

The organic chemistry of silver acetylides

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Silver acetylides are among the oldest organometallics known; however, their applications in organic chemistry remained scarce until very recently. Indeed, several reactions involving silver salts as catalyst or silver acetylides have been reported in the past five years. The extreme mildness and very low basicity of these nucleophilic reagents nicely complement the behavior of other alkynyl metals, rendering them very useful in various transformations, especially in the synthesis of complex molecules. Silver acetylides are now seen as promising tools in organic chemistry. This *critical review* focuses on this emerging field, and, with emphasis on mechanistic aspects, cover the synthesis of silver acetylides, their applications in organic chemistry and reactions involving silver salts as catalysts where silver acetylides are probable intermediates.

1 Introduction

Silver acetylides – alkynyl silvers – are among the first organometallics ever produced. 3-Ethoxyprop-1-ynyl silver and phenylethynyl silver were reported as early as 1865 and 1870, respectively.^{1–3} Their structural and coordination chemistries are quite well known.^{4,5} However, despite their venerable age, these organometallics were only sparingly applied to organic chemistry.

Only a handful of reports indeed mentioned silver acetylides as reagents for years, but a clear burst of interest is currently emerging with several reactions involving silver salts as catalysts and a few examples using silver acetylides in stoichiometric processes published in the past five years. Indeed, these nucleophilic reagents exhibit an extreme mildness and a very low basicity rendering them very useful in various

transformations, their reactivity thus nicely complements the behavior of other alkynyl metals.

This review focuses on this emerging field, and covers the synthesis of silver acetylides and their applications in organic chemistry, as well as reactions involving silver salts as catalysts where silver acetylides are probable intermediates. A strong emphasis on mechanistic aspects is provided to help readers to further design reactions based on these reagents.

2 Synthesis of alkynyl silver compounds

Surprisingly, only two methods are so far known to prepare silver acetylides, yet only a single one was known until very recently.

The older method is based on the well-known diagnostic test for the presence of the terminal acetylenic group used up to the mid-20th century.^{6,7} The formation of a precipitate from a solution of ammoniacal silver nitrate was indeed characteristic of terminal alkynes. The precipitate proved to be the corresponding alkynyl silver (eqn (1)).⁸

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Ulla Halbes-Letinois

Ulla Halbes-Letinois studied at the “Carl-von-Ossietzky-Universität” at Oldenburg in Germany and obtained a Master of Chemistry in 2000 working on a joint program between this University and the University of Champagne-Ardenne, France, under the guidance of Dr Jacques Muzart and of Dr Jürgen Martens. She then moved to Strasbourg at the University L. Pasteur in the group of Prof. P. Pale working on dienediynes synthesis and on PdAg-catalyzed cross-coupling reactions.

She also worked at the University of Leipzig, Germany, with Prof. S. Berger, and she obtained a PhD in 2003 from both Universities. After two post-doctoral stays in France (Dr B. Meunier in Toulouse (Interaction Pt^{IV}–DNA),



J.-M. Weibel

then Dr J. P. Sauvage in Strasbourg (Cu rotaxanes), in 2005 she received a position at DSM Nutritional Products Ltd working on vitamins.

J.-M. Weibel obtained his PhD in chemistry in 1994 from the University Louis Pasteur of Strasbourg under the supervision of Dr D. Heissler. After a two years stay at University College of London as a post-doctoral fellow with Prof. W. B. Motherwell, he joined Prof. Pale's group in the Chemistry

Institute of Strasbourg in 1996 as an Assistant Professor. His research interests focused on the development of new tools for the organic chemist and on their application in total synthesis of molecules with biological activities.

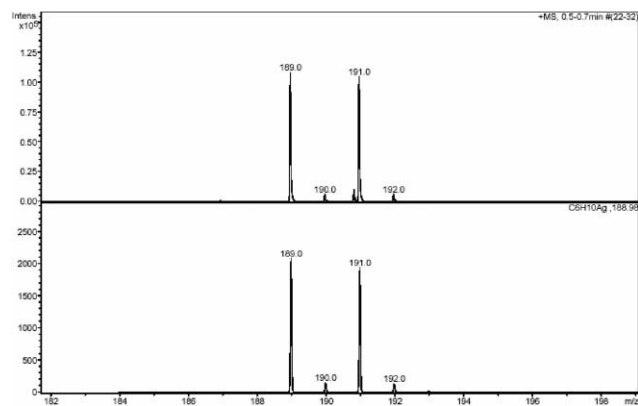
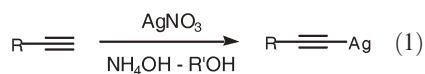
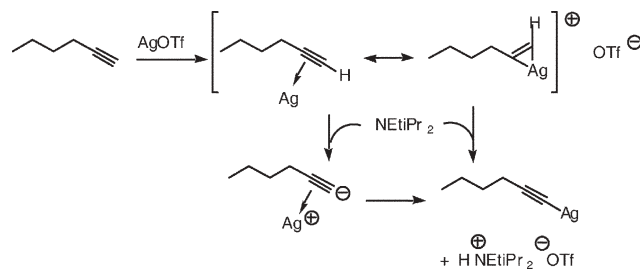


Fig. 1 ESI-MS spectrum of a 1 : 1 mixture of 1-hexyne and AgOTf in benzene. The upper spectrum is the measured one, the lower one is the calculated one (silver is a mixture of two isotopes ^{109}Ag , ^{107}Ag in a 52 : 48 ratio). (Reprinted from ref. 10. Copyright 2005, American Chemical Society.)



More recently, it has been demonstrated that this reaction proceeds with various silver salts in various solvents and the mechanism of this reaction has been studied.^{9,10} Indeed, ^1H , ^{13}C and ^{109}Ag NMR investigations revealed that a π -complex intermediate is first formed between silver ion and the alkyne, which is stable enough in solution to be fully characterized by mass spectrometry (Fig. 1). This complex is immediately deprotonated upon addition of bases such as amines leading without any detectable intermediate to the alkynyl silver (Scheme 1; also see section 5.2).¹⁰

Although most of the known silver acetylides have been prepared through the treatment with ammoniacal silver nitrate



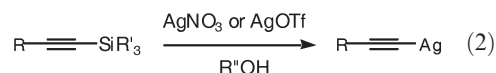
Scheme 1

aqueous solution, such basic conditions are not always compatible with functionalized alkynes. For example, silver acetylides derived from ethynyl epoxides or from some acetylenic esters cannot be obtained through this method.¹¹

To solve such synthetic problems and extend the chemist's toolbox, an alternative synthesis of alkynyl silvers has been developed.¹²

Mechanistic studies in connection with Pd/Ag-catalyzed cross-coupling reactions (see section 5.2) suggested again the formation of a π -complex between silver ion and silylated alkynes.¹³ The silyl group being activated, a nucleophilic attack of the silver counter-ion displaced this silyl group, leading to the alkynyl silver (Scheme 2).

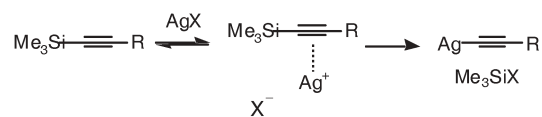
Based on these mechanistic grounds, various alkynyl silvers were efficiently prepared under mild conditions (eqn (2)). The yields are comparable and often better than the yields obtained through the classical method based on ammoniacal silver nitrate treatment.¹⁴



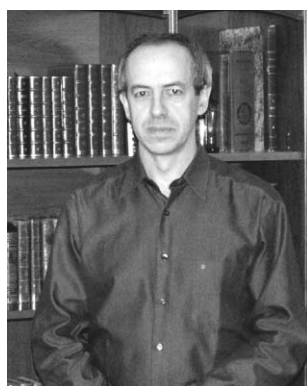
3 Reactivity and stability of alkynyl silvers

Alkynyl silvers, as for other organometallics derived from silver(I), suffer from the reputation of being "notoriously unstable". Although alkyl silvers indeed are unstable, usually giving dimers through radical formation, alkynyl silvers are by far more stable. However, one can not exclude explosive decomposition during recovering or scraping "dry" silver acetylides with metallic spatula as mentioned in two cases, in the preparation of 3-phenyl- and 3,3-diphenyl-3-hydroxyprop-1-ynyl silver.^{15,16} and in the preparation of the silver acetylides derived from propiolic esters.¹⁷

Nevertheless, alkynyl silvers can easily be obtained on gram scales, usually in the presence of air and, once prepared, alkynyl silvers proved stable enough as solids and can be kept for weeks and even months, as far as light (and sometimes air) are excluded. Alkynyl silvers can thus be used as reagents in various reactions (see below), where they can conveniently replace more conventional and more sensitive alkynyl metals, such as alkynyl lithium, sodium, magnesium, zinc, etc., which cannot be stored.



Scheme 2



P. Pale

P. Pale studied at the University of Champagne-Ardenne, France, where he obtained a PhD in 1982 under the direction of Prof. J. P. Pete and J. Muzart. After an industrial stay in a pharmaceutical company, he joined the group of Prof. L. Ghosez at Louvain-La-Neuve in Belgium for postdoctora work on the development of azadienes. In 1984, he returned to the University of Champagne-Ardenne as a CNRS fellow. Working on rearrangements and reaction mechanisms, he obtained a "Doctorat d'Etat" in 1988, and then a research associate position at Harvard University in the group of Prof. G. Whitesides in 1988–1990. He returned to the University of Champagne-Ardenne, and took up his present position in 1995 as Professor of Organic Chemistry at the University L. Pasteur in Strasbourg. Subsequently, he was awarded a Professorship at the Institut Universitaire de France from 1996 to 2001. His scientific interests include total synthesis of bioactive compounds, organometallic chemistry, asymmetric synthesis, carbohydrate chemistry and enzymatic chemistry.

As seen in the previous section, alkynyl silvers can be prepared in the presence of water and/or other protic solvents, and proved to be stable in such solvents. No hydrolysis of the metal–carbon bond occurs in these conditions. This can be in part due to their poor solubility in these solvents, but also to the strength of the silver–sp carbon bond. Hydrolysis of alkynyl silvers required the presence of strong acids, such as HCl, HNO₃ or triflic acid (see sections 5.4 and 5.5).¹⁸

The poor solubility of alkynyl silvers as well as their stability toward hydrolysis can both be related to their polymeric structures, which have been characterized by crystallographic studies of the solids^{4,5} but also in solution by NMR, including ¹⁰⁹Ag NMR.¹⁴ Depolymerization readily occurs in solution in the presence of stoichiometric amounts of triphenylphosphine¹⁹ and other donor ligands.²⁰

4 Synthetic applications of alkynyl silvers

As expected for species containing a metal–carbon bond, alkynyl silvers behave as nucleophiles. However, compared to other alkynyl metals, they exhibit an extreme mildness and a very low basicity rendering them very useful in some transformations.

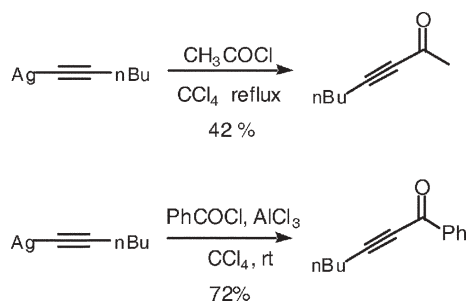
These facts make even more surprising the paucity of synthetic applications of these organometallics.

4.1 Additions to carbonyl compounds and related compounds

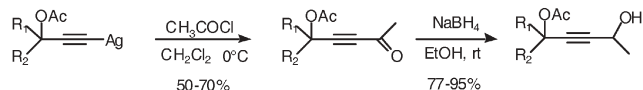
Alkynyl silvers are nucleophilic enough to add onto activated carbonyl groups or iminium but not nucleophilic enough to add to aldehydes or imines without activation.

4.1.1 Acylation and imidoylation. The major application of alkynyl silvers is in acylation reactions. The first example was described by Davis and Scheiber. These authors directly used a tetrachloromethane solution of a few silver acetylides obtained by extraction of an ammoniacal aqueous solution of silver nitrate and alkynes. These solutions were added either to an acyl halide and refluxed or to a premixed solution of acid halide and aluminium halide at room temperature, yielding ynones in moderate to good yields (36–72%) (Scheme 3).⁸

The group of Goré successfully used this reaction to prepare γ -acetoxy ynones, the reduction of which led to the corresponding γ -acetoxy ynols in good overall yields (Scheme 4). The latter were used as starting materials to investigate their conversion to functionalized allenes. Contrarily to the above mentioned conditions, isolated alkynyl silvers were used as starting materials.²¹



Scheme 3



Scheme 4

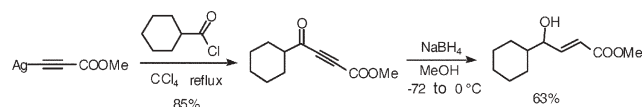
More recently, Koide and Naka described a rapid sequence to γ -hydroxy- α,β -(*E*)-alkenoic esters (Scheme 5). Acylation of the silver acetylide derived from methyl propiolate led to the corresponding ynones in good yields.²² Surprisingly, the borohydride reduction of these ynones did not give the expected propargylic alcohols but rather a product resulting from a further reduction of the acetylenic group. In some cases, a lactone resulting from the formation of the *Z* enoate was also isolated as a side-product (9–12%).

This route to ynones is shorter and milder than the conventional three-step protocol, which requires first the use of strong bases to obtain a metal acetylide, addition of the latter to aldehyde, and then oxidation of the resulting propargylic alcohol.

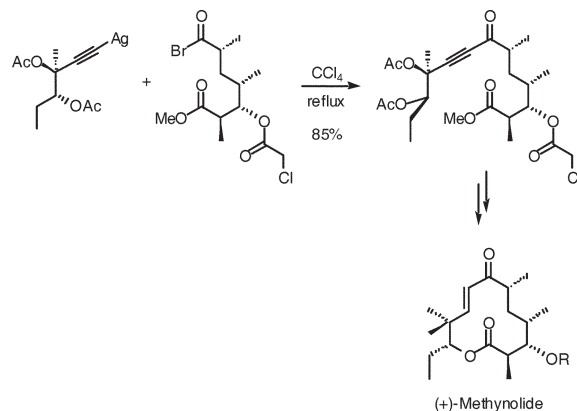
With such arguments, it is quite surprising that this sequence is not commonly used in organic synthesis. So far, and to the best of our knowledge, only one single application of alkynyl silvers in total synthesis is described, this acylation reaction being one of its key steps (Scheme 6).²³ In this synthesis, the macrolide antibiotic (+)-methynolide was obtained through acylation of an alkynyl silver followed by lactonisation.

A related reaction on imidoyl chloride has been reported by a Russian group in 1986.²⁴ Conjugated imino alkynes can be obtained through addition of alkynyl silvers to diphenyl- and bis(*p*-nitrophenyl)imidoyl chlorides. The imino alkynes so formed were easily converted to pyrazoles by treatment with hydrazine in isopropyl alcohol (Scheme 7).

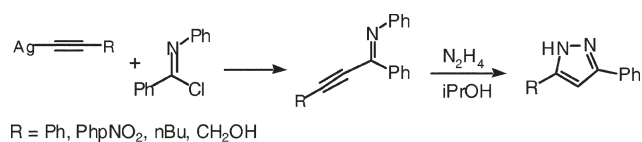
4.1.2 Carboxylation. Instead of carbonyl or imidoyl chlorides, carbon dioxide can also be attacked by alkynyl silvers. Indeed, Saegusa *et al.* in 1974 demonstrated that alkynyl silvers and coppers could react with carbon dioxide in the



Scheme 5



Scheme 6 Synthesis of (+)-methynolide involving an alkynyl silver.



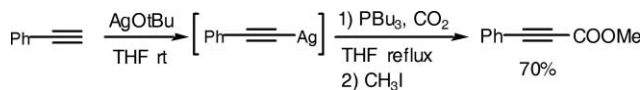
Scheme 7

presence of strong σ -donor ligands such as tri-*n*-butylphosphane and *tert*-butyl isocyanide (Scheme 8).²⁵ Weaker σ -donor ligands did not allow for CO₂ insertion. The resulting acetylenic carboxylates were trapped with methyl iodide, yielding the corresponding esters in good yields.

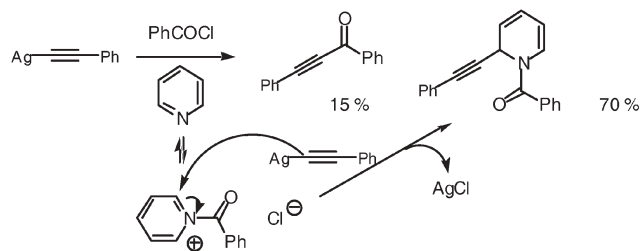
4.1.3 Addition to aldehydes and related compounds. So far, no direct addition of alkynyl silvers to aldehydes has been mentioned in the literature. As mentioned above, alkynyl silvers are probably not nucleophilic enough to directly add to non-activated carbonyl groups, including aldehydes. Nevertheless, a recent publication described the alkylation of aldehydes using the silver acetylide derived from methyl propiolate.²⁶ However, this process is only effective when a slight excess of Cp₂ZrCl₂ is added, suggesting a transmetalation prior to the nucleophilic addition. Therefore, this reaction will be commented in the corresponding section (section 4.5).

Treatment of phenylethyne silver or hexynyl silver with benzoyl chloride in pyridine yielded to the expected ynone (see section 4.1.1) but also to an unexpected product, the latter being the major one.²⁷ This compound proved to be also an addition product, but resulting from the addition of the silver acetylide to the 2-position of the *in situ* formed N-benzoylated pyridinium chloride (Scheme 9).

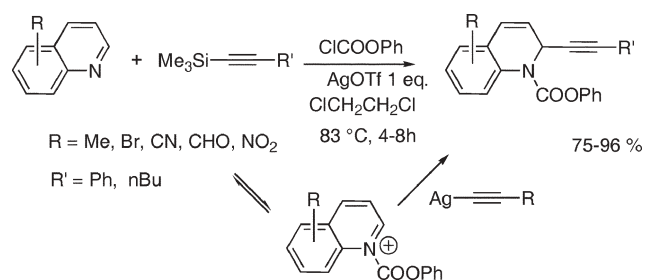
More recently, a similar process was reported for quinolines. Looking for an alternative route toward dynemycin A antitumor antibiotic, a Japanese group screened various conditions to alkynylate quinoline with various alkynyl derivatives, including 1-trimethylsilyl-1-alkynes. They observed that upon N-acylation of quinoline, a stoichiometric amount of silver triflate in refluxing 1,2-dichloroethane promotes alkylation with 1-trimethylsilyl-1-alkynes in good yields (Scheme 10).²⁸ Although no explanation is provided, it seems that alkynyl silvers are formed in such conditions (see sections 5.2, 5.3 and 5.5) and that they add to the N-acylquinolinium formed *in situ*.



Scheme 8



Scheme 9



Scheme 10

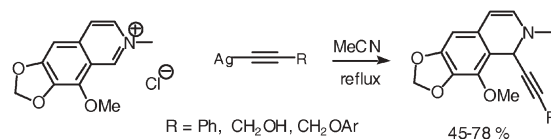
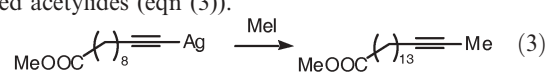
In a related process, a cyclic iminium natural product, cotarnine hydrochloride, has been alkynylated by various alkynyl silvers upon heating in acetonitrile (Scheme 11)²⁹

Following the discovery of C-nucleoside antibiotics, an interesting synthesis of ribofuranosyl propiolates was described based on the alkylation of a cyclic oxonium intermediate.^{30,31} Upon treatment with the silver acetylide derived from methyl or ethyl propiolate, protected ribofuranosyl chlorides or bromides were converted to the corresponding ribofuranosyl propiolates. Performed in a one-pot process without isolation of the ribosyl halides and in the presence of molecular sieves, reasonable yields and selectivity were obtained in acetonitrile (Scheme 12).

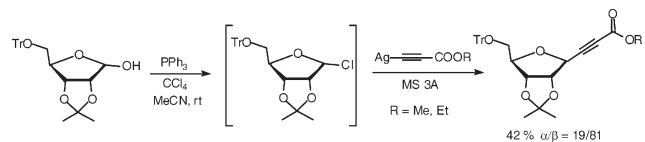
In this reaction, the silver reagent probably plays a dual role. On one hand, silver(I) can act as a mild and halophilic Lewis acid promoting the *in situ* formation of an electrophilic oxonium species; on the other hand, the alkynyl silver could then add to this highly reactive carbonyl form (Scheme 13).

4.2 Alkylation

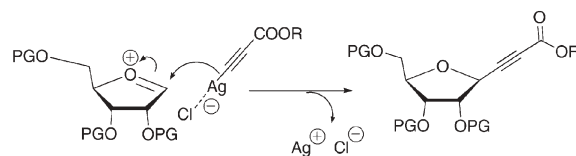
Alkynyl silvers could also be involved in alkylation reactions. Isabelle and Leitch showed that various silver acetylides readily react with methyl iodide leading to the corresponding methylated acetylides (eqn (3)).³²



Scheme 11

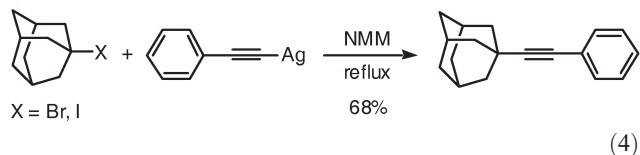


Scheme 12

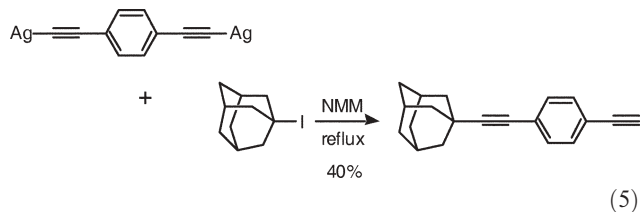


Scheme 13

More recently, Williams and co-workers demonstrated that silver arylacetylides can react with adamantyl bromide or iodide upon refluxing in *N*-methylmorpholine (NMM) leading to adamantyl alkynes (eqn (4)).³³ The corresponding aliphatic or silylated acetylides react but with a low yield (25–29%). Surprisingly, an aminophenyl substituted silver acetylide did not give the expected alkylation product but a product resulting from electrophilic aromatic substitution. For this adamantane alkylation reaction, an $S_{RN}1$ mechanism was suggested, supported by the fact that adamantane was detected as side-product.

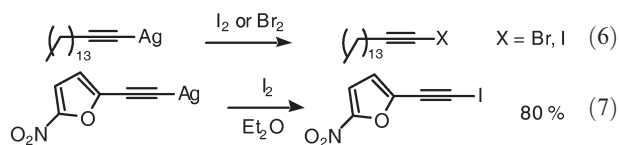


Surprisingly, only one end reacts when a silver diacetylide is used leading to a mono alkylated diyne (eqn (5)).

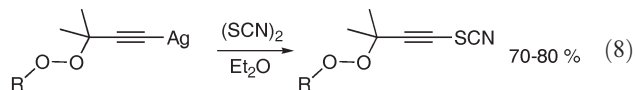


4.3 Halogenation and thiocyanation

Alkynyl silvers react readily with dibromine or diiodine yielding the corresponding halogenated alkynes. Aryl or alkyl acetylides give similar yields indicating no significant differences in reactivity (eqn (6), (7)).^{34–36}



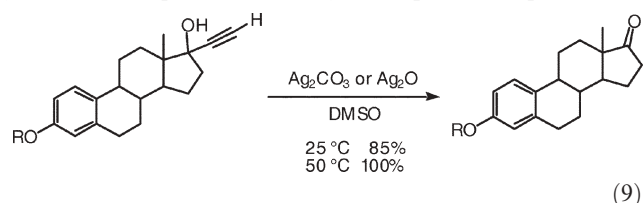
A single example mentioned the reaction of an alkynyl silver with $(\text{SCN})_2$. The corresponding alkynylthiocyanate was obtained (eqn (8)).³⁷



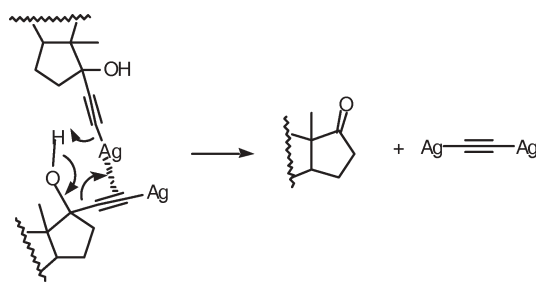
4.4 Fragmentation

An Italian group reported in 1972 a surprising reaction, which may correspond to a retro-alkylation process.³⁸

Indeed, derivatives of 17-ethynyl oestradiol and norethindrone led to the corresponding 17-ketone by treatment with an excess of silver carbonate or oxide in DMSO at room temperature. The yield was even quantitative at higher temperature (eqn (9)).



Several evidences suggested that a silver acetylide is formed in these conditions and that this fragments in a concerted



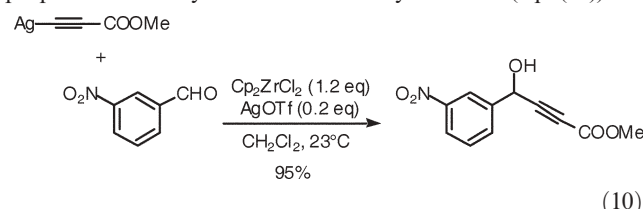
Scheme 14

process to the ketone. The formation of ethynyl disilver would be the driving force of this cleavage (Scheme 14).

4.5 Transmetalation

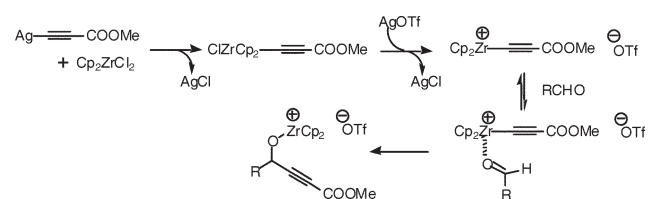
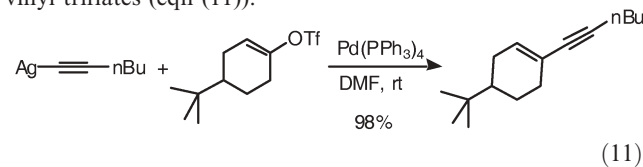
As for the above mentioned processes, the number of reactions involving alkynyl silvers in transmetalation processes is surprisingly quite limited. To the best of our knowledge, only two examples are so far reported.

Nucleophilic addition of the silver acetylide derived from methyl propiolate to aldehydes has been recently described (eqn (10)).²⁶



This reaction proved to be effective only when a slight excess of Cp_2ZrCl_2 is added, and the reaction became synthetically useful when a catalytic amount of silver triflate was also added. Although not mentioned in the corresponding paper, the data provided suggest a transmetalation of the silver acetylide to a halozirconium species, the halogen of which is abstracted by the added silver triflate in a process similar to that described by Suzuki and co-workers.³⁹ This abstraction opens up a coordination site on the zirconium atom, allowing the aldehyde to be coordinated and thus activated toward alkylation, probably within the zirconium first coordination sphere (Scheme 15).

Alkynyl silvers can participate in palladium-catalyzed cross-coupling reactions.⁴⁰ Tetrakis(triphenylphosphine)palladium catalyzes the coupling of various alkynyl silvers to different vinyl triflates (eqn (11)).



Scheme 15

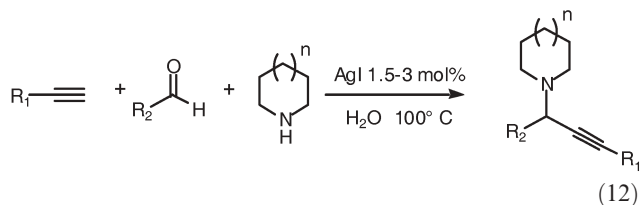
Therefore, alkynyl silvers are able to enter the palladium catalytic cycle at the transmetalation stage (Scheme 16). In a process analogous to what happens with other organometallics, the alkynyl silver probably reacts with the organopalladium halide or triflate, produced by oxidative addition of a zerovalent palladium species to an organic halide or triflate, and displaces the coordinated halide or triflate. The diorganopalladium species so formed then undergoes a reductive elimination, regenerating the active palladium species and liberating the coupling product.

5 Alkynyl silver and related species as intermediates in silver catalyzed reactions

Several reactions involving alkynes and silver salts as catalyst are known, most of which have been recently described. They can be divided into two classes depending on their mechanism. The majority of these reactions can be described through a mechanism probably involving alkynyl silvers as intermediates, they will therefore be detailed here. The remaining reactions could be explained by a mechanism involving a π -complex between the silver catalyst and the alkyne; they will be described elsewhere.

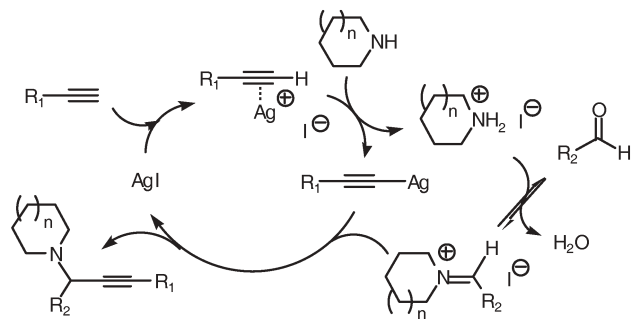
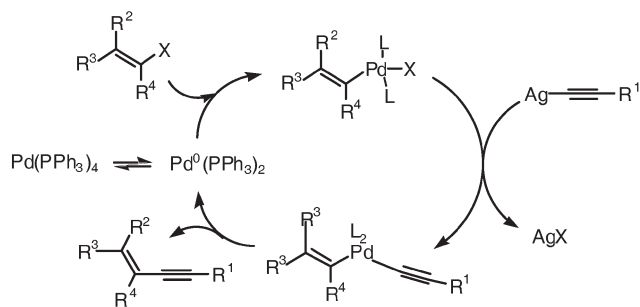
5.1 Silver catalyzed nucleophilic additions

A three-component coupling of aldehydes, alkynes and amines catalyzed by silver iodide was recently reported.⁴¹ Promoted as a greener and atom economic version of the Barbier–Grignard reaction, this reaction can indeed be performed in water but requires heating up to 100 °C during 14 h (eqn (12)). The reaction can also be performed in ionic liquids.⁴²

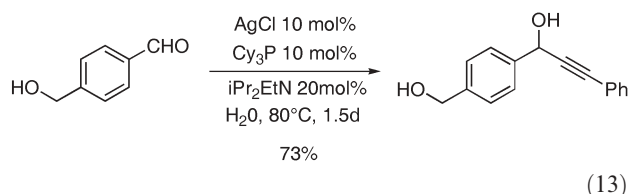


In such conditions and especially in the presence of amine, a silver acetylide is probably formed (*cf.* sections 2 and 5.2). The latter should act as a nucleophile toward the iminium formed *in situ* by condensation of the amine with the aldehyde, in a reaction similar to the addition of phenylethynyl silver to *N*-benzoyl pyridinium chloride (*cf.* section 4.1.3) (Scheme 17).

Very recently, the same group reported what seems to be the first nucleophilic addition of an intermediate alkynyl silver to

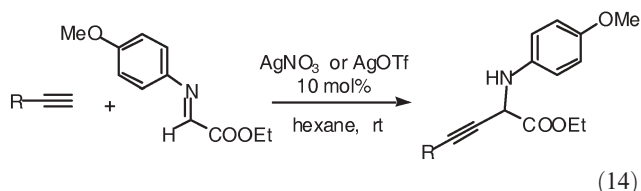


aldehydes.⁴³ Upon screening silver catalysts, they found that silver chloride coordinated with tricyclohexylphosphine catalyzes the addition of terminal alkynes to aldehydes in the presence of ethyldiisopropylamine (eqn (13)).

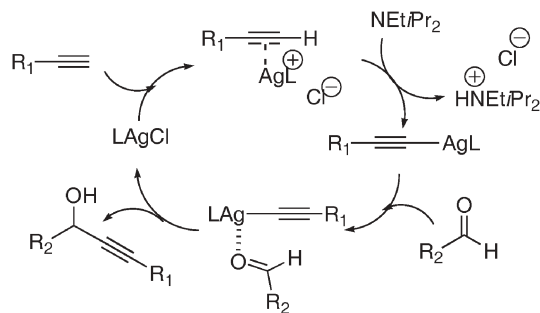


Preliminary mechanistic investigations revealed that in similar conditions phenylethynyl silver adds to cyclohexyl aldehyde. Based on these results, the following mechanism can be proposed (Scheme 18).

In a related reaction, Chan and co-workers recently reported the Ag-catalyzed condensation of terminal alkynes with an α -iminoester derived from ethyl glyoxylate (eqn (14)).⁴⁴ Among the silver salts screened for catalysis, silver nitrate and triflate proved to be the most efficient. As one could expect, non-coordinating solvents allowed for a rapid and efficient reaction.



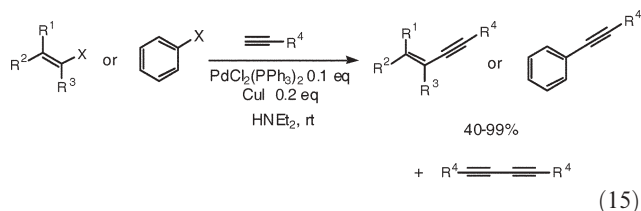
The mechanism of this reaction is probably very similar to the preceding ones. The imine is probably basic enough to deprotonate the *in situ* formed π -complex, leading on the one hand, to the alkynyl silver, and on the other to an iminium. Both intermediates react then with each other giving the



corresponding adduct and regenerating the silver salt (Scheme 19).

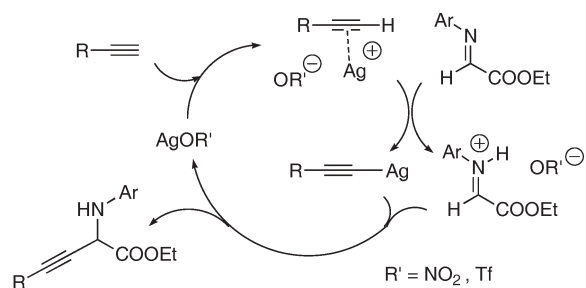
5.2 Silver assisted palladium-catalyzed cross-coupling reactions

The construction of organic frameworks bearing alkynyl groups by cross-coupling reactions have gained a wide interest due to the presence of such motifs in natural compounds and due to the interesting properties associated with this motif in non-natural compounds (organic materials). The most common route to prepare these oligo- or poly-alkynylated frameworks is based on the Sonogashira reaction. This reaction discovered in 1975 by Sonogashira *et al.*⁴⁵ is a Pd and Cu-catalyzed version of the so-called Stephens–Castro reaction.⁴⁶ With this method, terminal alkynes can conveniently be coupled with aryl or vinyl iodides, bromides and triflates in the presence of palladium complexes and copper salt (eqn (15)). Good yields are generally obtained but diyne dimers are usual contaminants in this reaction, due to copper-catalyzed Glaser-type oxidative coupling.^{47–49} Moreover, the highly basic conditions, due to the use of pure amine as solvent or of an excess of base, are not always compatible with fragile compounds. Therefore, various variants of the original Sonogashira protocol have been proposed.^{50,51}

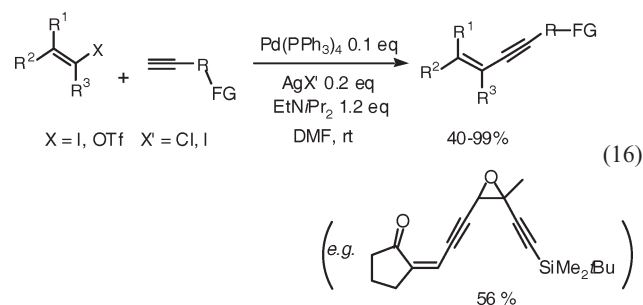


In an effort to get an $sp-sp^2$ coupling reaction compatible with various sensitive functional groups, especially epoxides, and to avoid the formation of diynes, our group came up with a Pd and Ag catalyzed version of the Sonogashira reaction.^{52–54} Based on mechanistic grounds and on related reactions (see sections 2 and 4), a screening of catalysts and conditions showed that silver iodide and chloride were the best catalysts and DMF the best solvent, although the reaction can also be run in benzene, chloroform, *etc.*¹⁰ Silver iodide is usually preferred with very sensitive compounds, such as the epoxydiene in eqn (16). Although very mild and without any side-products, these conditions are so far limited to the coupling of vinyl or aryl iodides or triflates.

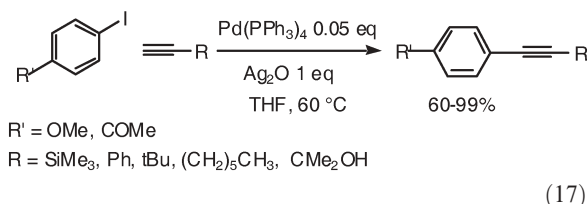
A few years later, Mori *et al.* demonstrated that silver oxide in refluxing THF could also promote coupling between



Scheme 19



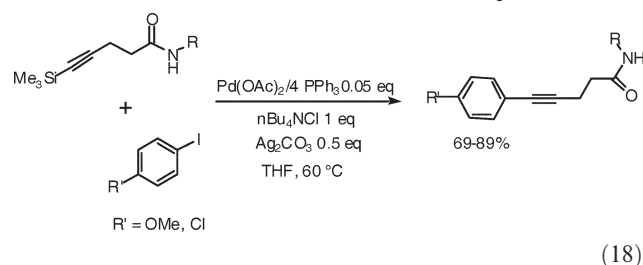
aryl iodides and terminal alkynes (eqn (17)). However, a stoichiometric quantity of silver oxide—*i.e.* two equivalents of silver ion—were required as well as heating. This reaction did not allow the coupling of aryl bromides or triflates, but the coupling of (*E*)-1-bromo-2-phenylethene was nevertheless reported in these conditions.⁵⁵

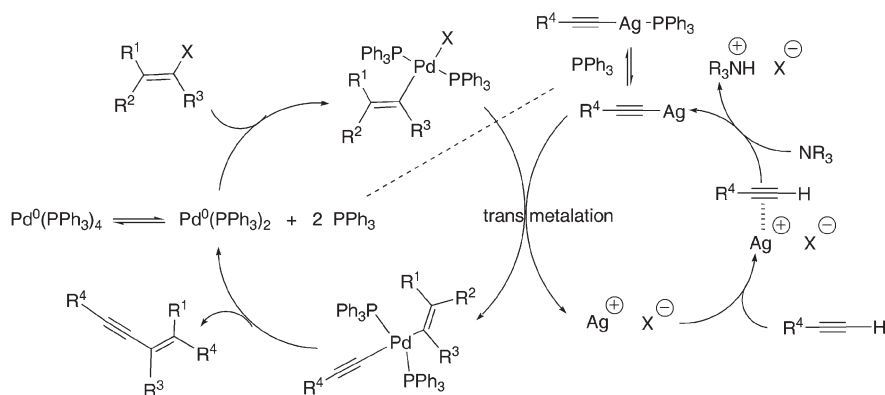


As demonstrated by an NMR survey of the reaction and independent experiments (see sections 2 and 4.5), the formation of alkynyl silvers occurred in the conditions of these reactions (Scheme 16). Indeed, ¹⁰⁹Ag NMR and ESI-MS monitoring of the Pd/Ag-catalyzed coupling reactions showed that the alkyne was first coordinated by the silver salt, resulting in a more fragile C–H bond, and that this π -complex was converted to the corresponding alkynyl silver upon addition of base.¹⁰ The latter was then stabilized and rendered more soluble by coordination with the phosphane present in solution coming from the palladium source.¹⁹ The alkynyl silver then entered the palladium catalytic cycle at the transmetalation step⁴⁰ (Scheme 20).

Related Pd-catalyzed coupling reactions involving silylated alkynes were also disclosed by the same groups and a few others.

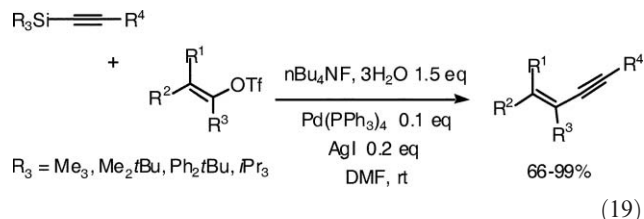
In one of their papers, Mori *et al.* mentioned the use of silver oxide as a promoter for the coupling of trimethylsilyl alkynes with aryl iodides. As in the corresponding coupling of terminal alkynes, two equivalents of silver ion were required.⁵⁵ Independently, Nagasaka and co-workers reported that silver carbonate as well as silver oxide in the presence of tetrabutylammonium chloride is effective for the coupling of 5-trimethylsilyl-4-pentynamides with aryl iodides but not with aryl bromides (eqn (18)). A stoichiometric amount of both the silver and the chloride ions was nevertheless required.⁵⁶



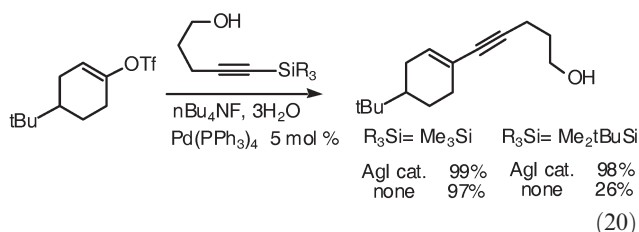


Scheme 20

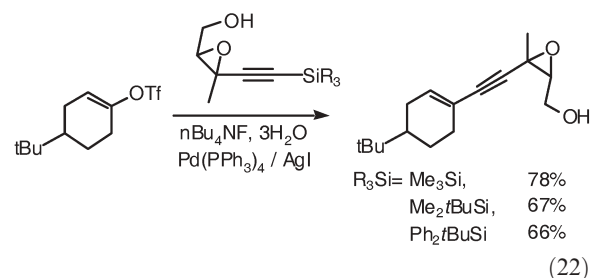
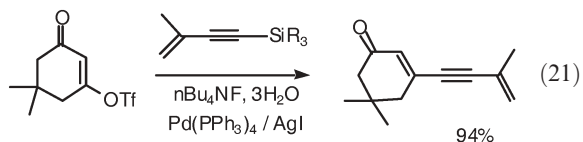
In parallel, and for a highly convergent synthesis of the antitumor dienediynes natural products, Pale and co-workers developed catalytic conditions allowing the direct cross-coupling of any 1-trialkylsilyl-1-alkyne.^{57,58} In the presence of catalytic amounts of Pd(PPh₃)₄ and silver salt, trimethylsilyl-, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or triisopropylsilyl alkynes underwent cross-coupling with vinyl triflates in good to excellent yields (eqn (19)). The common, cheap and easy to handle solid tetrabutylammonium fluoride trihydrate (TBAF·3H₂O) could be used as an activator. The reaction worked best in DMF but could also be run in other solvents such as THF, chloroform and benzene.



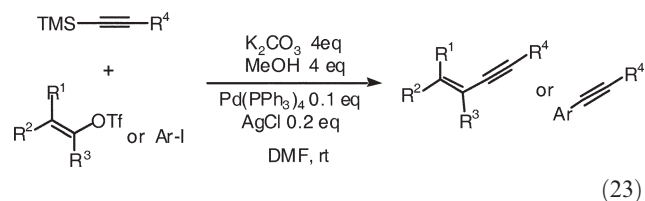
Interestingly, this cross-coupling reaction could also proceed without silver salt, becoming thus similar to a method described by Hiyama *et al.*⁵⁹ However, this coupling without silver co-catalyst seemed to be limited to trimethylsilylalkynes, indicating the key role of the silver ion (eqn (20)).^{57,58,60}



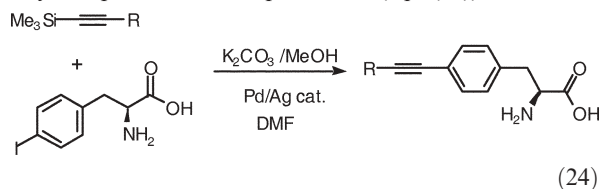
No protecting group was required and the conditions were mild enough to allow for the coupling of trialkylsilyl ethynyl epoxides or trialkylsilylenynes, leading to functionalized enynes in good to excellent yields (eqn (21), (22)).



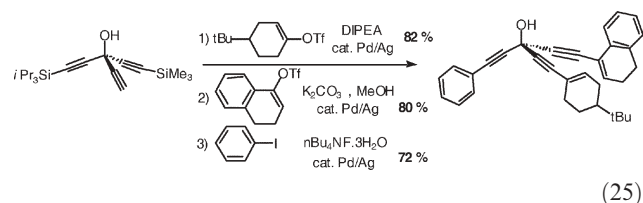
Again for the synthesis of natural products but also for selective synthesis of organic materials, the same group also reported a Pd/Ag-catalyzed cross-coupling of vinyl triflates or aryl iodides selective for trimethylsilylalkynes (eqn (23)).^{61,62}

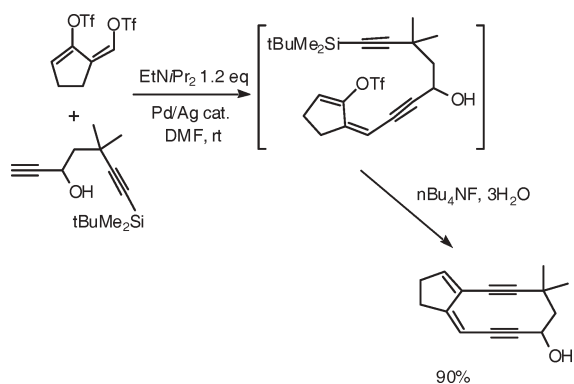


The silver ion played again a crucial role since without it, no reaction took place and the starting trimethylsilylalkyne was recovered *without desilylation*. The conditions seemed to be very mild since alcohol, acid and amine groups proved perfectly compatible without protection (eqn (24)).⁶³



These Pd/Ag-catalyzed couplings methods allowed for one-pot sequential coupling of monosilylated diynes (Scheme 21) (ref. 62 and unpublished results) and selective sequential coupling of polyalkynes bearing different silyl groups (eqn (25)).⁶⁴

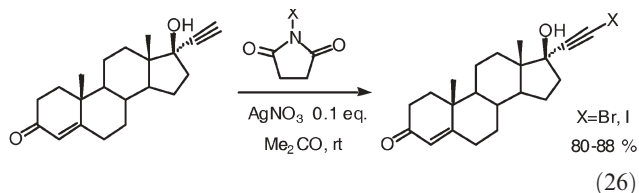




Scheme 21

The mechanism of these coupling reactions is similar to that demonstrated for the Pd/Ag-coupling of terminal alkynes. Experimental as well as multinuclear NMR data support the coordination of the silylated alkyne by silver ion and the *in situ* formation of an alkynyl silver.⁶⁵ Upon coordination, the silyl group is activated and prone to displacement by the added promoter (fluoride or methylate ion), leading to the formation of an alkynyl silver (Scheme 22).

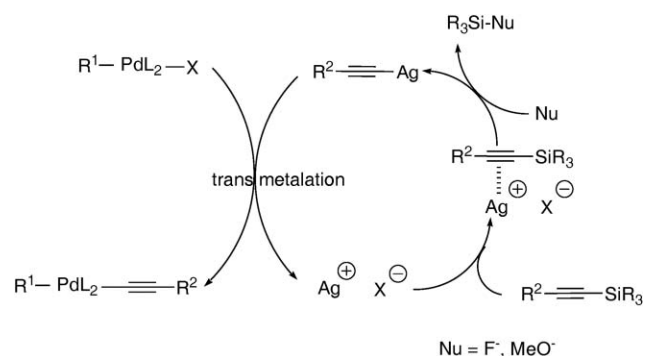
In 1984, a German industrial group reported an Ag-catalyzed formation of 1-halogeno-1-alkynes from the corresponding terminal alkynes.⁶⁶ They showed that silver nitrate in acetone catalyzed the halogenation of alkynes with *N*-bromo or *N*-iodosuccinimide as the halogen source in high yields and very mild conditions (eqn (26)).



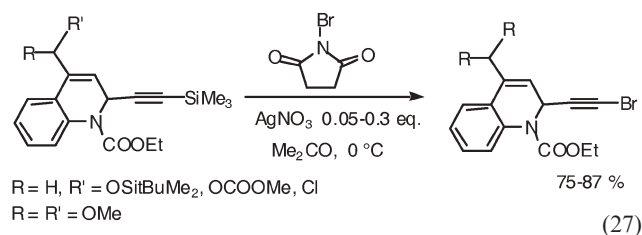
Ten years later, Isobe and co-workers described a very similar reaction starting from 1-trimethylsilyl-1-alkynes (eqn (27)).⁶⁷

Both methods have been used in various syntheses of natural products and of precursors for organic materials.

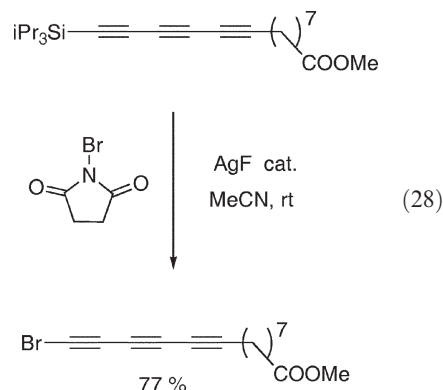
Recently, in an iterative synthesis of unsymmetrical polyynes, a Korean group reported a variant of the Isobe method.⁶⁸ They showed that triisopropylsilylalkynes can be



Scheme 22

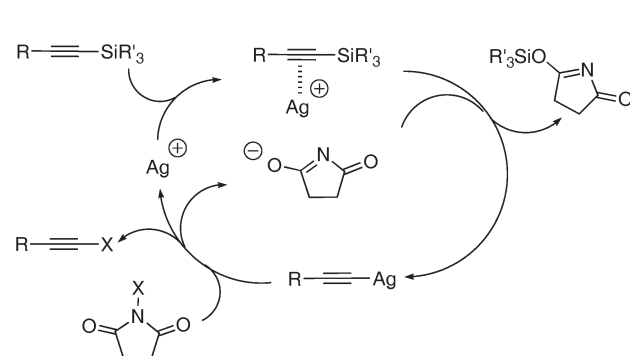
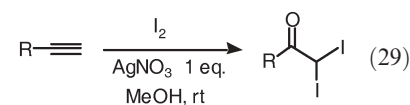


directly halogenated with *N*-bromosuccinimide in the presence of silver fluoride in acetonitrile (eqn (28)).



In these halogenation reactions, alkynyl silvers are probably formed *in situ* as in the coupling reactions of silylated alkynes (see section 5.2). Coordination of the silylated alkyne by silver ion would favor nucleophilic displacement of the silyl group, leading to the formation of the alkynyl silver. Once produced, the latter is probably nucleophilic enough (see section 4.3) to react with the *N*-bromo or iodosuccinimide present in the reaction mixture, leading to the corresponding haloalkyne and succinimide, which can act as nucleophiles towards the silyl group (Scheme 23).

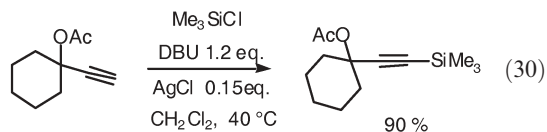
Interestingly, a related halogenation reaction performed in methanol with iodine in the presence of a stoichiometric amount of silver nitrate led mainly to the corresponding diiodoketone.⁶⁹ As diiodoketals were detected in this reaction, it is however unclear whether an alkynyl silver or an intermediate π -complex was formed in these conditions (eqn (29)).



Scheme 23

5.4 Silver catalyzed silylation

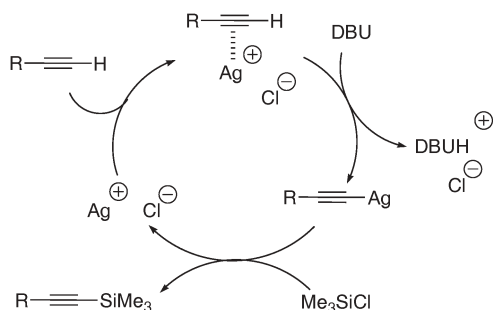
In a process similar to the silver assisted halogenation reactions, a Japanese group reported a silver-catalyzed silylation.⁷⁰ Silver chloride or nitrate catalyzed the direct introduction of a trimethylsilyl group to a terminal alkyne in the presence of DBU in refluxing dichloromethane (eqn (30)).



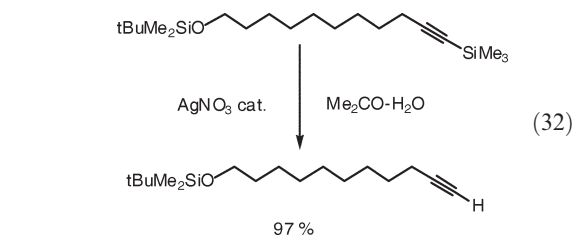
Interestingly, silver chloride was the most efficient catalyst, copper chloride was less effective and zinc chloride almost useless. Surprisingly, triethylamine was not effective. As mentioned before (see sections 2, 5.1 and 5.2), a terminal alkyne in the presence of silver salt and base leads to the corresponding alkynyl silver. So, it seems that in dichloromethane, a stronger base is required. Once formed, the alkynyl silver should react with trimethylsilyl chloride yielding the corresponding trimethylsilyl alkyne (Scheme 24).

5.5 Silver catalyzed desilylation

In 1967, Schmidt and Arens reported a mild procedure for the desilylation of trimethylsilyl alkynes. This method required a large excess of silver nitrate in ethanol–water and a further treatment with an excess of aqueous potassium cyanide.⁷¹ Despite these toxic and expensive conditions, this deprotection method was successfully applied in various total syntheses. Surprisingly, it took more than 35 years to get a catalytic version of this useful reaction. Indeed, in 2005, two similar sets of conditions were disclosed independently.^{72,73} Both groups reported that silver nitrate and silver triflate were the most effective catalysts and that the reaction required a mixture of protic and aprotic solvents. Interestingly, these catalytic versions were selective toward other silyl protecting groups, even in differently protected polyynes (eqn (31), (32)).



Scheme 24



In these reactions, an alkynyl silver is formed after silver coordination probably by nucleophilic displacement of the TMS group (see section 2 and 5.2) by the nucleophilic solvent usually required (ethanol, methanol or water and/or mixture of them). In the stoichiometric version, KCN in water hydrolyzes the so-formed alkynyl silver while in the catalytic versions, the acid which is liberated upon silyl displacement, must be strong enough to hydrolyze the alkynyl silver *in situ* and regenerate the silver salt (Scheme 25).

6 Conclusion

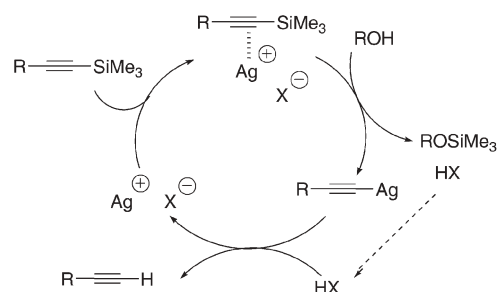
This survey of the synthesis and reactivity of silver acetylides showed the usefulness of these reagents and the diversity of the reactions where they are involved.

More known for their structural and coordination chemistries,² these organometallics exhibit a very mild nucleophilicity and a very low basicity. These properties, complementary to those of other alkynyl metals, allowed for very mild C–C and C–heteroatom bond formations. These possibilities have recently promoted a strong development of their applications in organic synthesis, especially in the formation of C_{sp}–C bonds. Indeed, reactions involving silver acetylides in stoichiometric and mainly in catalytic processes are clearly burgeoning in recent years.

In the future, it is clear that the unique properties of these organometallics will certainly attract more and more interest. A few trends can easily be identified, leading to new investigations in this area:

Stereoselectivity is so far not an issue. However, in the C–C bond formation already described, stereocenters are often concomitantly created. Therefore, the next challenge is to induce stereoselectivity, either as diastereoselection—or more interestingly—as enantioselection, in these processes.

Expanding the scope of these C–C bond formations is clearly another challenge.



Scheme 25

The formation of C–heteroatom bonds has so far been limited to halogen and silyl derivatives, but clearly other elements could be introduced, leading to more functionalized acetylenic derivatives.

Thus, silver organic chemistry is still in its infancy but will steadily grow, especially with the use of silver acetylides as reagents or intermediates.

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