, while the higher the crowding near the triple bond, the lower the chemoselectivity. A detailed investigation regarding the interaction between the substrates structure and reactivity follows.

2.1.1 Silylformylation of terminal alkynes

Matsuda[14] reported that the reaction of 1-alkynes characterized by a linear aliphatic chain afforded exclusively the corresponding 2-substituted-3-silyl propenals in high yields and regioselectivity as summarized in Scheme 6. On the contrary when the reactivity of branched acetylenes was investigated[15] the products distribution resulted remarkably affected by the steric hindrance of the alkynes (Table 1). While 5-methyl-1-heptyne showed a chemoselectivity similar to 1-hexyne (Table 1, entries 1 and 2), when the reaction was carried out with alkynes with a substituent in α or β position to the triple bond, a decrease in both the reaction rate and selectivity was observed (Table 1, entries 3–5) and relevant amounts of hydrosilylation by-products were detected.

In particular, in the cases of 3-alkyl-1-butynes a fine tuning of the experimental conditions was necessary to improve the chemoselectivity of the reaction (Table 2). A nearly complete selectivity towards silylformylation of 3-methylpentyne (Table 2, entry 1) was achieved when the carbon monoxide pressure, the rhodium extent and the alkyne/silane ratio (2:1) were increased. In the case of a quite hindered alkyne such as 3,4-dimethyl-1-pentyne the aldehyde yield didn't exceed 55 %,

even raising the CO pressure to 50 atm and the reaction time (48 h), the formation of large quantities of β-silylalkenals hydrosilylation products being detected (Table 2, entry 2).

A particular behaviour was observed when 3-phenyl-1-butyne was reacted with Me_2PhSiH in the presence of 0.1 mol- % of Rh/mesitylene (Table 2, entry 3). A good conversion and a high yield of the aldehyde were achieved when the reaction was carried out at 50 atm of CO, indicating an important role of the aromatic ring on the alkyne reactivity. This effect was enhanced when benzene was directly conjugated to the triple bond. Indeed, a competitive reaction carried out by Matsuda et al. using Me_2PhSiH as hydrosilane revealed that phenylacetylene reacted much faster than 1-hexyne, as shown in Scheme 7.[16]

Analogously, the reactions of aromatic acetylenes with triethylsilane and carbon monoxide were performed by Doyle[17] under mild experimental conditions (room temperature, 10 atm CO) and afforded the desired aldehydes in high yields and complete chemoselectivity (Scheme 8).

2.1.2 Silylformylation of internal alkynes

Few examples of silylformylation of internal alkynes have been reported. As described by Matsuda et al.[16] (Table 3), 2-butyne, 2-hexyne, 1-phenylpropyne and diphenylacetylene (entries 1–4) gave the corresponding β-silylalkenals in good yields.

Two regioisomers were formed in the reaction of unsymmetrically substituted alkynes (Table 3, entries 2 and 3). The regioselectivity seems to be governed by the steric requirements of the substituents: the silyl group was mainly introduced at the sp carbon bearing the less hindered groups. According to previous results[15] (see Tables 1 and 2) trimethylsilylacetylenes (Table 3, entries 5 and, 6) did not gave any carbonylated products due to the high steric hindrance arising from the bulkiness of the Me_3Si group.

2.1.3 Silylformylation of functionalised alkynes

As already mentioned, the silylformylation reaction can be performed in the presence of several functional groups that are not involved in the silane addition. Indeed when Ojima reacted a few alkynals (Scheme 9) with different hydrosilanes in the presence of Rh or Rh-Co catalysts the formyl moiety of the precursors remained intact even when excess silane was used.[18]

Similarly the reaction of different ω-functionalised acetylenes[19] generally afforded the corresponding aldehydes with high yields regardless of the electronic and steric requirements of the alkynes and the length of the aliphatic chain (Table 4, n = 2–4). Double or triple bonds, halogens, nitrile, tosylate, hydroxyl, epoxide, ester functionalities could be present in the molecule without affecting the reactions that yielded the expected products quantitatively in most cases. Only in the

presence of a free amino group or a COCl moiety it was not possible to isolate the β-silylalkenal although a complete conversion of the reagents was observed with concomitant formation of some unidentified materials. Moreover, small amounts of by-products of double silylation were detected when 1,7-octadiyne was used even if the reaction was carried out with excess alkyne and under high CO pressure (Table 4, entry 10). A different behaviour was observed when propargyl derivatives were considered.[20] The presence of a functional group in the alpha position of the triple bond requested stronger experimental condition (100 °C, 24 h).

The data reported in Table 5 indicated that the nature of the propargyl~~ic~~ substituents was a key element of the process. Indeed, while 3-bromopropyne and the corresponding sulphonates were completely decomposed during the reaction (Table 5, entries 1, 3, 4), 2-propyn-1-ol, propargyl benzoate and acetate (Table 5, entries 2, 5, 6) were successfully converted into the β-silylalkenals derivatives. As far as the propargyl amides, both *tert*-butoxy carbonyl (BOC) and tosyl protections of the nitrogen atom were effective for the formation of the functionalised aldehydes (Table 5, entries 7 and 8). In particular the reaction of the propargyl tosylamide was quantitative affording the expected product in high yield (91 %).

The latter results were particularly interesting since Matsuda et al. reported[21] that propargyl amine derivatives reacted under carbon monoxide with two equivalents of hydrosilane to generate 2-silylmethyl-2-alkenals. They could not isolate the expected β-silylalkenals. A deep analysis[21b] of the mechanistic aspects of this process (Scheme 10) revealed that the β-silylalkenal was probably the unstable intermediate that was converted into the double silylated derivative, susceptible to an elimination step to form the observed products. The nature of the substituents on the nitrogen atom highly affected the reaction, the benzyl groups providing clear results with high yields. On the other hand, the desired β-silylalkenals were exclusively obtained simply changing the nitrogen protection from benzyl to tosyl and operating with an equivalent of silane.[20]

In order to verify the potentialities of this reaction tosylamides and arylsilanes with different steric and electronic requirements were investigated.[20]

As can be easily deduced from the data described in Table 6, the silylformylation of propargyl amides was appreciably affected by the structure of the acetylenic reagents, in agreement with the results previously observed studying the reaction of non functionalised branched 1-alkynes[15]. Indeed, the less hindered tosyl amides reacted rapidly with almost total selectivity towards the corresponding β-silylalkenals (Table 6, entries 1–3). On the other hand, decreases on both the reaction rate and selectivity were detected when the silylformylation was carried out on acetylenes with bulky substituents on the propargyl carbon, relevant amounts of Matsuda's aldehydes being detected (20 %, Table 6, entry 4). In particular, in the case of *N*-(1-*tert*-butyl-1-methyl-2-propynyl)-

p-toluenesulphonamide (Table 6, entry 5), the conversion after 24 h was only 53 % and the hydrosilylation reaction resulted highly competitive with the formylation one (62 % vs. 38 %). An analogous reaction trend was observed when hindered arylsilanes were employed: the use of *ortho*-tolyldimethylsilane resulted in a significant lowering of the reaction rate with respect to Me_2PhSiH (Table 6, entry 6 vs. 1). However, the chemoselectivity of the process was quite good, thus allowing the extension of the silylformylation of propargyl amides to functionalised hydrosilanes.

2.1.4 Hydrosilanes in the silylformylation reaction

The hydrosilane structure exercises a pronounced influence on the chemoselectivity of the silylformylation reaction. Indeed Ojima et al.[22] compared the reactivity of some hydrosilanes towards 1-hexyne and observed an increasing of hydrosilylation side reaction when alkyl silanes were used (Scheme 11).

Matsuda and co-workers found[16] that silylformylation performed with hydrosilanes bearing a phenyl group proceeded approximately 10 times faster than that with trialkylsilanes. The high reactivity of Me_2PhSiH was also reflected in the result that 3-(dimethylphenylsilyl)-2-phenylpropenal was predominantly formed in a competitive reaction starting from phenylacetylene and 1 equivalent each of Me_2PhSiH and $^tBuMe_2SiH$. In sharp contrast to dimethylphenylsilane, Ph_2SiH_2 did not cause silylformylation at all: hydrosilylation was the sole reaction pattern observed.

Recently the reactivity and selectivity of aryl silanes with substituents on the aromatic ring has been tested in the silylformylation of 1-hexyne chosen as model substrate (Table 7). [19, 23] Both aromatic and heteroaromatic silanes were employed, yielding the pure products with complete regio and stereoselectivity. According to the trend observed for the alkynes, when the steric hindrance of the silane increased the aldehydes yields lowered (Table 7, entries 1 and 6). Electron donating and electron withdrawing groups can be present on the aromatic ring without affecting the reaction (Table 7, entries 2–5). Moreover thienyldimethylsilane was successfully reacted thus representing the first application of heteroarylsilanes to the silylformylation process.

2.1.5 Mechanistic considerations

As already underlined, the silylformylation reaction can be considered as a hydrosilylation process performed under carbon monoxide atmosphere. It is then reasonable that the mechanism of alkynes silylformylation should be closely related to that of the hydrosilylation reported by Chalk and Harrod[24] and involving first of all the insertion of the rhodium atom into the Si-H bond. Indeed, by means of deuterium labelling experiments, Matsuda and co-workers[16] suggested that the interaction between the hydrosilane and the rhodium complex is fundamental in the silylformylation

process. They proposed two catalytic cycles, A and B, as possible reaction mechanisms (Scheme 12).

In cycle A, [Rh]-SiR'_3 (i.e. $Rh(CO)_4SiR_3$) (I) initially formed by declustering of $Rh_4(CO)_{12}$ with $R_3'SiH$, reacts with acetylene to form the vinyl-rhodium species (III). Insertion of CO between the carbon-rhodium bond of (III) affords the acyl-rhodium intermediate (IV). Oxidative addition of a Si-H bond to the rhodium metal generates (V) which gives the silylformylation product by reductive elimination and regenerates the [Rh]-SiR'_3 specie. In the alternative cycle B, complex (VI), derived from (I) by the oxidative addition of $R_3'SiH$, interacts with an alkyne to form (VIII) via (VII). The insertion of CO into the rhodium-carbon (vinyl) bond of (VIII) leads to (V) and then to the β-silylalkenal. In whichever cycle silylformylation may take place the findings obtained so far are consistent with both of those shown in Scheme 12.

2.1.6 Rhodium catalysts

Most of mechanistic investigations on the silylformylation reaction were performed with $Rh_4(CO)_{12}$ since it is a widely used specie. Recently several Rh(I) and Rh-Co mixed complexes were successfully employed. Ojima et al.[22, 25] showed that homogeneous bimetallic species are effective to catalyse the silylformylation of 1-hexyne at 25 °C and under 10 atm of CO. They analysed the effect of the catalyst structure on the selectivity of the reaction using $(t\text{BuNC})_4RhCo(CO)_4$, $Rh(acac)(CO)_2$, $Co_2Rh_2(CO)_{12}$, $Rh_4(CO)_{12}$, and $RhCl(PPh_3)_3$ in the reactions of 1-hexyne with dimethylphenylsilane (Scheme 13).

$(^t\text{BuNC})_4RhCo(CO)_4$ turned out to be the best catalyst for silylformylation while $Co_2(CO)_8$ and Wilkinson's $RhCl(PPh_3)_3$ were totally inactive. The bimetallic synergism in the reaction catalysed by cobalt-rhodium mixed-metal cluster was deeply elucidated by Ojima and Nakamura.[26] They carried out a reaction of $Co_2Rh_2(CO)_{12}$ with two equivalents of 1-hexyne at 25 °C and 5 atm of carbon monoxide. A Rh-Co mixed metal butterfly alkyne complex was isolated as a reddish-orange solid. Then it was allowed to react with excess dimethylphenylsilane and 1-hexyne to give cleanly the silylformylation product and the complex (Scheme 14). These results indicated that the butterfly complex was an active catalyst species or its direct precursor.

Doyle's group[17] investigated the catalytic activity of cationic $Rh_2(pfb)_4$ (perfluorobutyrate) in the silylformylation of terminal alkynes. The reaction proceeded even at atmospheric pressure of CO, at 0 °C, if the alkyne was added in a controlled manner (4–5 h) to the solution of Me_2PhSiH and the catalyst (Scheme 15).

Recently, a few dirhodium (II) cationic complexes were prepared by Basato et al.[27] and tested in the silylformylation of 1-hexyne with dimethylphenylsilane (Scheme 16).

The parent $Rh_2(OAc)_4$ exhibited very poor productivity, whereas the cationic complexes were much more effective. Only the *Z* isomer of the silylformylated product was observed which highlighted the high regio and stereoselectivity obtained with these catalysts. The best results were achieved using the cationic complex with acetonitrile ligands, while $[Rh_2(OAc)_2(Naft)_4](BPh_4)_2]$ was almost inactive.

Alonso and co-workers[28] compared the behaviour of several neutral and cationic rhodium (I) complexes with P, N donor ligands in the catalysis of the silylformylation of 1-hexyne with Et_3SiH (Scheme 17). All the tested compounds catalysed the reaction under atmospheric pressure of CO affording exclusively the expected (*Z*)-β-silylalkenal. The cationic complexes exhibited lower catalytic activity than the neutral ones while the number or the kind (Py or amine) of the nitrogen chelating atoms did not have a relevant effect on the catalytic activity.

In the last decade the chemistry of transition nanoparticles has been rapidly developing and their use in many catalytic reactions has been increasing. Rhodium nanoclusters dispersed into a mesitylene solution can be obtained according to the Metal Vapour Synthesis technique,[29] consisting of the simultaneous condensation of both the metal and the organic solvent on the walls of a glass reactor cooled to liquid nitrogen temperature. On warming up the obtained solid matrix to room temperature, a red-brown ‘‘solution’’ is produced. The interaction of the organic ligand with the metal particles is so weak that the obtained solvated metal atoms can be regarded as naked nanoclusters. Rh/mesitylene (Rh/MVS) species have been successfully employed in the silylformylation of 1-hexyne and dimethylphenylsilane and their catalytic activities (turnover numbers, TONs, calculated as [mmol (silane) /mmol (Rh) x time of reaction (h)] x conv. %) were compared with those of $Rh_4(CO)_{12}$ chosen as reference catalyst.[15] As it is evident from Table 8, both rhodium species displayed good catalytic activity in the silylformylation process, but the Rh/mesitylene cocondensate showed better TONs, probably due to its highly reactive rhodium nanoclusters. Very low turnover numbers were observed for both catalysts when the reactions were carried out under atmospheric pressure of carbon monoxide (Table 8, entries 1 and 2), while improved reaction rates resulted on increasing P_{CO} to 10 bar (Table 8, entries 3 and 6). When the reaction was performed in the presence of 1 mol-% of Rh/mesitylene cocondensate (Table 8, entry 4), a strong reduction in chemoselectivity was observed, large quantities (50 %) of hydrosilylation by-products being formed. These results clearly indicate that the amount of catalyst has a prominent influence on the chemoselectivity of the reaction (silylformylation versus hydrosilylation). The observed trend was confirmed by the reactions carried out with $Rh_4(CO)_{12}$ as catalytic species. In the presence of a very small quantity (0.01 mol-%) of the catalyst (Table 8, entry 5), a marked decrease in the reaction rate was measured but high chemoselectivity was detected.

When 0.1 mol- % of $Rh_4(CO)_{12}$ was employed (Table 8, entry 6), the β-silylalkenal was obtained in nearly quantitative yield. Increasing the amount of the rhodium species to 1 mol- % (Table 1, entry 7) a strong reduction in chemoselectivity resulted, the hydrosilylation products constituting 49 % of the reaction mixture. Total absence of the silylformylation product was observed if a relatively large amount of catalyst was used (3 mol-%, Table 1, entry 8), even under 25 atm of carbon monoxide pressure. The importance of the amount of catalyst in the silylformylation reaction is underestimated in the literature. Only Murai[30] reported a competitive formation of *n*-hexylsilanes in the silylformylation of 1-hexene, performed with a 1:10 catalyst/hydrosilane ratio [10 mol-% $Co_2(CO)_8$]. The effect of the amount of rhodium on the chemoselectivity of the process could be explained considering that the silylformylation and the hydrosilylation reactions are competitive processes, since both of them involve initially a metal-catalysed interaction between an acetylene and a hydrosilane (see mechanism above, Scheme 12). The presence of large quantities of the rhodium species seemly causes the reductive elimination to be faster than the CO insertion and hence the hydrosilylation process to prevail on the silylformylation one.

2.1.7 Solvents

The silylformylation reactions are commonly performed in organic solvents such as dichloromethane, benzene, toluene. The first and sole example of silylformylation carried out in ionic liquids has been described by Yamamoto and co-workers[31] in 2001 (Scheme 18).

1-Butyl-3-methylimidazonium hexafluorophosphate ([Bmim][PF_6]) was selected as catalyst medium. The reaction in the ionic liquid was examined in order to construct a reusable catalyst system. The zwitterionic rhodium complex [$Rh^+(COD)(\eta^6\text{-}C_6H_5BPh_3)^-$] was dissolved into [Bmim][PF_6], Me_2PhSiH and 1-octyne were added and the two-phase system was reacted under 40 atm of CO. After 24 h the upper phase, which contained the product, was separated and the lower layer was reused three times without significant loss of reactivity, thus indicating that almost the whole amount of catalysts remained in [Bmim][PF_6] phase and could be recycled.

2.2 Silylhydroformylation

If alkylsilanes or arylsilanes are reacted with terminal acetylenes under a mixed CO/H_2 atmosphere a different reaction takes place. Alper and co-workers called this process "silylhydroformylation" since it consists of the addition of hydrogen and carbon monoxide to gave the α,β-unsaturated aldehyde (hydroformylation) together with the contemporary insertion of a silyl moiety (Table 9, Scheme 19).[32]

According to Alper's investigations, the (silylmethyl)alkenals are presumably formed by rearrangements of the vinyl rhodium species initially formed (Scheme 19, I) to (II) and (III), insertion of CO into the rhodium-carbon bond and finally reductive elimination.

2.3 Intramolecular silylformylation and silylcarbocyclisation of alkynes

As already stressed, the silylformylation reaction of 1-alkynes gives 1-silyl-2-formyl-1-alkenes with high regio and stereoselectivity. However, this regioselectivity was completely reversed by designing the intramolecular version of this reaction that proceeds via exo-dig cyclisation exclusively. For example the reactions of ω-dimethylsiloxyalkynes afforded the corresponding (*Z*)-5-exo-formylalkylideneoxasilacycloalkanes in excellent yields (Scheme 20). [33]

In a similar manner, the reactions of ω-dimethyl-silylalkynes yielded 5-formylalkylidene-1-silacycloalkanes (Scheme 21). [34]

The same regioselectivity towards the exocyclic isomer was detected when branched ω-silylalkynes[35] were reacted with carbon monoxide in the presence of a catalytic amount of the zwitterionic complex $[Rh^{+}(COD)(\eta^{6}\text{-}C_6H_5BPh_3)^{-}]$ (Table 10).

The steric hindrance of the C_3-substituent affected both the rate and the stereoselectivity of the process. Indeed, when a bulky substituent such as *tert*-butyl was present on the substrate longer reactions times (Table 10, entry 3) and higher CO pressure (50 atm, Table 10, entry 4) were necessary to improve the yield of the silacyclane. In this case the reaction resulted completely selective towards the formation of the *trans* diastereoisomer. However, when the substituent was a methyl group, no stereoselectivity was observed, i.e. *cis/trans* = 1.

More interesting than the intramolecular process are the reactions of silylcarbocyclisation[36] that provide efficient and useful methods for the synthesis of cyclic and polycyclic compounds of medicinal interest. When carbocyclisation of functionalised alkynes occurs together with silylation and carbonylation, the vinylidene silyl moiety and the CO group can be outside or inside the formed cycles and the obtained products depend on the functional group present on the alkynes (Scheme 22).

In 1999 Matsuda reported[37] the first study on the carbonylative silylcarbocyclisation (CO-SiCaC) of enynes (Scheme 22, route 1, R^1, R^2 = COOMe). The reactions were initially performed with Me_2PhSiH, under 20 atm CO pressure, at 90 °C in the presence of a catalytic amount (0.5 %) of $Rh_4(CO)_{12}$. The formylated cyclopentenyl product was obtained in good yield and chemoselectivity. Other silanes, Me_2EtSiH, Et_2MeSiH and *t*$BuMe_2SiH$ reacted under the same reaction conditions to give the expected molecules, though a decrease of the yield was observed as soon as the steric hindrance of the silanes increased (34 % with *tert*-butyldimethyl silane). More recently Ojima and

co-workers[38] deeply investigated the CO-SiCaC reactions of several enynes (Scheme 22, route 1, R^1, R^2 = COOEt, CH_2OMe, CH_2OAc, CH_2OH...) and pointed out the importance of the experimental conditions on the chemoselectivity of the process. Indeed, the optimal conditions consisted of $Rh_4(CO)_{12}$ (0.5 %) and a ligand such as $P(OEt)_3$ (10 mol- %), at 105 °C and 20 atm of CO, at 0.02 M substrate concentration in dioxane. Thus highly functionalised exo-silylmethylene-cyclopentane derivatives bearing a formyl moiety at the C2 positions were generated in very good yields (83–91 %). Chung et al. found[39] that cobalt/rhodium nanoparticles (Co_2Rh_2) derived from $Co_2Rh_2(CO)_{12}$ were very efficient catalysts for the carbonylative silylcarbocyclisation of 1,6-enynes to silylated carbocycles bearing an aldehyde group, under 1 atm of carbon monoxide and without the addition of any ligand (Scheme 22, route 1, R^1, R^2 = COOEt, COOMe, CH_2OH, 52–98 %).

The reaction of 1,6-diynes under the CO-SiCaC conditions afforded 2-silylbicyclooctenones (Scheme 22, route 2). The reaction of diethyl dipropargylmalonate (Scheme 22, route 2, R^1, R^2 = COOEt) with *t*BuMe$_2$SiH under 15 atm of CO, catalysed by $Rh_2Co_2(CO)_{12}$ or Rh(acac)$(CO)_2$ was described for the first time by Ojima's group[40] and gave cleanly the bicyclo derivative in > 90 % isolated yield. The internal double bond generally resulted at the 3–4 carbon-carbon position even when 1,6-heptadiynes with different functional groups[41] were reacted (Scheme 22, route 2, R^1, R^2 = H, Me, COOMe, COOEt,, CH_2OAc, CH_2OTIPS).

When propargyl alcohols and propargyl amines derivatives were treated with a hydrosilane, CO and a strong base the obtained products were β-lactones and β-lactams rings (Scheme 22, route 3 and 4), the nucleus of very important pharmaceutical molecules usually prepared through multistep synthetic sequences. Matsuda and co-workers reported the first examples of a one-pot synthesis of β-lactones and β-lactams through the rhodium catalysed carbonylative silylcarbocyclization of propargyl alcohols[42] and amides[43]. A few α-silylmethylene-β-lactones (Scheme 22, route 3, R^1, R^2 = H, Me, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-) were initially prepared[42] by means of carbonylation of the propargyl alcohols in the presence of Me_2PhSiH and Et_3N. The use of the base was fundamental for the cyclisation reaction to take place. Indeed the formation of the corresponding 3-silylpropenal by direct silylformylation was competitive with the carbocyclisation process. A dramatic improvement of the selectivity towards the β-lactones was attained by the use of either a bulkier silane such as *t*BuMe$_2$SiH or a stronger base such as DBU (68–86 % yields). Analogously the synthesis of some β-lactams rings was exclusively achieved[43] operating with DBU and a quite hindered propargyl amines derivatives (Scheme 22, route 4, R^1, R^2 = Me, *i*Bu, -$(CH_2)_5$-). The nucleofilicity of the nitrogen atom had a remarkable effect on the chemoselectivity of the reaction since the use of $NHCO_2Me$ or $NHCO_2CH_2Ph$ instead of the *p*-toluensulfonamides determined the exclusive formation of the β-silylalkenal. These preliminary data prompted us to explore the

applicability of the CO-SiCaC reaction to propargyl amides and aryl silanes with various steric and electronic features.[20] Initially the reactivity of *N*-(1-*tert*-butyl-2-propynyl)-*p*-toluene sulphonamide (Scheme 23) chosen as a model substrate was investigated. The reactions were performed with equimolar amounts of silane and amide and catalytic quantities both of $Rh_4(CO)_{12}$ (0.1 mol-%) and DBU (10 %). Despite of the presence of a very hindered group such as *tert*-butyl, the silylformylation process resulted highly competitive with the silylcarbocyclisation reaction. Only in the presence of a steric hindered hydrosilane such as *ortho*-tolyldimethylsilane a good amount of the desired β-lactam was formed, but the reaction rate was quite slow (Scheme 23, 59 % of conversion after 4 h).

This reaction trend completely changed when amides with a quaternary α-carbon atom were employed. Indeed high chemo selectivity towards the β-lactam was observed when dialkyl functionalised propargyl amides were reacted (Table 11) regardless of the steric requirements of the hydrosilanes. Polyfunctionalised β-lactams (Table 11, entries 4–6) were prepared. In particular, the reaction with dimethylthienylsilane determined the addition of the heteroaromatic ring on the silylmethylene portion of the product. The obtained results clearly indicated that the structure of the propargyl precursors played a crucial role in the selectivity of the reaction, the presence of a bulky propargyl carbon being essential to force the closure of the ring. As already pointed out by Matsuda, the high acidity of the NH-tosyl proton seemed to be fundamental for the β-lactams formation since the cyclisation process requires the removal of the nitrogen proton by the base DBU. This hypothesis was confirmed by the results obtained reacting different arylsilanes with 3-amino-3-methyl-1-pentyne protected by a benzyl or a *tert*-butoxy carbonyl group. As it is evident from the data described by Scheme 24, the presence of BOC or CH_2Ph functionality on the nitrogen atom clearly favoured the silylformylation reaction that occurred without breaking of the N-H bond.

These results indicated that it was possible to force the chemo-selectivity of the reactions towards cyclisation or silylformylation process selecting the reagents with suitable steric and electronic requirements.

3. Reactivity of the silylformylation products

The reactions of the silylformylation products can be divided into two main groups on the basis of a different chemical approach: i) tandem reactions, in which the β-silylalkenals are not isolated but transformed in situ by means of a suitable reactant; ii) reactions of either the vinylsilane or the carbonyl group of the β-silylalkenal after its isolation and purification.

3.1 Tandem reactions

The first example of tandem process was described by Eilbracht and co-workers in 1998.[44] Studying the hydroaminomethylation of alkynes they found a dramatic improvement of the chemo-, regio- and stereoselectivity of the reaction by employing a hydrosilane instead of hydrogen in the reaction mixture (Scheme 25).

Indeed the β-silylalkenals, generated in situ by the silylformylation of the alkyne, condensed with the primary amine to give the imine derivatives that were isolated in very good yield. These azabutadienes were submitted to Diels - Alder reaction affording 4-silylated-1,4-dihydro-pyridines, precursors for various dihydro- or tetrahydropyridine systems, e.g. as NADH models.

When the amine was replaced by a carbon nucleophile such as an ylide a new carbon-carbon bond was formed.[45] As described in Scheme 26 the rhodium catalysed sequential silylformylation/Wittig olefination of terminal acetylenes with hydrosilanes and carbon monoxide in the presence of a stabilised *P*-ylides led to substituted 2,4-dienoic esters in a one pot procedure. The unsaturated esters were generated with high (2*E*, 4*Z*) stereoselectivity in good to excellent yield and successfully employed in the synthesis of cyclopropan carboxylic esters using diazomethane in the presence of catalytic amounts of $Pd(OAc)_2$.

Recently Leighton's group has developed tandem silylformylation-allylsilylation reactions as new approach to the synthesis of polyketides.[46] Given that allyl silanes are well-known aldehydes allylation agents, they prepared allyl silyl homopropargyl ethers that were reacted under the silylformylation conditions (Scheme 27).

The initially formed β -silylalkenals (I) was not isolated but immediately allylsilylated affording the bicyclic intermediate (II). This step provided the 1,5 anti products as the major diastereoisomer. Direct correlation between the steric size of the homopropargylic substituent and the diastereoselectivty of the reaction was observed (*dr* = 10:1 when R = *t*Bu). The unpurified product was directly subjected to protodesilylation affording the 1,5-diols with good yields (Scheme 27, route A). Treatment of the alcohols with acetic anhydride gave the corresponding diesters (Scheme 27, route B). As an alternative to the protodesilylation workup procedure, Tamao oxidation was also investigated and led to ketodiols with identical diastereoselectivity (Scheme 27, route C).

3.2 Chemical transformation of silylformylation products

In 1993 Ojima et al. reported the first application of the silylformylation reaction to the synthesis of pyrrolizidine alkaloids precursors (Scheme 28).[47]

Silylformylation of 5-ethynyl-2-pyrrolidinone was carried out with a catalytic amount of $Rh(acac)(CO)_2$ under 300 psi of carbon monoxide in toluene at ambient temperature to afford the

pyrrolidinone derivative (I) as only product in 97 % yield. The reduction of the formyl group was easily achieved with sodium borohydride and yielded the corresponding alcohol (II) quantitatively. This intermediate was submitted to desilylation, protection of the OH group and finally ~~amidocarbonylation~~ hydroformylation with subsequent O,N-acetal formation affording the precursors of isoretronecanol and trachelanthamidine alkaloids.

Panek and co-workers employed the silylformylation reaction of terminal acetylenes as starting step for the synthesis of crotylsilanes (Scheme 29).[48] The reaction was carried out by addition of the alkynes to a solution of dimethylphenylsilane and dirhodium(II)perfluorobutyrate under one atmosphere of carbon monoxide. The derived (*Z*)-β-silylalkenals were isomerised to the more stable (*E*) isomer with a catalytic amount of I_2 and then submitted to a nucleophilic addition of methyllithium. Subsequent enzymatic resolution of the racemic vinylsilane followed by ortho ester-Claisen rearrangement afforded the desired chiral β-substituted (*E*)-crotylsilanes useful reagents for highly diastero- and enantioselective addition reactions to aryl acetals.

Both cases described so far are concerned with the reactivity of the carbonyl moiety of the β-silylalkenals. On the other hand, vinylsilanes have been widely used for the preparation of functionalised olefins by means of electrophile substitutions[5] and palladium-catalysed coupling reactions with aryl and alkenyl halides.[1c, 1g] Nevertheless only Denmark reported the silicon assisted synthesis of α,β-unsaturated aldehydes through a cross coupling reaction (Scheme 30) of cyclic silylether prepared by means of intramolecular silylformylation of alkynyloxy hydrosilanes (Scheme 20).[33]

The reaction requested an extensive optimisation of the experimental conditions, i.e. the choice of the palladium species, the solvent and the fluoride sources, necessary for activation of the silicon-carbon bond. The use of $[(allylPdCl)]_2$ and CuI in a 1 to 1 ratio resulted the optimal combination of catalysts. Although the role of the copper cocatalyst is not clear, the mechanism might involve transmetalation from silicon to copper prior to transmetalation to palladium. The in situ reduction of the palladium complex was achieved by means of a hydrosilane additive. The commercial available methylhydrocyclosiloxanes $[-MeSi(H)O]_{3-5}$ was chosen because of its low cost and ready availability. Finally, even if TBAF is commonly employed for organosilicon cross-coupling reactions, in this case, $KF{\cdot}2H_2O$ resulted the best activator for the base sensitive organosilane substrate and product in terms of yield, reaction rate and minimization of by-products extent.

During our studies on the silylformylation of terminal acetylenes with hydrosilane we investigated the synthetic potentialities of (*Z*)-2-(dimethylphenylsilylmethylene)hexanal chosen as model compound and obtained by silylformylation of 1-hexyne. According to the data reported by Ojima

(Scheme 28) quantitative reduction of the carbonyl group was achieved by means of $NaBH_4$ (Scheme 31, step 1).

The protodesilylation process of the allylic alcohol was easily performed since the presence of the OH in the β position to the silyl moiety promotes the removal of the silicon group (Scheme 31, step 2).[49] Finally, the oxidation with pyridinium dichromate (PDC) of the alcohol yielded the corresponding unsaturated aldehyde (Scheme 31, step 3). Considering that these three reactions were performed under mild experimental conditions and that the crude products were employed in the next step without any further purification, the described sequence could represent an alternative preparation of α,β-unsaturated aldehydes from alkynes with respect to the direct hydroformylation of the triple bond. Indeed, while hydroformylation of alkenes is one of the most important industrial processes with 7 millions tons of aldehydes produced every year, few examples of hydroformylation of alkynes are described since it usually suffers from a lack of regio-, chemo-, and stereoselectivity (Scheme 32, route A).[50] On the other hand, it has already been underlined that the silylformylation reaction results in a highly regioselective and stereoselective introduction of the formyl moiety on the internal carbon of the unsaturated group. The removal of silicon from the β-silylalkenals would exclusively generate the α-alkylated-α,β-unsaturated aldehydes (Scheme 32, route B). Since no data about the protodesilylation of β-silylalkenals are reported in the literature we were particularly intrigued by the possible substitution of the silane with hydrogen in order to afford α,β-unsaturated aldehydes in one step.

3.2.1 Fluoride promoted transformation of silylformylation products

Protodesilylation of vinylsilanes is usually performed under acidic conditions (HI, *p*-toluensulfinic acid)[51] or in the presence of a fluoride ion source. [52] It is well known that F^- adds to the silicon atom creating pentacovalent species that can easily move away from the molecule. Hence, our first attempts of removal of the silyl moiety from the β-silylalkenals[13] were performed with fluoride carriers such as KF, BF_3, TBAF and the obtained results are reported in Table 12. KF/MeOH and TBAF/MeOH were completely ineffective (Table 12, entries 1 and 2) and the aldehydic precursor was fully recovered. This lack of activity could be due to the strong hydrogen bonds between the hydroxy group of methanol and the fluoride ion which resulted shielded and could not co-ordinate the silicon atom. The reaction with BF_3-acetic acid complex generated a mixture of (*E*)-2-(dimethylphenylsilylmethylene)hexanal **(*E*)-1** and 2-benzylhexanal **2** (Table 12, entry 3). The formation of the trans isomer **(*E*)-1** (thermodynamically more stable) can be easily explained considering that the acidic experimental conditions (CH_3COOH) could cause addition of proton to

the double bond, formation of a β-stabilised carbocation[53] which, after rotation through the sp^3 C-C σ bond and consequent deprotonation, could afford **(*E*)-1a** (Scheme 33).

Indeed, when paratoluensulfinic acid (*p*-TsH) was used, exclusive isomerization of the β-silylalkenal was detected (Table 12, entry 4). On the other hand, 2-benzylhexanal was exclusively formed from the reaction between (*Z*)-2-(dimethylphenylsilylmethylene)hexanal **(*Z*)-1** and tetrabutylammonium fluoride in a polar aprotic solvent, (THF, DMSO, CH_3CN), (Table 12, entries 5–9).

Indeed, when the reaction was performed at room temperature (25 °C) with tetrabutylammonium fluoride in DMSO and hydrolysed immediately after adding TBAF, the complete conversion of the substrate to 2-benzylhexanal **2** was observed. One mole of fluoride source was sufficient (Table 12, entries 5–7) and the reaction proceeded smoothly under mild experimental conditions. For instance, when **(*Z*)-1** was reacted with an equimolar amount of TBAF in CH_3CN, the yield of 2-benzylhexanal was quantitative within 1 minute at –60 °C (Table 12, entry 8). These results appeared extremely promising from the synthetic point of view. The reaction seemed to involve an anionotropic 1,2-migration of a phenyl group from silicon to the adjacent carbon atom of the α,β-unsaturated aldehyde. Fleming and co-workers described in 1992 a similar rearrangement of a β-dimenthylphenylsilyl ketone induced by fluoride ions (Scheme 34).[54] When they tried to remove the Me_2PhSi group, the double silylated enone underwent a fluoride ion attack to the dimethylphenylsilyl moiety yielding the pentacovalent silyl ion (I). The phenyl group migrated to the β-position to give the enolate intermediate (II) that could acquire a proton and loose both the silyl groups, that α to the ketone and that from the benzyl~~ic~~ position.

Migration of groups from silicon to neighbouring electrophilic sites is well known when the electrophilic site is a carbon atom carrying a good leaving group (LG) such as a halide or a triflate (Scheme 35).[55]

In these cases the rearrangement involves an intramolecular nucleophilic attack to the C-nucleofugal bond and the good migratory aptitude of the phenyl group accounts for the benzyl silyl derivative obtained. Moreover, the overall rearrangement-displacement reactions are accelerated when electron-withdrawing groups are present on the aromatic ring.

More recently, contemporary to our first paper on TBAF induced aryl migrations from β-silylalkenals, Jung and Piizzi observed an unexpected formation of 4-phenylbutan-2-one while investigating Michael additions to 4-(dimethylphenylsilyl)but-3-en-2-one.[56] In the presence of nuclophiles (X^-) such as KF in wet DMSO, NaOMe/MeOH and KO*t*Bu/*t*BuOH they detected desilylation together with 1,2-rearrangement of the phenyl from the Me_2PhSi group to the carbon atom. As shown in Scheme 36, they suggested an initial attack of X^- to the silicon atom to give a

silyl anion (I) that undergoes a 1,2-migration of the phenyl from silicon to the electrophilic adjacent carbon atom to generate the enolate (II). After protonation and/or addition of another molecule of nucleophile, the silyl moiety is eliminated affording the observed product.

Taking into account the mechanistic hypothesis reported by Fleming and Jung, the formation of 2-benzylhexanal from (*Z*)-2-(dimethylphenylsilylmethylene)hexanal **(*Z*)-1** (Table 12, entries 5–9) can be the result of fluoride addition to the silicon atom followed by phenyl-1,2-anionotropic shift to the adjacent carbon atom yielding the enolate (II) (Scheme 37). This intermediate can undergo a Brook rearrangement with the complete conversion to enol silyl ether (III) and final removal of the silyl group by water or fluoride itself (THF solutions of TBAF commonly used contain 4–5 % water). The intramolecular 1,2-anionic migration of a silyl group from a carbon to an oxygen atom was originally recognized and studied by A. G. Brook.[57] The migratory aptitude of silyl groups in this context has since been observed to be more general, comprising a family of [1,*n*]-carbon to oxygen silyl migrations commonly referred to as Brook rearrangements.[58] The strength of the oxygen-silicon bond (120±130 kcal mol) compared to the carbon-silicon bond (75±85 kcal mol) provides sufficient driving force for the anionotropic shift. Aryl groups generally show a very good migratory aptitude and this trend was in agreement with our reported data, i.e. no methyl displacement was observed (Scheme 37).

Analogously, exclusive aryl migration was obtained when several aryldimethylsilyl derivatives such as *o*,*p*-tolyl-, *p*-metoxy-, *p*-dimethylamino, *p*-fluoro, polycondensated and even thienyldimethylsilylalkenal were treated with tetrabutylammonium fluoride, confirming the large applicability and the high synthetic potentialities of the rearrangement process (Table 13).[19,23]

Preliminary experiments pointed out that it was necessary to optimise the reaction conditions since the desilylated aldehyde was obtained with good but not excellent yield after purification on silica gel column. Indeed, lack of purified product (60 % yield vs. 100 % conversion) was observed (Table 13, entry 1), probably due to the well known basicity of fluoride ion[59] that could favour the formation of high weighted polycondensated products, detected by GC analysis. With the aim of minimizing the extent of by-products, hydrolysis with a pH 7 buffer (KH_2PO_4/ NaOH) was carried out (Table 13, method B, entry 2). Yet, no increase of the product amount was observed, even operating at low temperature (Table 13, methods B and C). A remarkable improvement of the yield (78 %) was achieved by means of reverse addition of the β-silylalkenal to a solution of excess TBAF in THF (Table 13, method E). The same trend was observed when these experimental conditions were applied to different β-silylalkenal (Table 13, entries 6–14). In all cases, the yields of the corresponding 3-arylaldehydes were clearly enhanced (Table 13, entries 7–9). The excess tetrabutylammonium probably favours the fast hydrolysis of enol silyl ethers (Scheme 37, III)

reasonably formed during the process, speeding up the formation of aldehyde. The steric features of the aryl moiety didn't affect the migration-desilylation process since β-silylalkenals characterised by hindered group such as *o*-tolyl- and 1-naphtyldimethylsilane easily afforded the corresponding aldehydes in good yields (Table 13, entries 7, 13, vs. entries 8, 14, method E). It is noteworthy that the original configuration of the Ar group on the silicon atom (*o*-tolyl, *p*-tolyl, 1-thienyl…) was maintained during the rearrangement process. It can be supposed that the migration step occurs with a concerted mechanism involving a bridged intermediate (Figure 1).

The anionotropic migration was successfully extended to a large variety of β-silylalkenal characterised by different steric and electronic features.[19, 23] According to method E (see Table 13) the reactions were performed at room temperature, with addition of aldehyde (2 mmol) to TBAF (1 M in THF solution, 5 mL) and hydrolysis of the resulting solution with water immediately afterwards. As it is clear from the data in Table 14 α-branched acetylenic derivatives reacted with complete regio and chemoselectivity (entries 1–3) as well as ω-functionalised β-silylalkenal (entries 4–7). Indeed, unsaturated moieties (C=C, C≡C), nitrile or hydroxy groups in the terminal positions of the alkynes were not involved in the migration step but were directly transferred to the saturated aldehydic products.

In contrast, the presence and the position of a leaving group on the aliphatic chain of the acetylene precursors had a dramatic effect on the chemo- and regioselectivity of the process.[19] When a halide or a tosyl substituent was positioned at the end of the hydrocarbon chain, *exo-tet* ring-closure reactions took place with the formation of three-, five- and six-membered ring products, all favoured according to Baldwin's rules[60] (Table 15).

Cycloalkanecarbaldehydes **3**, **6**, **7** (Table 15, entries 1, 2, 6, 7) and 5-benzyl-3, 4-dihydro-2*H*-pyran (**4**, Table 15, entries 3–5) were obtained as major products. In particular, aldehydes **3** and **7** were generated by intramolecular *C*-alkylation of the carbanion (I) formed after the fluoride addition to the silicon atom and subsequent phenyl migration (Scheme 38, route A). The benzyldihydropyran **4** (Table 15, entries 3–5) was obtained by kinetically favoured intramolecular *O*-alkylation of the enolate form of (I) (Scheme 38, route B).

Complete chemoselectivity towards **4** was observed in the presence of an excellent leaving group such as tosylate (Table 15, entry 5), while the reactions of ω-chlorinated and ω-brominated β-silylalkenales involved the formation of relevant amounts of by-products (Table 15, entries 3 and 4). In the case of 5-chloro-2-(dimethylphenylsilyl)-methylene-pentanal (Table 15, entry 3) the TBAF-mediated reactions yielded the linear 1-benzylaldehyde **5** together with the pyranyl derivative, probably due to the poor leaving group properties of chlorine. Analogously, when 6-chloro-2-(dimethylphenylsilyl)-methylene-hexanal was treated with TBAF the formation of the

chloro-aldehyde **8** was detected (Table 15, entry 6). The presence of bromine in the ω position of the β-silylalkenale induced the formation of carbacyclic aldehyde **6** (Table 14, entry 4), which can be ascribed to the carbanion (II), generated by Brook rearrangement [57-58] of (I) (Scheme 38, route C).

To check the stereoselectivity of the cyclisation process α-branched acetylenes (Scheme 39) were tested. It was observed that the cyclisation reactions took place with good diastereoselectivity, with (*Z*)-**9** and (*Z*)-**10** being formed as major isomers.

The obtained results prompted us to extend our investigation to β-silylalkenal functionalised in the alpha position. As it is shown in Scheme 40, silylformylation product derived from propargylamine protected as NHBOC yielded exclusively the "normal" rearrangement aldehyde **11**.

Otherwise β-silylalkenal characterised by a good leaving group such as acetate, benzoate or tosylamide in the α position afforded exclusively α,β-unsaturated aldehydes when treated with TBAF (Table 16).

Complete consumption of the reagents was observed and the products were recovered in good yields. In this case, the 1,2-anionotropic rearrangement is coupled with an elimination step of the leaving groups (COMe, COPh, *p*-TsNH) yielding 2-methylaryl-2-alkenals **12**. The reaction was totally diastereoselective when alkyl substituents with quite different steric requirements were present in the propargyl~~ic~~ position of the precursors (Me/H, *t*Bu/H, Table 16, entries 1–3, 7) and the more stable isomer (*E*) was exclusively formed. The 1,2-rearrangement of the aromatic ring occurred with complete retention of the original configuration of the Ar, as obtained in the cases of ortho- and para-functionalised phenyl silanes (Table 16, entries 7 and 8). The observed results are consistent with the mechanism depicted in Scheme 41 and can be easily explained by considering that the carbanion generated after the aryl migration induces the elimination of the good leaving groups (X) and consequent double bond formation (Scheme 41).

Finally α-silylmethylen-β-lactams, prepared from propargyl *p*-tosylamides according to silylcarbocyclisation reaction conditions, were submitted to TBAF induced rearrangement in order to verify if the β-lactam ring could survive to the fluoride promoted aryl migration. As it is shown in Table 17, azetidinones **13** were successfully reacted with 1 equiv of TBAF affording the corresponding α-methylaryl substituted rings **14**. All the reactions proceeded smoothly with good yields of purified products. A very high diastereoselectivity towards the formation of the less hindered (*trans*) β-lactams was observed in all cases regardless of the steric requirements of the silyl moiety of the employed substrates (Table 17, entries 2–6). The configuration of the substituents on the β-lactam rings was confirmed by means of the NOESY spectra (Figure 2).

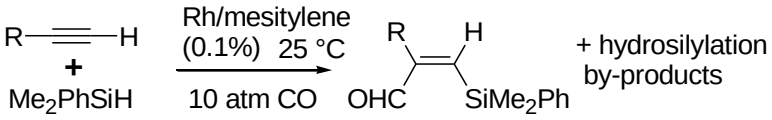
Relevant NOE effects between the *tert*-butyl protons and the adjacent CH(CH_2Ar) hydrogen were detected in the (*trans*)-products (i.e., *tert*-butyl and CH are in a *cis* configuration). In agreement with the results reported for β-silylalkenal rearrangements both functionalised benzene rings and the heteroaromatic thiophenyl ring were transferred from the silicon to the carbon atom with total retention of the initial configuration.

All the observed results seemed to indicate that the formation of arylmethyl-β-lactams is achieved through a reaction pathway very similar to the one proposed for β-silylalkenals. As shown in Scheme 42 a plausible mechanism involves the addition of fluoride to silicon yielding a pentavalent Si atom (I), aryl-1,2-anionotropic rearrangement to the adjacent carbon atom with formation of enolate (II), its possible Brook rearrangement (III, IV) or direct protonation (V) and final removal of silyl moiety.

Conclusion

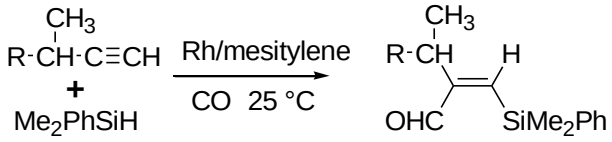
In conclusion, the silylformylation reaction represents a useful tool for the synthesis of polyfunctionalised molecules both in its inter and intramolecular version. Many rhodium catalysts are active and selective towards the addition of a formyl moiety to triple bonds. A wide range of dimethylarylsilanes with different steric and electronic requirements have been reported to react quantitatively affording aryldimethylsilylalkenals. The aryl group can be easily transferred form silicon to the adjacent carbon by the fluoride induced 1,2-migration that takes place with complete retention of the configuration of the benzene ring. Functionalised terminal acetylenes can be easily submitted to the silyformylation reaction that occurs without involving the functional group. The chemo-, regio- and stereoselectivity of the subsequent desilylation-migration reaction turned out to be strongly dependent on the nature and the position of the functional group present on the silylformylation product. Cycloalkanecarbaldehydes and dihydropyrans are obtained by silylformylation-desilylation protocol applied to alkynes with a good leaving group such as tosylate in the ω position. Propargyl *p*-tosylamides are precursors of both α-substituted-β-silylalkenals and α-silylmethylen-β-lactams. In the first case the fluoride promoted aryl migration is coupled with an elimination step that yields exclusively α,β-unsaturated aldehydes, useful building blocks for organic chemistry.[61] As far as β-lactams derivatives, treatment with tatrabutyl ammonium fluoride does not affect the lactam ring affording 3-methylaryl azetidinones useful precursors to amino acid derivatives and potential enzyme inhibitors.[62]

Table 1. Silylformylation reactions of acetylenes and dimethylphenylsilane.



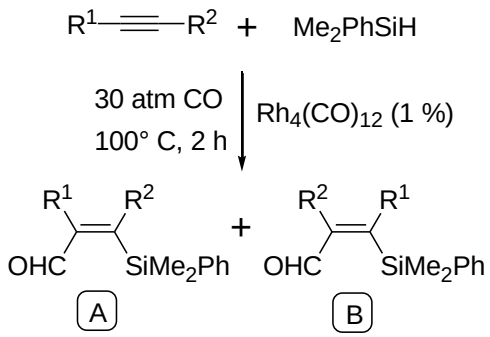
Entry	R	t (h)	Conv. (%)	Selectivity (%)	
				CHO	hydrosilylation by-products
1	$CH_3CH_2CH_2CH_2$	24	100	97	3
2	$CH_3CH_2CH(CH_3)CH_2CH_2$	24	94	98	2
3	$CH_3CH_2CH(CH_3)CH_2$	48	95	72	28
4	$CH_3CH(CH_3)$	24	78	75	25
5	$CH_3CH_2CH(CH_3)$	48	80	74	26

Table 2. Silylformylation reactions of 3-alkyl-1-butynes and dimethylphenylsilane.



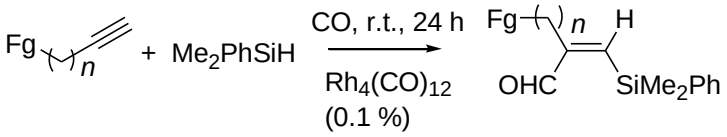
Entry	R	Cat. (%)	P_{CO} (atm)	t (h)	C≡C/ SiH	Conv. (%)	Chemo-selectivity
1	Et	1	25	24	2	100	94
2	*i*Pr	1	50	48	2	100	55
3	Ph	0.1	50	24	1	84	82

Table 3. Silylformylation of internal alkynes with dimethylphenylsilane.



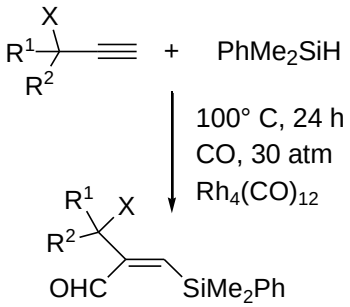
Entry	R^1	R^2	Yield (%) A	Yield (%) B
1	Me	Me	94	
2	Me	*n*Pr	60	26
3	Me	Ph	74	8
4	Ph	Ph	90	
5	Me	$SiMe_3$	0	0
6	Ph	$SiMe_3$	0	0

Table 4. Silylformylation of ω-functionalised acetylenes.



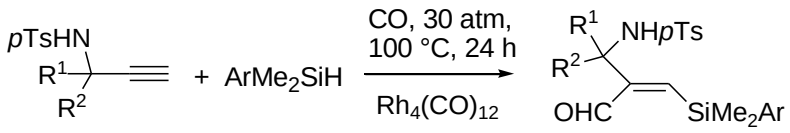
Entry	Fg	*n*	P_{CO} (atm)	Yield (%)
1	Ts	2	30	91
2	Br	2	35	100
3	$HC{=}CH_2$	3	10	100
4	CN	3	10	99
5	COOEt	3	30	73
6		3	30	95
7	Cl	3	20	99
8	Br	3	30	100
9	Ts	3	40	95
10	$C{\equiv}CH$	4	40	70
11	OH	4	20	74
12	Cl	4	30	99
13	Br	4	10	100

Table 5. Silylformylation of α-functionalised acetylenes.



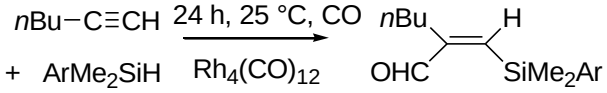
Entry	X	R^1	R^2	Yield (%)
1	Br	H	H	dec
2	OH	H	H	83
3	OSO_2Me	H	H	dec
4	OSO_2Ph	H	H	dec
5	OCOPh	Me	H	78
6	OCOMe	Me	Et	100
7	NHBOC	Me	Et	70
8	NH-*p*Ts	Me	H	91

Table 6. Silylformylation of tosylamides with aryldimethylsilane.



Entry	R^1	R^2	Ar	Conv. (%)	Chemo-selectivity (%)
1	H	Me	Ph	100	91
2	H	*t*Bu	Ph	73	95
3	Me	Me	Ph	100	87
4	Me	Et	Ph	79	80
5	Me	*t*Bu	Ph	53	38
6	H	Me	*o*-Me-C_6H_4	65	100
7	Me	Me	*p*-MeO-C_6H_4-	68	87

Table 7. Silylformylation of 1-hexyne with aryl- and heteroarylsilanes.



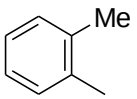
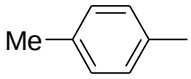
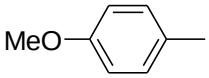
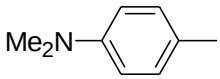
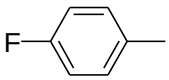
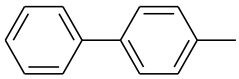
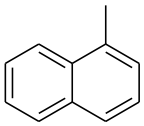
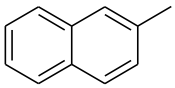
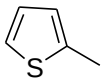
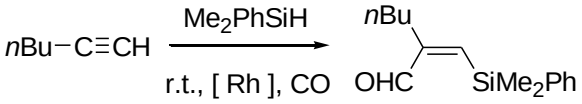
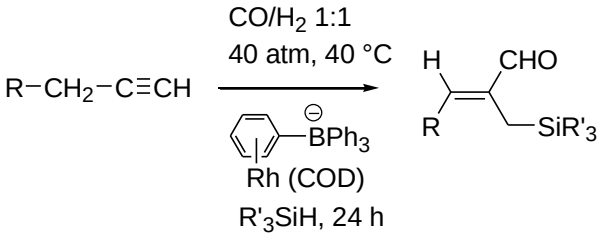
Entry	Ar	P_{CO} (atm)	Yield (%)
1		30	56
2		30	73
3		30	77
4		30	63
5		30	66.5
6		45	55
7		30	74
8		30	81
9		30	85

Table 8. Silylformylation of 1-hexyne catalysed by Rh species.



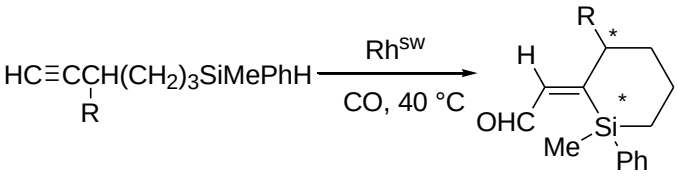
Entry	Cat.	%	t (h)	P_{CO} (atm)	Conv. (%)	TON	Silylformylation/ hydrosilylation
1	$Rh_4(CO)_{12}$	0.1	24	1	38	4	68:32
2	Rh/MVS	0.1	24	1	41	17	72:28
3	Rh/MVS	0.1	6	10	91	152	92:8
4	Rh/MVS	1	6	10	92	15	50:50
5	$Rh_4(CO)_{12}$	0.01	24	10	47	n.d.	93:7
6	$Rh_4(CO)_{12}$	0.1	6	10	98	41	96:4
7	$Rh_4(CO)_{12}$	1	6	10	100	4	51:49
8	$Rh_4(CO)_{12}$	3	24	25	95	n.d.	0:100

Table 9. Silylhydroformylation of terminal acetylenes.



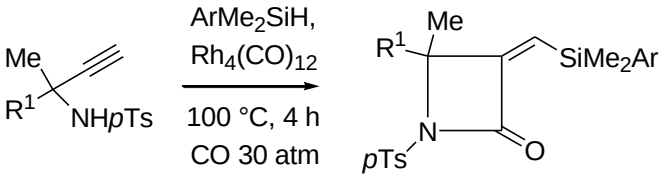
Entry	R	Silane	Yield (%)
1	*n*Bu	Me_2PhSiH	73
2	*n*Bu	Et_3SiH	62
3	CH_2Ph	Et_3SiH	71
4	CH_2Ph	Me_2PhSiH	64
5	CH_2Ph	Ph_3SiH	54

Table 10. Intramolecular silylformylation of branched ω-silylalkynes.



Entry	R	P_{CO}	t	Yield (%)	*cis*/*trans*
1	Me	20	24	73	50:50
2	*t*Bu	20	24	20	0:100
3	*t*Bu	20	48	58	0:100
4	*t*Bu	50	24	70	0:100

Table 11. Silylcarbocyclisation reactions of propargyltosyl amides with aryldimethylsilanes.



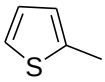
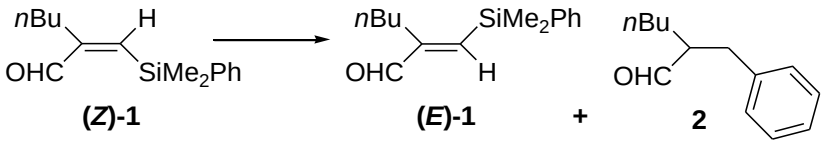
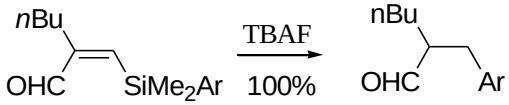
Entry	R^1	Ar	t (h)	Conv. (%)	Selectivity
1	Me	Ph	4	100	95
2	Et	Ph	4	100	96
3	*t*Bu	Ph	4	100	100
4	*t*Bu	*p*-CH_3-C_6H_4-	6	58	100
5	*t*Bu	*p*-NMe_2-C_6H_4-	6	67	100
6	*t*Bu		6	77	100

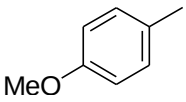
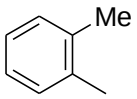
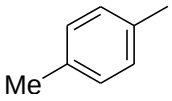
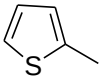
Table 12. Synthesis of 2-benzylhexanal from β-silylalkenal.



Entry	Reaction conditions: reagent / solv. / temp. / time	Reagent / Solvent (molar ratio)	Yield (%)	
			(*E*)-1	**2**
1	KF / MeOH / r.t. / 24 h	10	/	/
2	TBAF / MeOH / r.t. / 24 h	1	/	/
3	BF_3-2CH_3COOH CH_2Cl_2 / r.t. / 24 h	1	80	20
4	*p*TsH / CH_3CN / 80 °C / 24 h	0.2	100	/
5	TBAF / DMSO / r,t. / 1 min	5	/	100
6	TBAF / DMSO / r.t. / 1 min	1	/	100
7	TBAF / THF / r.t. / 1 min	1	/	100
8	TBAF / CH_3CN / –60 °C / 1 min	1	/	100
9	TBAF / THF / r.t. / 1 h	0.1	/	100

Table 13. TBAF-induced anionotropic rearrangement of β-silylalkenal.



Entry	Ar	Reaction conditions	Yield (%)
1	Ph	Method A: 1 mL of TBAF (1 M in THF) added to 1 mmol of aldehyde in 10 mL of THF at r.t., then hydrolysed with water	60
2	Ph	Method B: 1 mL of TBAF (1 M in THF) added to 1 mmol of aldehyde in 10 mL of THF at r.t., then hydrolysed with KH_2PO_4-NaOH (pH 7)	55
3	Ph	Method C: 1 mL of TBAF (1 M in THF) added to 1 mmol of aldehyde in 10 mL of THF at 0 °C then hydrolysed with KH_2PO_4-NaOH (pH 7)	45
4	Ph	Method D: 1 mmol of aldehyde added to 1 mL of TBAF (1 M in THF) dissolved in 10 mL, at r.t., then hydrolysed with water	55
5	Ph	Method E: 1 mmol of aldehyde added to 2.5 mL of TBAF (1 M in THF) dissolved in 10 mL, at r.t., then hydrolysed with water	78
6		Method A	35
7		Method A	51
		Method E	61
8		Method A	35
		Method E	63
9		Method A	25
		Method E	58

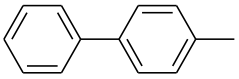
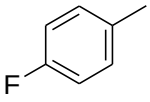
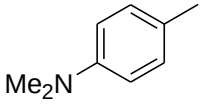
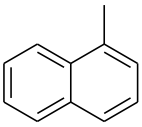
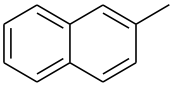
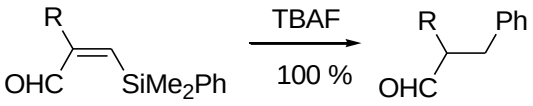
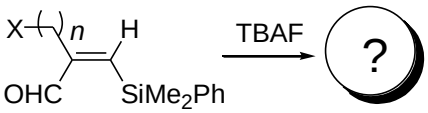
10		Method E	54
11		Method E	73
12		Method E	70
13		Method E	52
14		Method E	50

Table 14. TBAF promoted phenyl migration.



Entry	R	Yield (%)
1	$CH_3CH(CH_3)$	46
2	$CH_3CH_2CH(CH_3)$	71
3	$CH_3CH(Ph)$	60
4	$(CH_2)_3CH=CH_2$	67
5	$(CH_2)_3CN$	58
6	$(CH_2)_4C\equiv CH$	78
7	$(CH_2)_4OH$	53

Table 15. Phenyl migration reactions of β-silylalkenals in the presence of a leaving group (X).



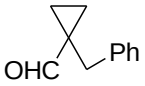
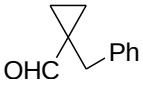
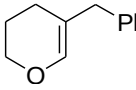
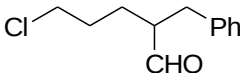
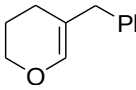
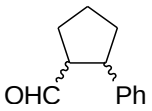
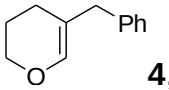
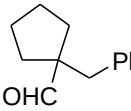
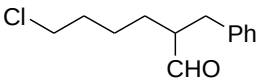
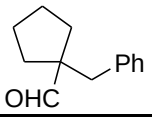
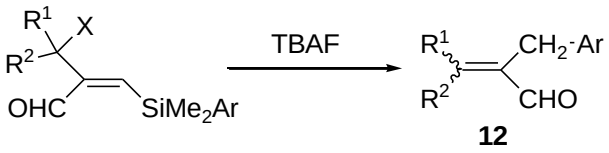
Entry	**X**	*n*	Products, chemoselectivity (%), (yield %)
1	Br	2	 **3**, 100 (90)
2	OTs	2	 **3**, 100 (68)
3	Cl	3	 **4**, 60 (52)  **5**, 40 (25)
4	Br	3	 **4**, 75 (43)  **6**, 25 (9.5, *trans*/*cis* = 90:10)
5	OTs	3	 **4**, 100 (75)
6	Cl	4	 **7**, 73 (58)  **8**, 27 (13.5)
7	Br	4	 **7**, 100 (82)

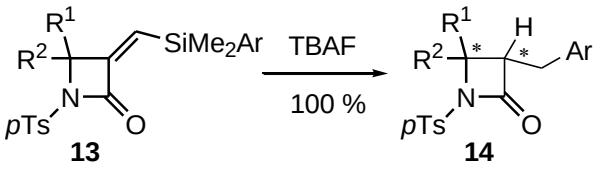
Table 16. Synthesis of α,β-unsaturated aldehydes via desilylation reactions of propargyl amides.

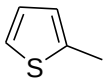


12

Entry	X	R^1	R^2	Ar	Yield (%)	*E/Z*
1	OCOPh	H	Me	Ph	69	100:0
2	NH-*p*Ts	H	Me	Ph	52	100:0
3	NH-*p*Ts	H	*t*Bu	Ph	45	100:0
4	NH-*p*Ts	Me	Me	Ph	75	//
5	NH-*p*Ts	Me	Et	Ph	59	65 :35
6	OCOMe	Me	Et	Ph	75	57:43
7	NH-*p*Ts	H	Me	*o*-Me-C_6H_4	67	100:0
8	NH-*p*Ts	Me	Me	*p*-MeO-C_6H_4-	55	//

Table 17. TBAF mediated aryl migration-desilylation reactions of *p*Ts-β-lactams.



Entry	R^1	R^2	Ar	yield (%)	diastero selectivity
1	Me	Me	Ph	60	//
2	Me	Et	Ph	58	91:9 (*trans/cis*)
3	Me	*t*Bu	Ph	91	95:5 (*trans/cis*)
4	Me	*t*Bu	*p*-CH_3-C_6H_4-	82	100 (*trans*)
5	Me	*t*Bu	*p*-NMe_2-C_6H_4-	51	100 (*trans*)
6	Me	*t*Bu		63	100 (*trans*)

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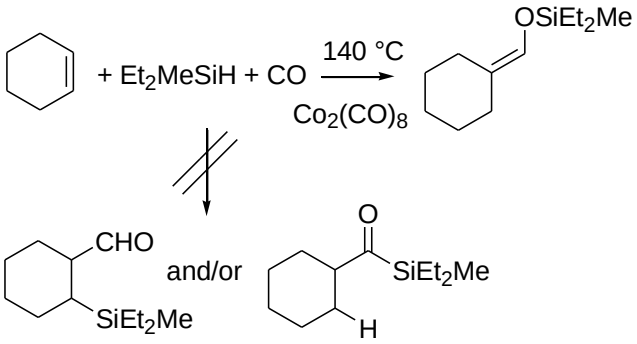
Scheme 1



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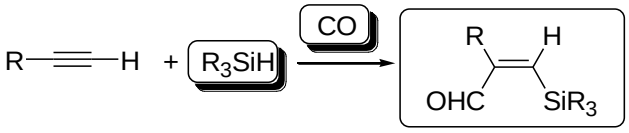
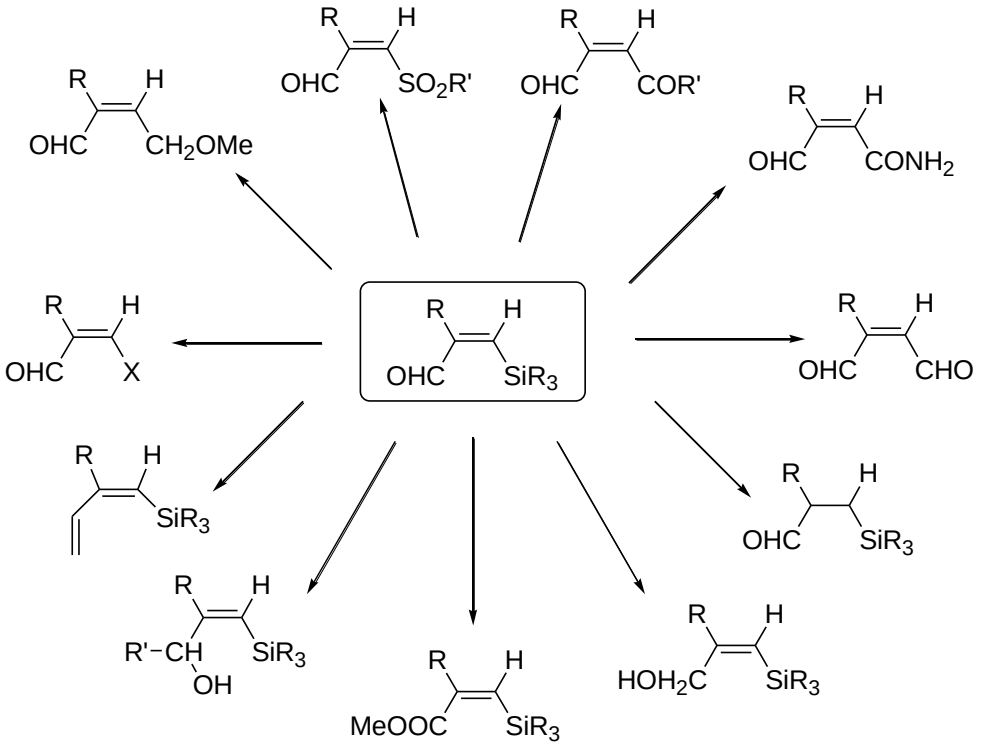
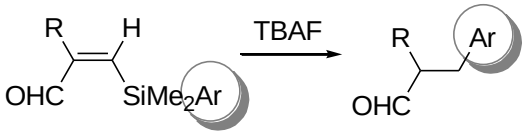
Scheme 2



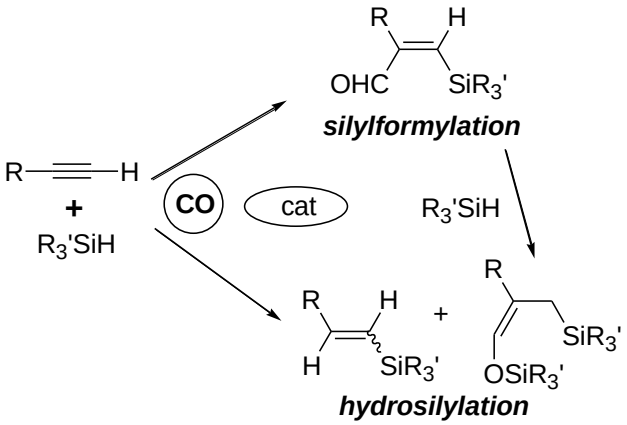
Scheme 3



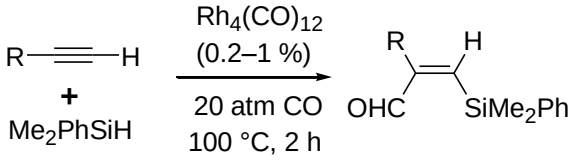
Scheme 4



Scheme 5

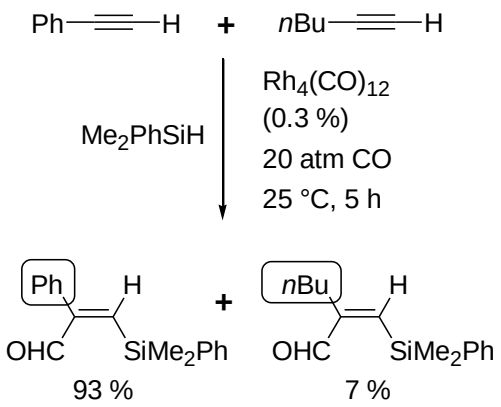


Scheme 6

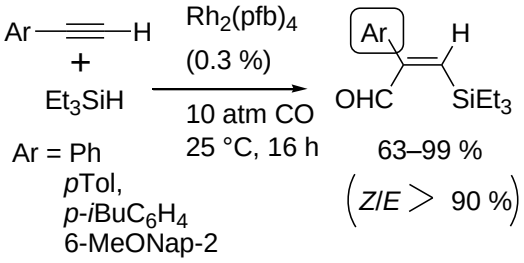


R	Yield (%)	*Z*/*E*
Me	99	80:20
Et	91	100:0
*n*Pr	93	95:5
*n*Bu	86	85:15
*n*Pent	71	87:13

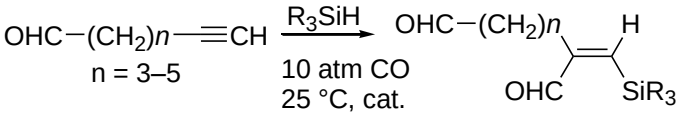
Scheme 7



Scheme 8



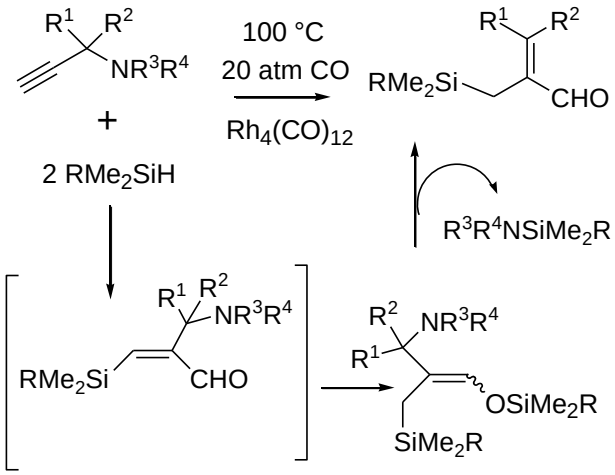
Scheme 9



R_3Si = Me_2Ph, Et_3, tBuMe$_2$, Ph_2Me, Ph_3

Cat. = Rh(acac)$(CO)_2$, $Rh_2Co_2(CO)_{12}$, $[Rh(NBD)_2]BF_4$

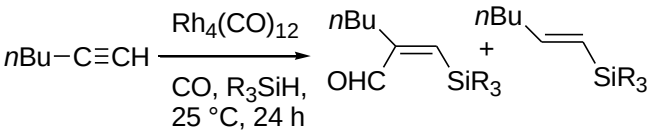
Scheme 10



R^1, R^2 = H, Me, C_5H_{11}, $(CH_2)_4$, $(CH_2)_5$

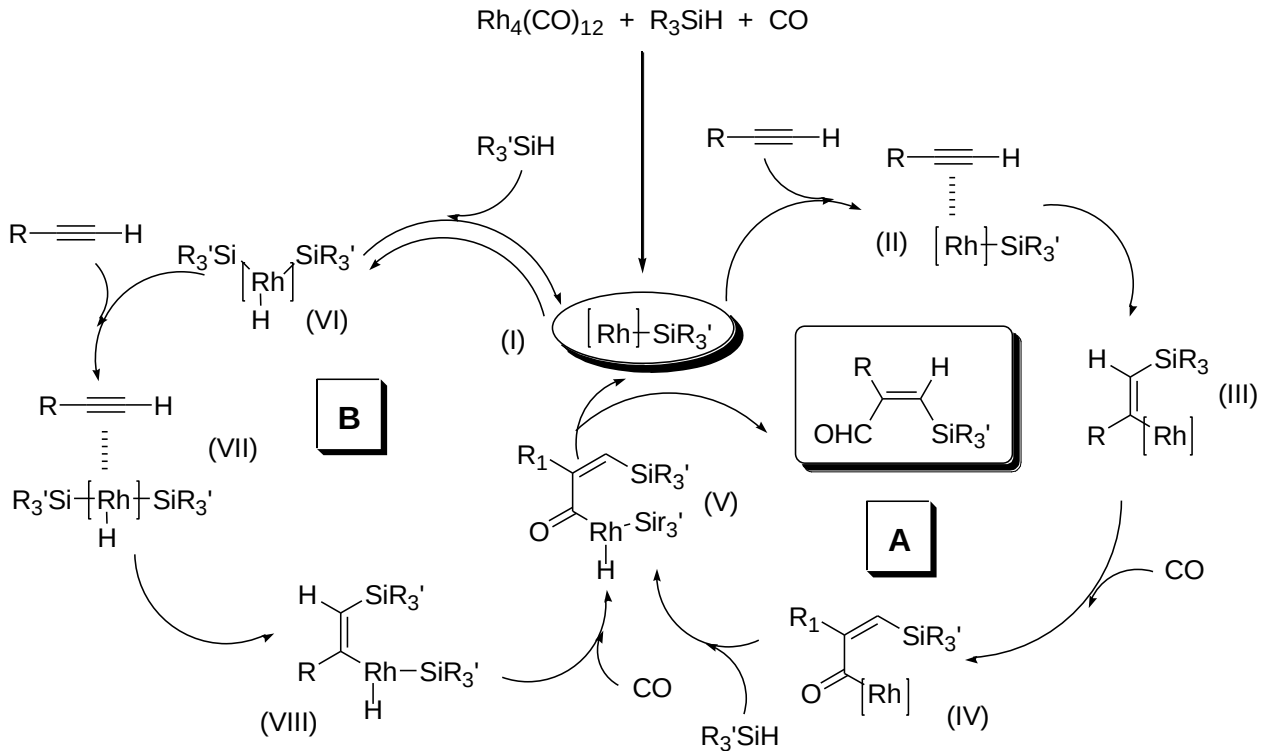
R^3, R^4 = H, CH_2Ph, Me, nBu, $(CH_2)_5$

Scheme 11

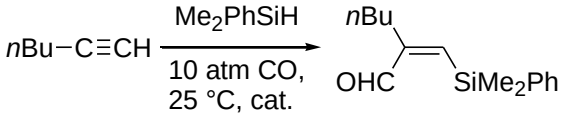


Me_2PhSiH	100 %	/
Me_2EtSiH	65 %	35 %
Et_3SiH	65 %	35 %
$(MeO)_3SiH$	/	100 %

Scheme 12

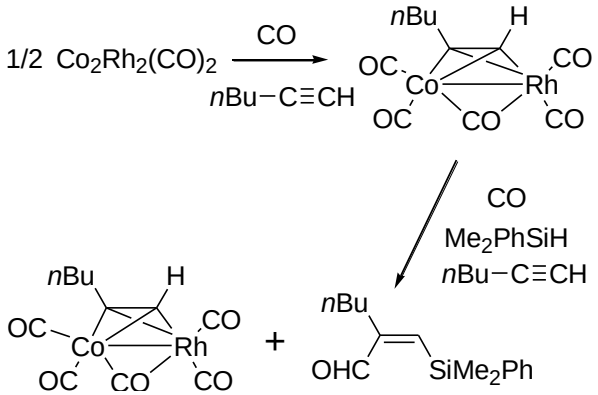


Scheme 13

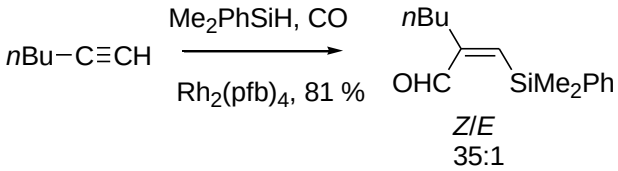


Cat.	Conv.
$(t\text{BuNC})_4\text{RhCo(CO)}_4$	99 %
Rh(acac)(CO)_{12}	96 %
$\text{Co}_2\text{Rh}_2\text{(CO)}_2$	92 %
$\text{Rh}_4\text{(CO)}_{12}$	90 %
$\text{RhCl(PPh}_3\text{)}$	0
$\text{Co}_2\text{(CO)}_8$	0

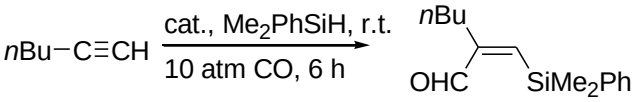
Scheme 14



Scheme 15

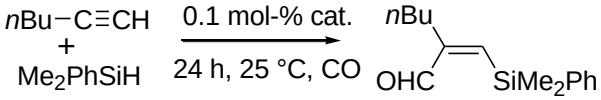


Scheme 16



cat.=	conv.	selectivity
$Rh_2(OAc)_4$	6 %	59 %
$[Rh_2(OAc)_2(MeCN)_6](BF_4)_2$	93 %	94 %
$[Rh_2(OAc)_3(Naft)](OAc)$	73 %	93 %
$[Rh_2(OAc)_2(Naft)_4](BPh_4)_2$	7 %	64 %
$[Rh_2(MeCN)_2(Naft)_4](BF_4)_4$	90 %	99 %

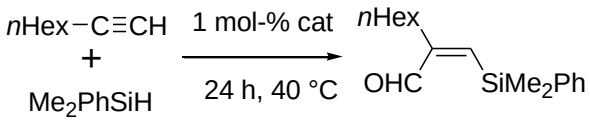
Scheme 17



cat.=	conv.
[RhCl(CO)(PePy)]	99 %
$[RhCl(CO)(PePy)_2]$	95 %
[RhCl(CO)(P(bzN))]	100 %
$[RhCl(CO)(P(bzN)_2)]$	100 %
$[Rh(PePy)(COD)](BF_4)$	11 %
$[Rh(P(bzN))(COD)](BF_4)$	-
$[Rh(P(bzN)_2)(COD)](BF_4)$	44 %

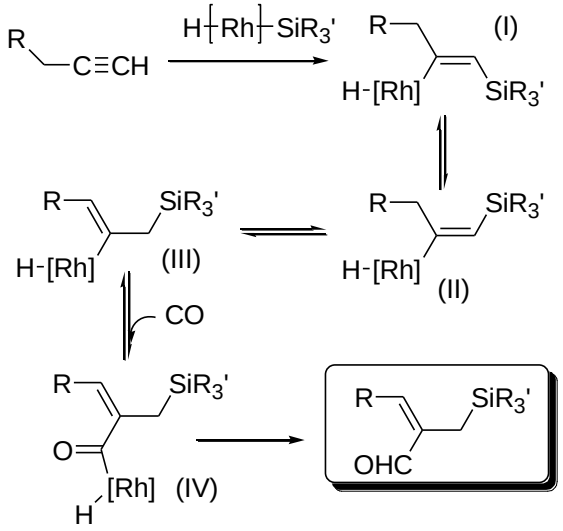
PePy = $P(CH_2CH_2Py)Ph_2$
bzN = 2-(dimethylaminomethyl)phenyl

Scheme 18

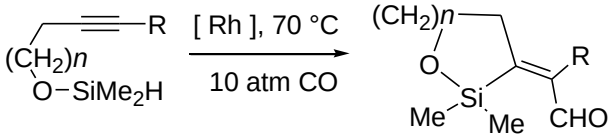


Run	Yield
1	71 %
2	76 %
3	78 %
4	67 %

Scheme 19

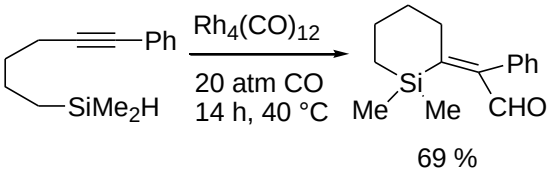


Scheme 20

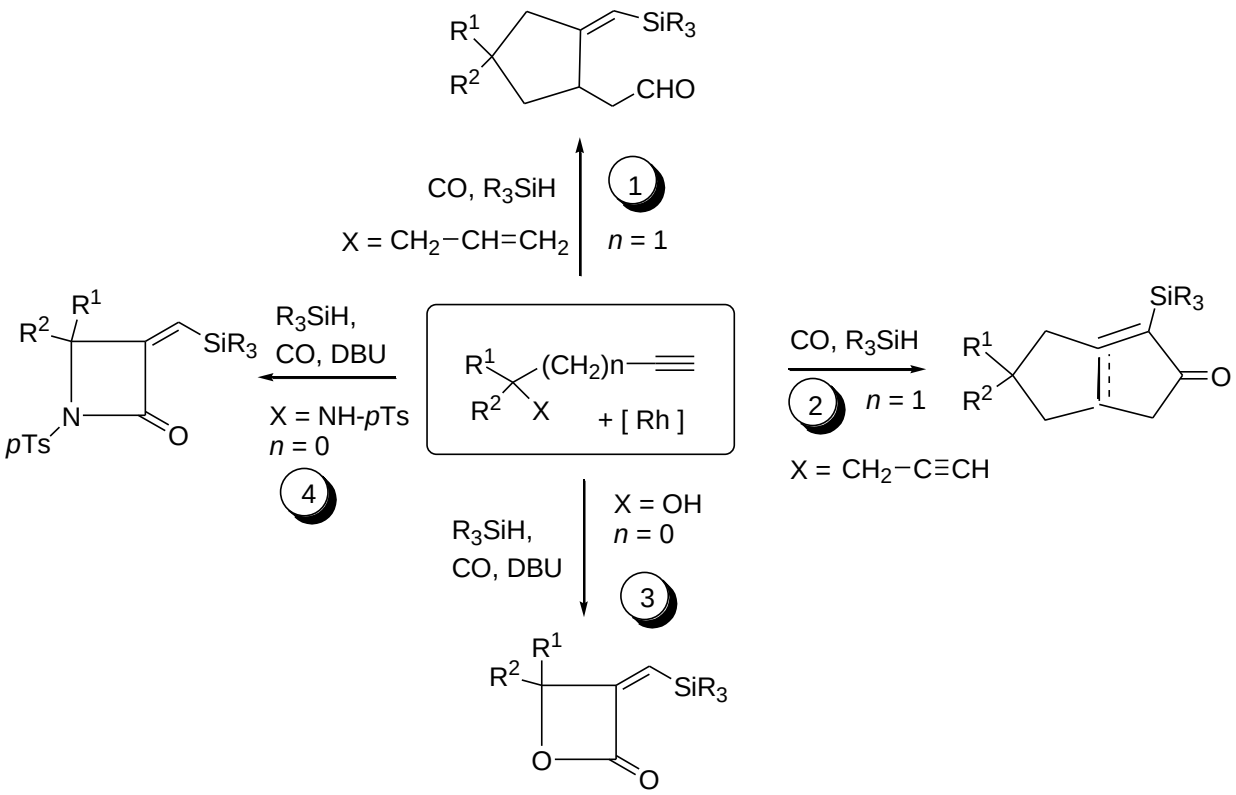


R	*n*	cat.	Conv.
H	1	(tBuNC)$_4$RhCo(CO)$_4$	89 %
H	2	(tBuNC)$_4$RhCo(CO)$_4$	81 %
Et	1	$Rh_4(CO)_{12}$	77 %
*n*Bu	1	(tBuNC)$_4$RhCo(CO)$_4$	99 %

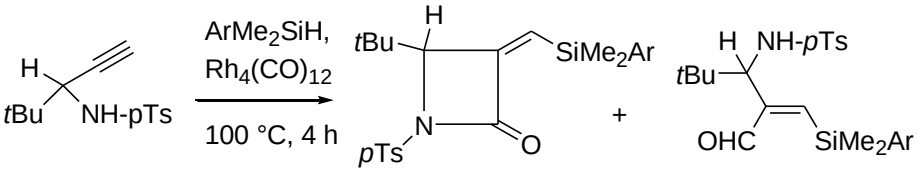
Scheme 21



Scheme 22

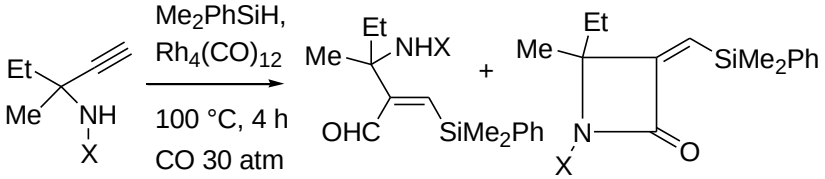


Scheme 23



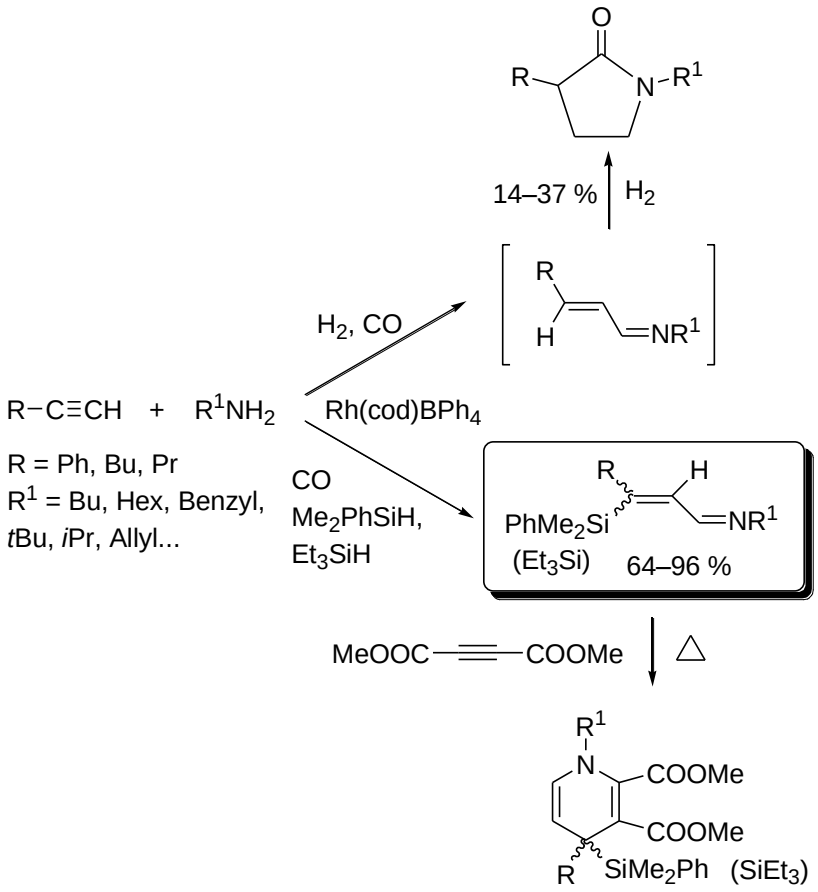
Ar	Conv.	Selectivity	
Ph	54 %	/	100 %
p-Ph-C_6H_4	50 %	/	100 %
o-Me-C_6H_4	59 %	70 %	30 %

Scheme 24

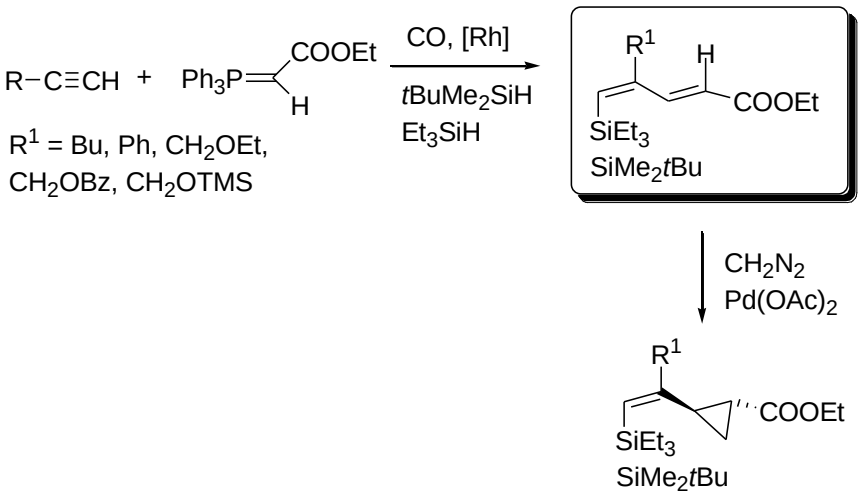


X	Selectivity	
BOC	100 %	/
CHPh	70 %	30 %

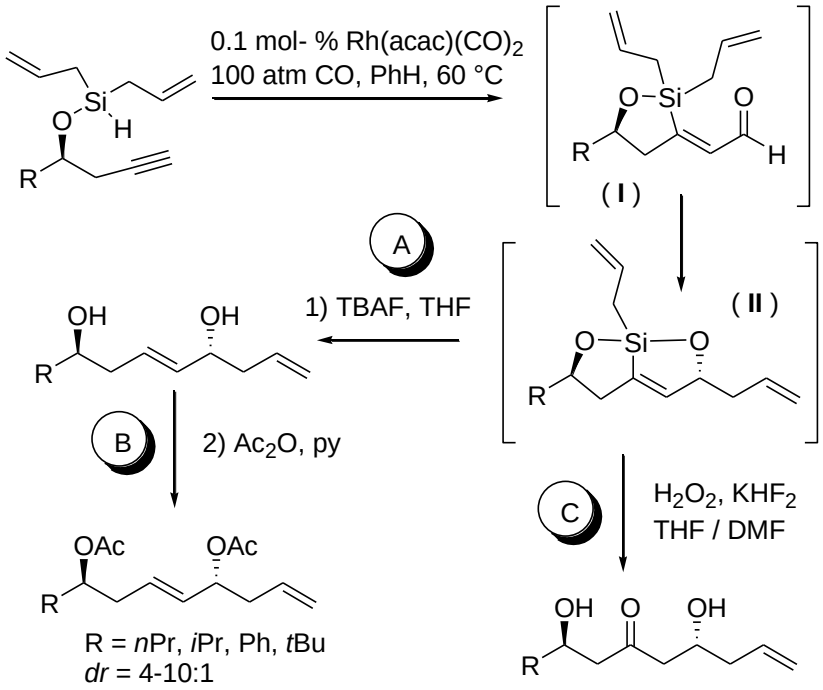
Scheme 25



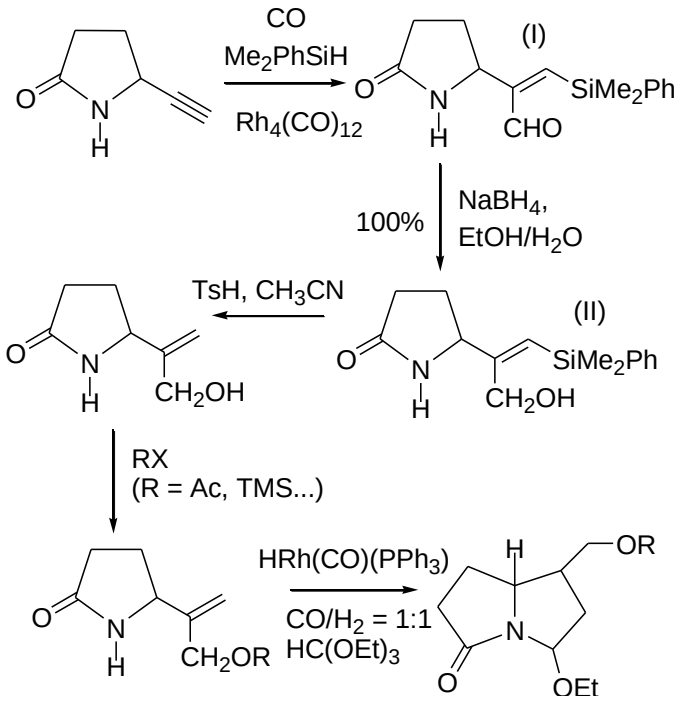
Scheme 26



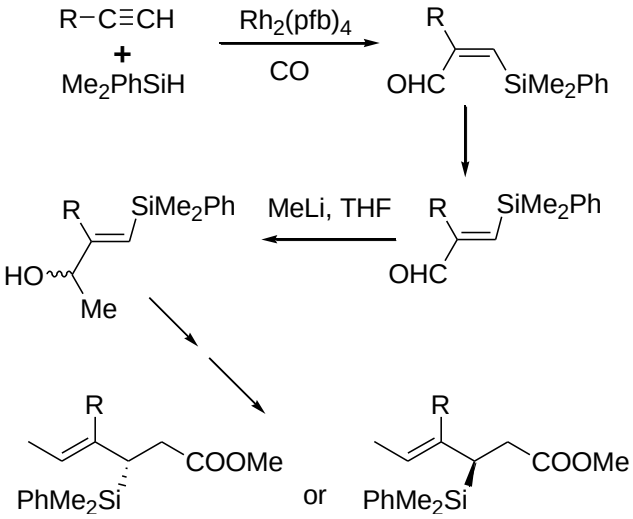
Scheme 27



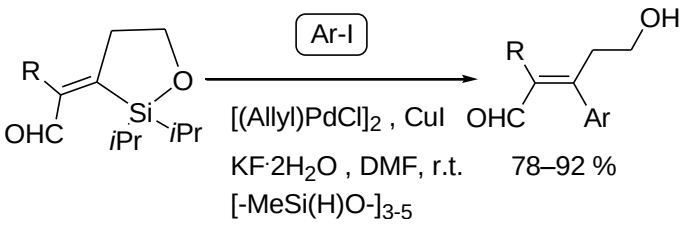
Scheme 28



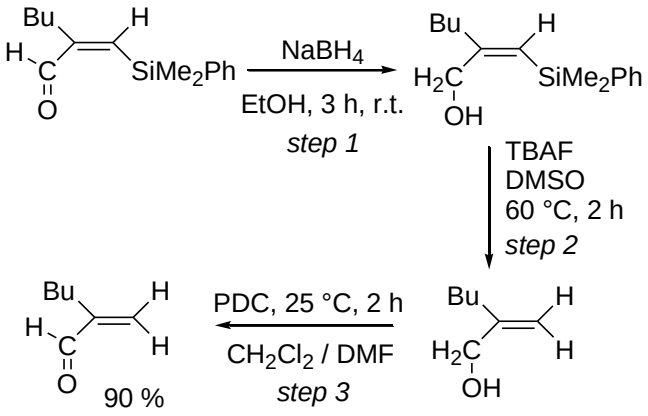
Scheme 29



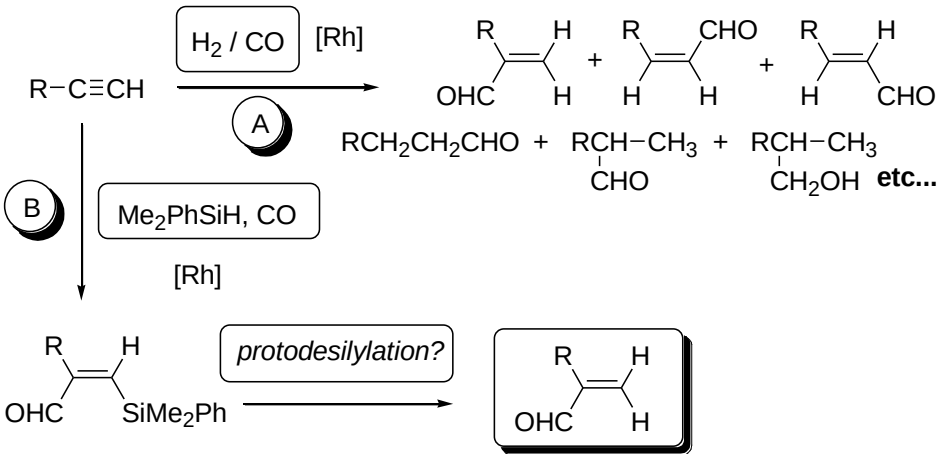
Scheme 30



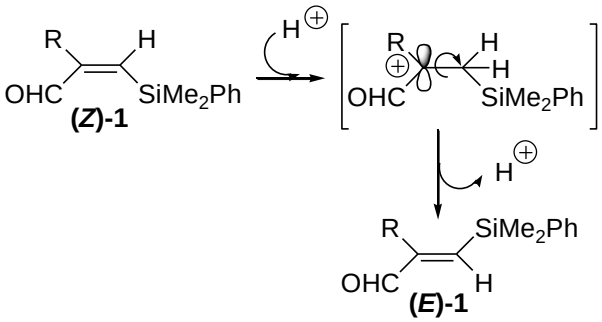
Scheme 31



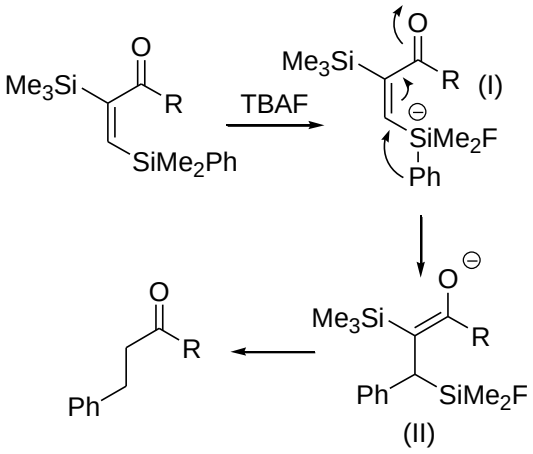
Scheme 32



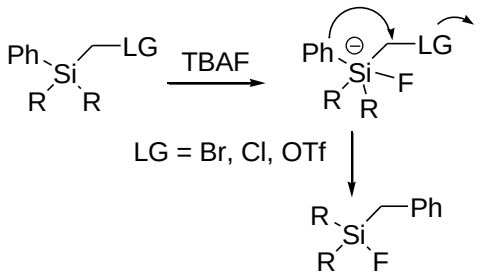
Scheme 33



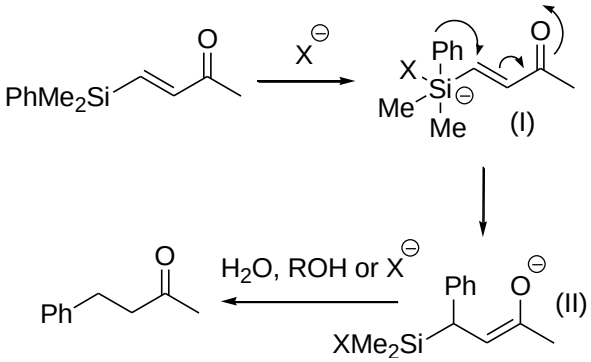
Scheme 34



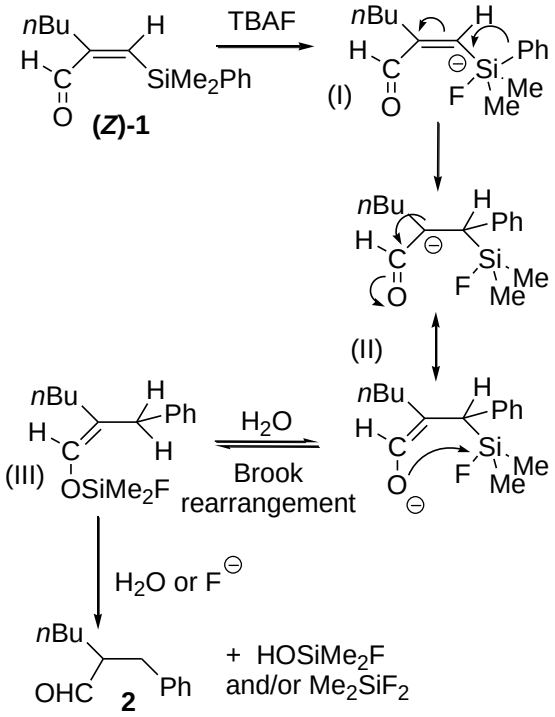
Scheme 35



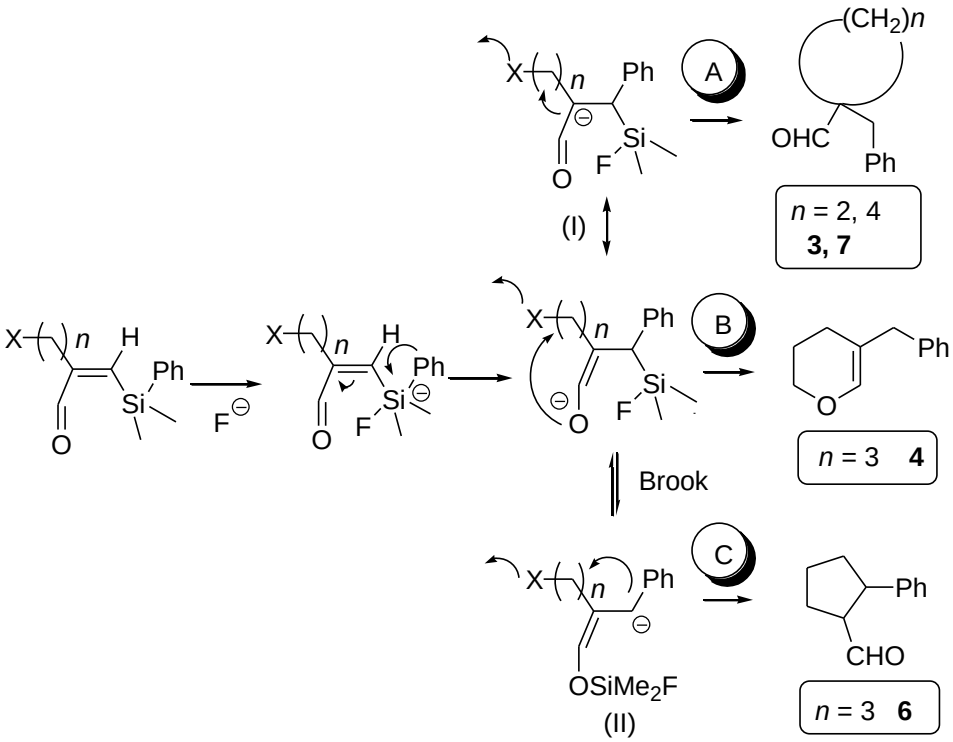
Scheme 36



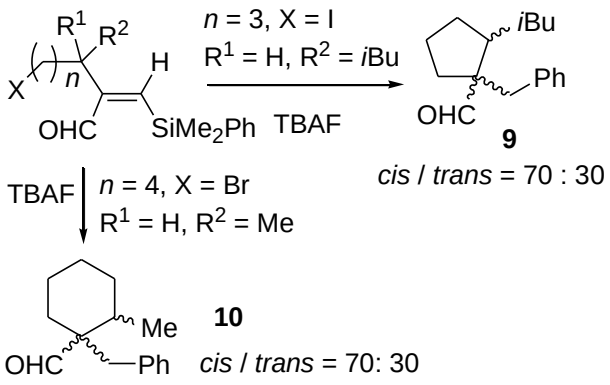
Scheme 37



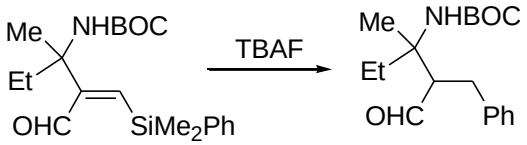
Scheme 38



Scheme 39

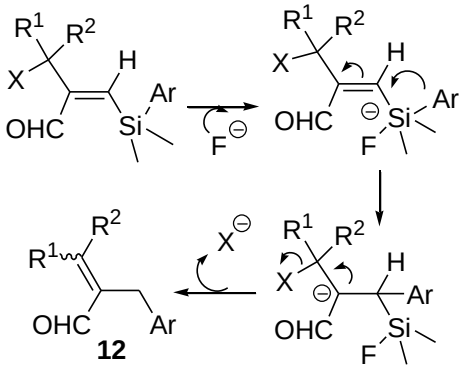


Scheme 40



11, 54 %

Scheme 41



12

X = OAc, OCOPh, *p*TsNH

Scheme 42

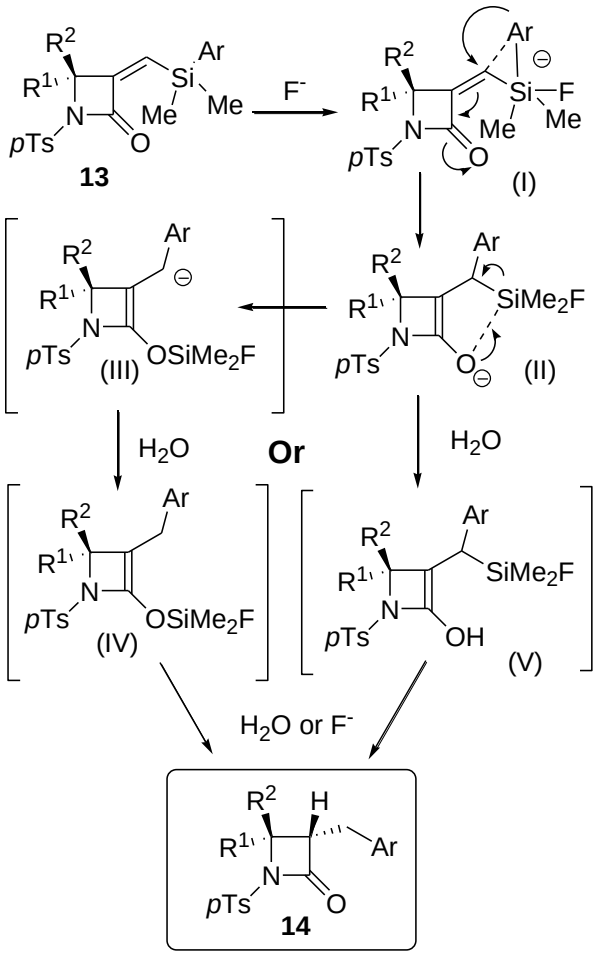

R2
R1
N
pTs
O
Si
Ar
Me
Me
F-
13
(I)
(II)
(III)
(IV)
(V)
SiMe2F
OSiMe2F
OH
H2O
Or
H2O or F-
H
14

Figure 1. Migration of aryl ring from silicon to carbon.

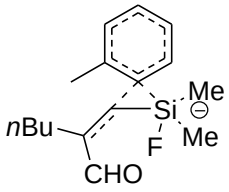
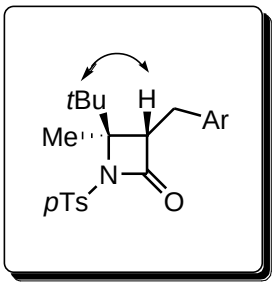


Figure 2. NOE effects between *tert*-butyl protons and the adjacent hydrogen



Synthesis and reactivity of silylformylation products derived form alkynes

Laura Antonella Aronica, Anna Maria Caporusso, Piero Salvadori*

Synthesis of polyfunctionalised molecules

The silylformylation reaction of alkynes introduces a silyl and a formyl moiety into the carbon-carbon triple bond, generating β-silylalkenals and α-silylmethylen-β-lactams if a base is present. The arylsilyl functionality can be used as carrier of the aryl group which can migrate from silicon to carbon when a fluoride source is present, affording different polyfunctionalised molecules depending on the structure of the alkyne precursors.