ARTICLE

Cationic cyclization reactions with alkyne terminating groups: a useful tool in biomimetic synthesis

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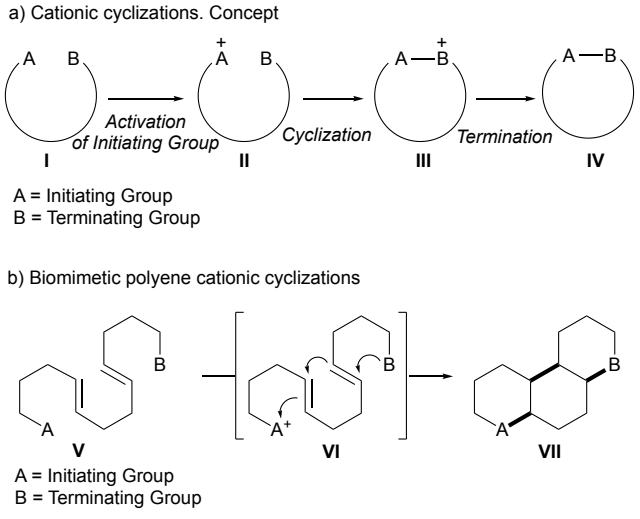
Cyclization reactions through cationic intermediates have become a highly valuable tool in organic synthesis. The use of alkynes as the terminating group in this type of cationic processes offers wide synthetic possibilities because this group can serve as precursor of different functionalities. This article shows relevant examples of cationic cyclization reactions with alkynes as terminating groups with the intention of demonstrating the potential of this type of processes particularly in the context of biomimetic synthesis of natural products.

Introduction

Cyclization reactions that proceed through cationic intermediates are widely used to construct carbo- and heterocyclic compounds.[1] The overall sequence of this type of cationic cyclization reactions is illustrated in Scheme 1a. As shown, the process involves an acyclic precursor **I** containing an electrophilic functionality (initiating group, A) and a complementary nucleophilic functionality (terminating group, B).



Scheme 1 Cationic cyclizations: Concept and biomimetic cyclizations.

Primarily, the initiating group is activated to generate a cationic intermediate **II** that is intramolecularly trapped by the terminating group in a cyclization step. The newly formed cationic species **III** is somehow stabilized through a termination step to give the final neutral cyclic product **IV**. Interestingly, the concept behind the cationic cyclization reactions has been beautifully extended to the context of biomimetic polyene cyclizations. In these processes, the initiating group (A) of the acyclic precursor **V** is separated from the terminating group (B) by a chain containing a series of alkene functionalities located at appropriate positions to successively trap the formed cationic intermediates (**VI**).[2] These reactions, which resemble the biosynthesis of polycyclic terpenes from acyclic precursors by the action of cyclase enzymes, result in the formation of complex products **VII** from simple starting materials in a highly efficient and selective way.

Cationic cyclizations usually involve the creation of carbon-carbon bonds. This means that the initiating and terminating groups (A and B in Scheme 1) typically are carbon-centred electrophilic and nucleophilic functionalities. Thus, once the initial activation occurs, the initiating group (A) is transformed into a carbenium ion. These cationic species might be stabilized by the presence of a vicinal heteroatom giving rise, for example, to oxonium, iminium or thionium species (Figure 1a). These cations are commonly known as heteroatom-stabilized carbenium ions. On the other hand, the initial cationic species might not be stabilized by any heteroatom. In this case, a typical carbenium ion (non-stabilized carbocation) is initially formed (Figure 1a).

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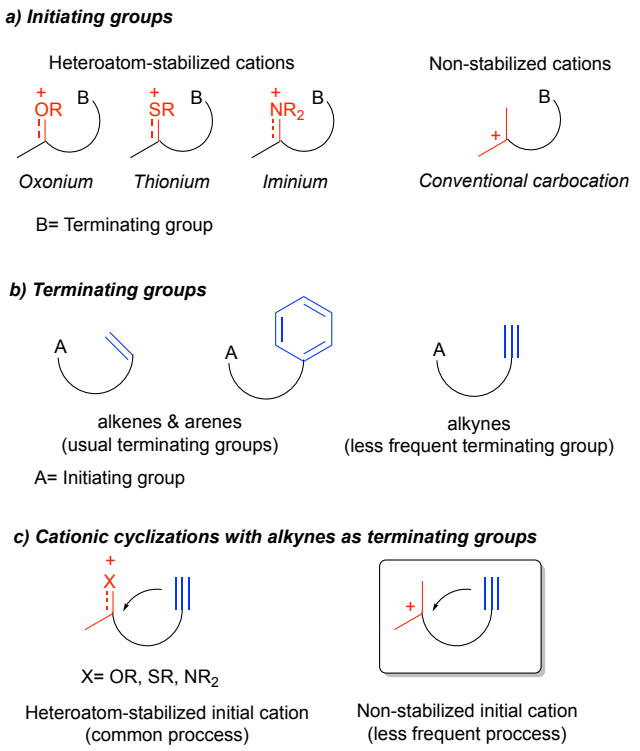
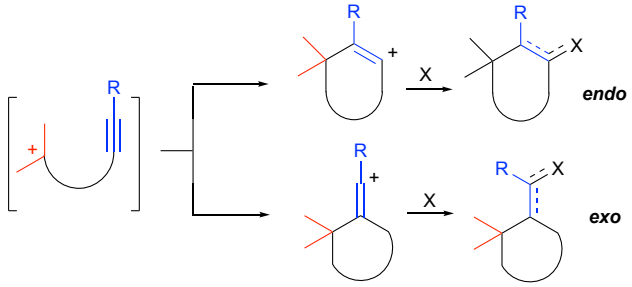


Figure 1 Activated initiating groups and terminating groups in the context of cationic cyclizations.

Regarding the terminating group (B in Scheme 1), apart from heteroatom-centred nucleophiles, alkenes (including enol ethers and allyl silanes) and (hetero)arenes are probably the most usual (Figure 1b). In contrast, the use of alkynes as the terminating functionality has been less studied. Furthermore, much of the progress in the field of cationic cyclization reactions with alkynes as terminating groups is limited to the use of heteroatom-stabilized initial cations (mainly oxonium or iminium). In contrast, the analogous processes with non-stabilized initial cations have received less attention (Figure 1c). Although this article is focused on this latter type of cationic cyclizations, W. N. Speckamp's pioneer works in the area of cyclization reactions with alkynes involving heteroatom-stabilized initial cations should be remarked upon at this point.[3,4]

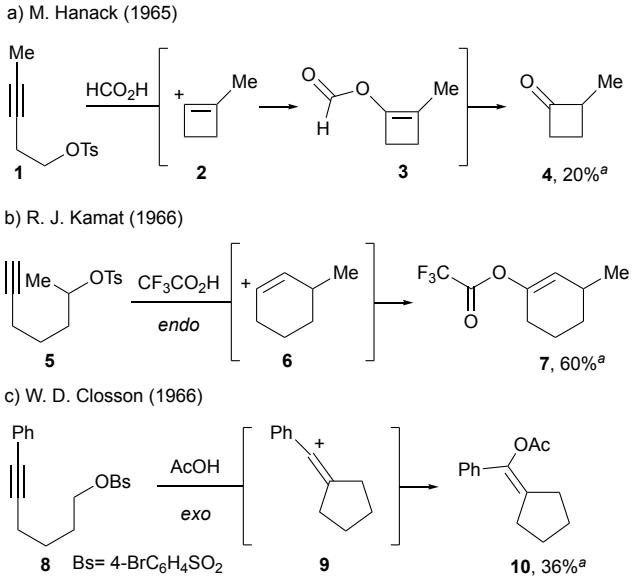
As noted above, this article is devoted to cationic cyclization reactions with alkynes as terminating groups involving non-stabilized initial cations. The interest of these type of cyclization processes resides in the wide synthetic opportunities that the alkyne substituent offers. Thus, depending on the reaction conditions used for the cationic cyclization, this moiety can be transformed into different functional groups. As shown in Scheme 2, the cyclization process involves the formation of an alkenyl cation intermediate that is usually trapped by an external nucleophile (X) leading to different final functionalities depending on the nature of that nucleophile. It should also be noted that the cyclization reaction may occur through two different ways (*endo* or *exo*) depending on which carbon atom of the alkyne moiety acts as nucleophilic centre trapping the initial cation (Scheme 2).



Scheme 2 Cationic cyclizations with alkynes as terminating groups implying non-stabilized initial cations. *Endo* and *exo* cyclization modes.

Pioneer works on cationic cyclizations with alkynes

The participation of alkynes as nucleophiles in cationic cyclization reactions was firstly reported by M. Hanack and co-workers in 1965. Thus, while studying the formolysis of 3-pentyn-1-yl tosylate (**1**), these authors observed the formation of 2-methylcyclobutanone (**4**; Scheme 3a).[5] This product is supposed to be the result of the hydrolysis of the corresponding enol ester **3** derived from the cyclobutenyl cation **2** produced after the cyclization reaction.



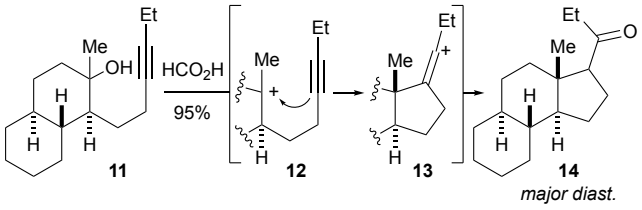
Scheme 3 Pioneer examples in the field of cationic cyclizations with alkynes. [a] By gas chromatography analysis.

Almost contemporaneously, the groups of R. J. Kamat and W. D. Closson described the triple bond involvement in related solvolytic cyclization processes (Scheme 3b,c).[6,7] Thus, solvolysis of 6-heptyn-2-yl tosylate (**5**) in trifluoroacetic acid gives predominantly the six-membered cyclic product 3-methylcyclohexenyl trifluoroacetate (**7**; Scheme 3b). This compound is formed by a cationic cyclization process where the

initially formed cation is trapped by intramolecular addition of the terminal carbon of the alkyne (*endo* cyclization) leading to the corresponding six-membered cyclic alkenyl cation **6** that is finally captured by the acid. Interestingly, when a similar reaction is performed with an internal alkyne (**8**; Scheme 3c), the cyclyzation process occurs through intermediate **9** formed by an *exo*-mode to finally give the five-membered ring containing an exocyclic enol ester **10**. Regarding the initiating group, it should be noted that all these early examples imply the use of similar sulfonate derivatives. These good leaving groups easily generate the starting alkyl cation that is subsequently trapped by the alkyne.

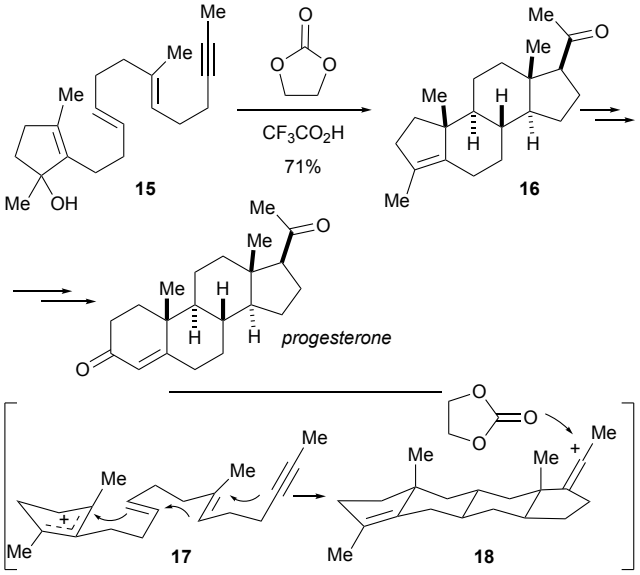
Early applications in natural products synthesis. Biomimetic cyclizations

The synthetic utility of the above-mentioned pioneer cationic cyclization reactions was rapidly identified. Thus, soon after those works appeared, P. T. Lansbury reported an efficient method for generating the D-ring of steroids by means of a cationic cyclization of an alcohol (**11**) appropriately substituted with an alkyne-containing alkyl chain (Scheme 4).[8] By treatment with formic or trifluoroacetic acid, a cationic cyclization process occurs to give a new five-membered ring. This product is the result of trapping the initially formed cation **12** by addition of the proximal carbon of the triple bond to give an exocyclic alkenyl cation **13** that is captured by the acid to form the corresponding enol ester that is converted into the ketone derivative **14** after hydrolysis.[9] It should be noted that the initial cation **12** that triggers the cyclization reaction is generated in this case by a dehydration process. It is also important to remark that the use of an internal alkyne favours the formation of a five-membered ring through an *exo*-cyclization process.



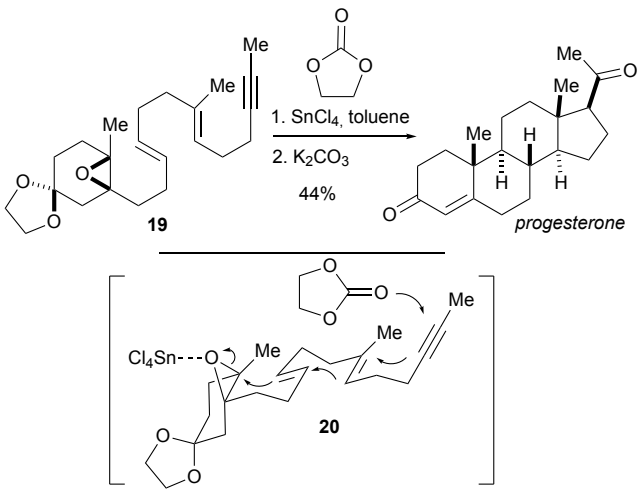
Scheme 4 Method for the generation of the D-ring of steroids developed by P. T. Landsbury.

Probably, the most remarkable application of those initial works on cationic cyclizations was achieved by W. S. Johnson in the context of biomimetic cyclization reactions of polyenes.[10] While working in this field, he realized of the potential of using alkynes as terminating groups to synthesize steroids.[11] W. S. Johnson's landmark total synthesis of progesterone nicely illustrates the imaginative use of alkynes in the context of biomimetic cyclization reactions (Scheme 5).[12] The key step of the synthetic sequence to get progesterone involves the cyclization of a polyene system **15** where the initiating group is an allylic alcohol and the terminating group is an internal alkyne. A dehydration reaction promoted by trifluoroacetic acid leads to the initial allylic cation **17**. The subsequent polycyclization process is believed to occur through a well-defined conformation by antiparallel additions to the alkenes.[13] The so-formed exocyclic alkenyl cation **18** is trapped by the ethylene carbonate and after hydrolysis, the corresponding ketone derivative **16** is obtained (Scheme 5). The most remarkable aspect of this cyclization regards the stereoselectivity of the process because basically only one isomer of the final product (containing six stereocentres) is obtained in a single operation.



Scheme 5 First biomimetic cationic cyclization with an alkyne as terminating group. W. S. Johnson's synthesis of progesterone.

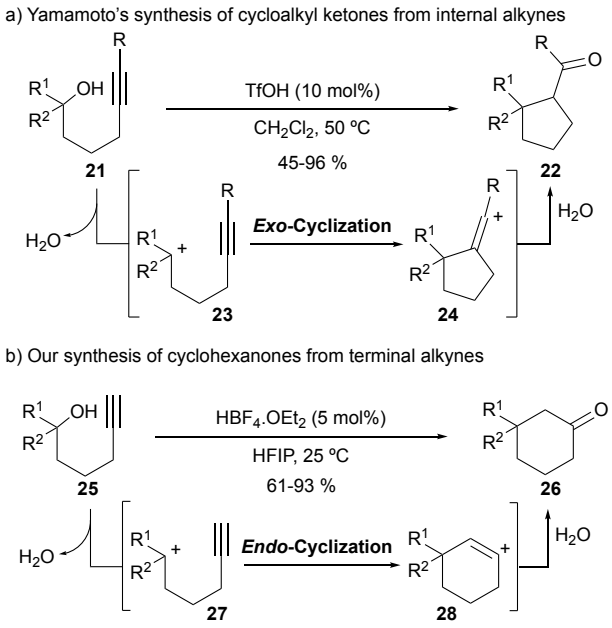
W. S. Johnson and co-workers further used the same approach, based on the biomimetic cyclization of polyene systems containing an allyl alcohol as initiating group and an internal alkyne as terminating group, for the synthesis of other steroidal substances.[14] Also, E. E. van Tamelen wisely expanded his investigations on biomimetic reactions with epoxides as initiating groups to the study of systems containing alkynes as terminating groups.[15] This strategy allowed the efficient synthesis of different steroids. For example, progesterone was easily obtained from epoxide **19** (Scheme 6).[16] The ring opening of the epoxide, promoted by a Lewis acid ($SnCl_4$), triggers the cationic cyclization reaction that proceeds in a highly stereoselective way through a well-defined conformation as shown in **20**.



Scheme 6 An early example of alkyne terminated biomimetic cyclizations with epoxides as initiating groups. Van Temelen's synthesis of progesterone.

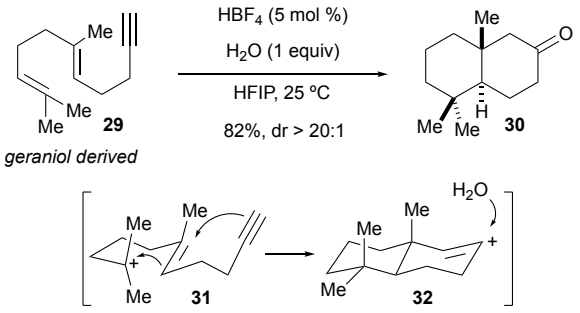
Further studies on cationic cyclizations involving alkynes as precursors of ketones

Independently on the initiating group (sulfonate, alcohol or epoxide), all the early studies on cationic cyclization reactions above disclosed rely on the use of the alkyne terminating group as a synthetic equivalent of a ketone (or its enol ether derivative precursor). Formation of this ketone functionality was particularly interesting in the context of biomimetic cyclizations to synthesize polycyclic steroid derivatives. However, extension of these initial works to the development of a general method to get ketone derivatives was not reported until 2009. More precisely, Y. Yamamoto and co-workers showed that simple tertiary alcohols **21** substituted with an appropriate alkyne-containing alkyl chain easily evolve through a cationic cyclization, in the presence of a catalytic amount of triflic acid, to get simple cycloalkyl ketone derivatives **22** (Scheme 7a).[17] The initial cation **23**, generated by a dehydration process, is directly trapped by the internal alkyne through an *exo*-cyclization process to form an alkenyl cation **24** that in the presence of water finally evolves to the cycloalkyl ketone derivative **22**. This work is limited to starting alkynol derivatives containing internal alkynes and, surprisingly, the behaviour of terminal alkynes was not evaluated.[18] We realized that the absence of studies on the reactivity of terminal alkynes was not limited to this particular work but was general in the context of cationic cyclizations. With the aim of filling this gap, we started a project on this issue and rapidly observed that the substitution at the terminal position of the alkyne had a crucial impact on the *exo* / *endo* cyclization mode. Thus, while internal akynes such as **21** led to cycloalkyl ketones **22** through an *endo*-type cyclization mode, terminal alkynes **25** evolved through an *exo* cyclization mode to get cyclohexanone derivatives **26** (Scheme 7b).[19] As shown, formation of one or the other type of ketones depends on which carbon of the carbon-carbon triple bond acts as nucleophilic centre trapping the initial cation **23** or **27**. Thus, internal alkynes tend to react through the proximal carbon while terminal alkynes react through the distal (terminal) carbon of the triple bond to give a six-membered cyclic alkenyl cation intermediate **28**.



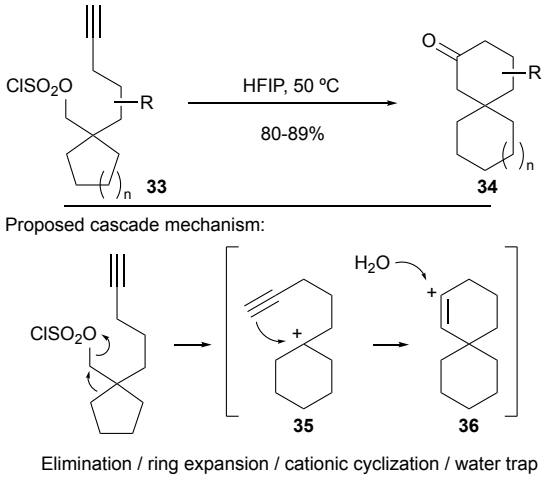
Scheme 7 Synthesis of simple cycloalkyl ketones or cyclohexanones depending on the substitution of the alkyne.

As shown in the previous section, the alkyne moiety was used in biomimetic cyclization of polyene systems as a promoter of the D-ring of steroids. To get this five-membered ring, an internal alkyne is required in order to favour the *endo*-cyclization. As the use of terminal alkynes was not considered in these initial works on biomimetic cyclizations, we extended our studies in this direction. Thus, we showed that terminal alkynes can be used in the context of biomimetic cyclizations of polyene derivatives as promoters of six-membered rings.[19] As shown in the example depicted in Scheme 8, the geraniol-derived dienyne (*E*)-6,10-dimethylundeca-5,9-dien-1-yne (**29**) was efficiently transformed into a *trans*-decalone derivative **30** by treatment with tetrafluoroboric acid in the presence of one equivalent of water and using 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as solvent. In this process, the acid promotes the protonation of the initial alkene to form cation **31**. The subsequent cyclization via antiparallel addition to the alkene through a chair-like folding leads to the endocyclic alkenyl cation **32** that is trapped by a molecule of water to finally render the decalone derivative **30**.



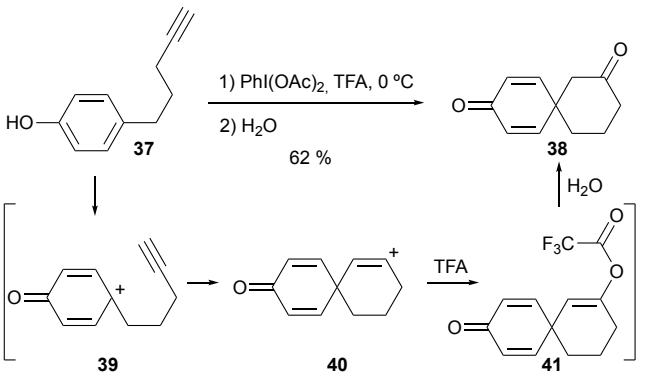
Scheme 8 Biomimetic cyclization reactions with terminal alkynes. Synthesis of a decalone derivative from a geraniol derived dienyne.

As another extension of our work on the use of terminal alkynes in the context of cationic cyclizations, we have recently developed a new method to access spirocyclic compounds **34** from chlorosulfate derivatives **33** containing an alkyne at appropriate position (Scheme 9).[20] In this reaction, the chlorosulfate moiety acts as the initiating group producing the original cationic species **35** through an unusual thermal elimination followed by a ring-expansion reaction. The initial cation thus formed is trapped by the alkyne through the expected *exo*-cyclization reaction typical of terminal alkynes to get an alkenyl cation **36** that is finally trapped by water.



Scheme 9 Synthesis of spirocyclic compounds by a cascade reaction implying a cationic cyclization with a terminal alkyne.

Another interesting method to get spirocyclic compounds by means of a cationic cyclization reaction was developed by S. Canesi and co-workers (Scheme 10).[21] The process involves the treatment of a phenol derivative, containing an alkyne at appropriate position, with (diacetoxyiodo)benzene. Under these conditions, the aromatic ring participates in a cyclization reaction to get a spirocyclic product. For example, the diketone derivative spiro[5.5]undeca-7,10-diene-2,9-dione **38** was easily obtained from 4-(pent-4-yn-1-yl)phenol (**37**; Scheme 10).

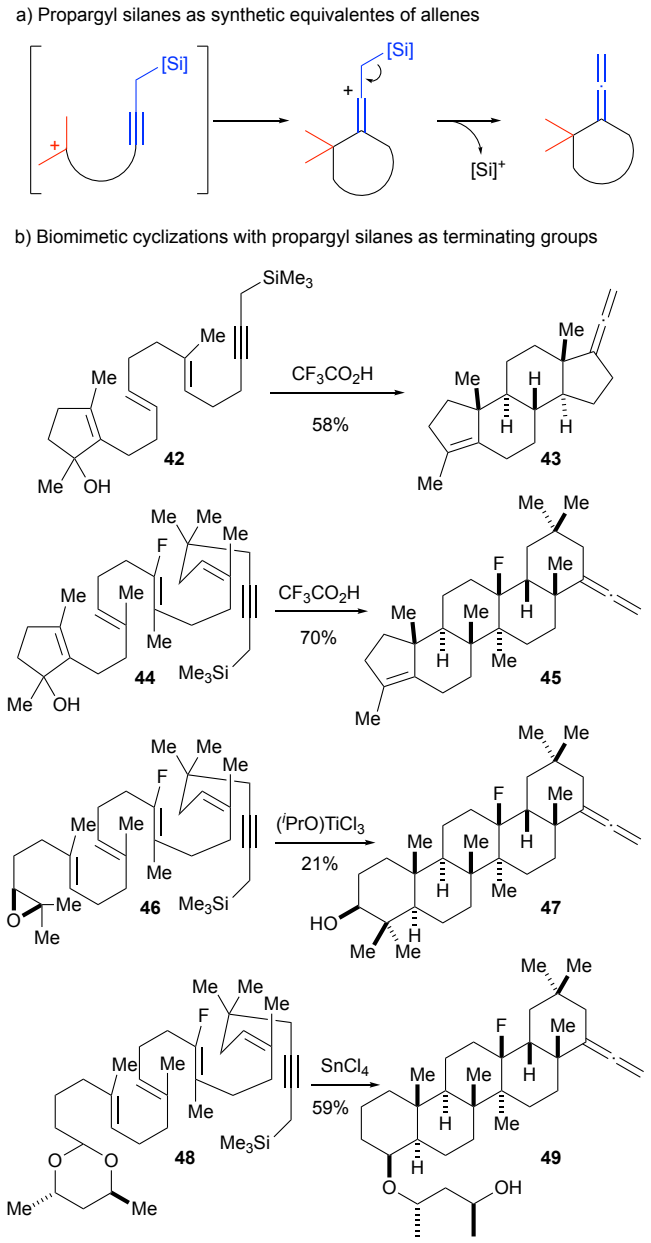


Scheme 10 Canesi's strategy to construct spirocyclicles through a cationic cyclization promoted by an oxidative activation of a phenol derivative.

Probably, the most remarkable aspect of this strategy regards the atypical initiating group and the way the starting cation is generated. Thus, the transformation involves the oxidative activation of the phenol to generate the highly electrophilic species **39** that is intramolecularly intercepted by the alkyne to form the alkenyl cation intermediate **40**. This new cation is captured by the solvent (trifluoroacetic acid) to render the enol ester **41** that is hydrolysed to get the final spirocyclic ketone derivative **38**.

Cationic cyclizations involving alkynes as precursors of allenes

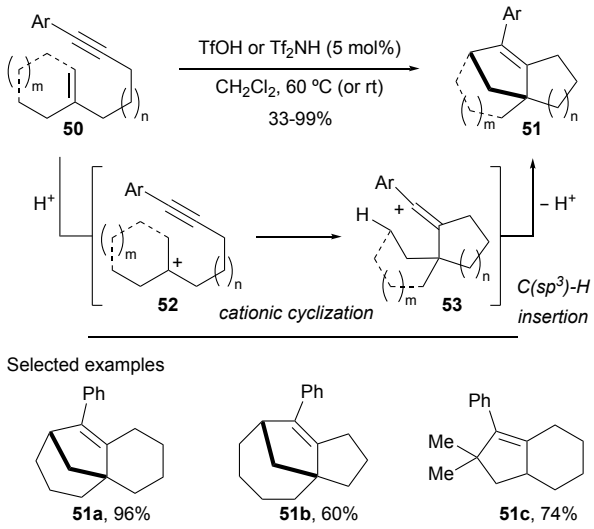
Propargyl silanes can be considered a particular type of alkynes. They are good nucleophiles that react by γ-addition to electrophiles generating an allene after elimination of the silane (Scheme 11a). Propargyl silanes were used as the alkyne terminating group by W. S. Johnson and co-workers in their studies on the application of biomimetic cationic cyclization reactions for the synthesis of complex polycyclic compounds (Scheme 11b).[22] As shown, the use of propargyl silanes as terminating groups allows the synthesis of polycyclic compounds with a terminal five- (**43**) or six-membered ring (**45**, **47**, **49**). It is also interesting to note that different initiating groups, including allyl alcohols (**42**, **44**), epoxides (**46**) and acetals (**48**), were used in this context. Particularly remarkable are those reactions with epoxides and acetals as initiating groups because they imply highly stereoselective one-pot pentacyclization processes. These examples well illustrate the power of biomimetic cationic cyclization reactions in the area of organic synthesis to construct structurally complex molecules from relatively simple starting materials.



Scheme 11 Propargyl silanes as terminating groups in biomimetic cationic cyclizations.

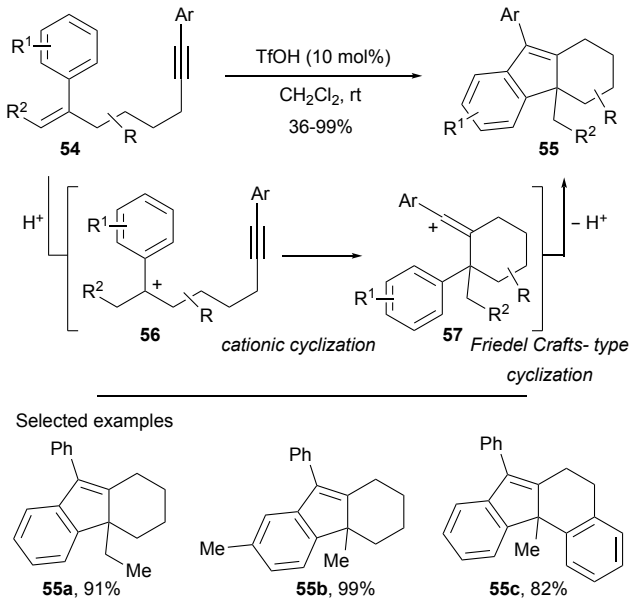
Cationic cyclizations involving the capture of the alkenyl cation intermediate by formation of a C-C bond

In the previous sections, it has been shown how the cationic cyclization reactions involving alkynes as terminating groups proceed through the formation of an alkenyl cation intermediate. When a propargyl silane is used as the alkyne counterpart, this cation evolves by an elimination of the silane moiety to give an allene. Alternatively, when a simple alkyne is used, the alkenyl cation intermediate may be neutralized by reaction with a nucleophile. When an oxygen-centred nucleophile is present in the reaction media, an enol ether derivative is initially formed and, usually, a ketone is finally isolated. However, it has been shown that this alkenyl cation intermediate may participate in reactions implying the formation of a new carbon-carbon bond. A remarkable example was reported by Y. Yamamoto and co-workers in 2010 (Scheme 12).[23] In this process an enyne derivative **50** is treated with a catalytic amount of triflic acid (TfOH) or triflimide (Tf_2NH) to give a product **51** coming from a cationic cyclization reaction where the alkenyl cation intermediate **53**, formed from **52**, evolves by a carbon-hydrogen (C-H) insertion into an unactivated sp^3 C-H bond.[24]



Scheme 12 Cationic cyclization implying a final intramolecular C-C bond formation through a $C(sp^3)$-H insertion process.

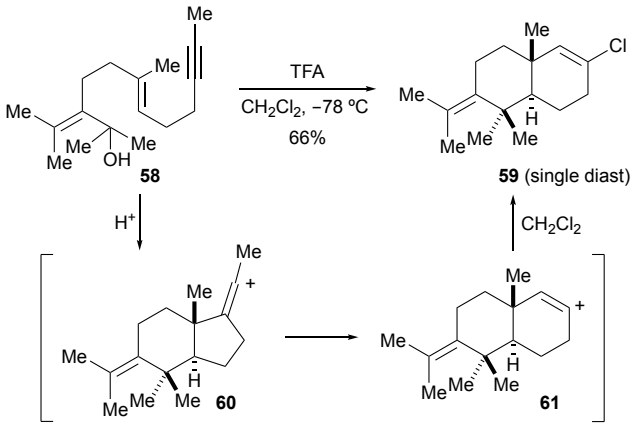
Interestingly, this reaction was later extended to a process involving a final carbon-carbon bond formation through a sp^2 C-H insertion reaction.[25] More precisely, 1,7-enynes **54** containing an arene at appropriate position react in the presence of a catalytic amount of triflic acid (TfOH) to form various fused poly carbocycles **55** under mild conditions in high yields (Scheme 13). In this process, the alkenyl cation **57**, generated by the cationic cyclization reaction of **56**, is trapped through a formal Friedel-Crafts reaction.



Scheme 13 Cationic cyclization implying a final intramolecular C-C bond formation through a Friedel Crafts type reaction.

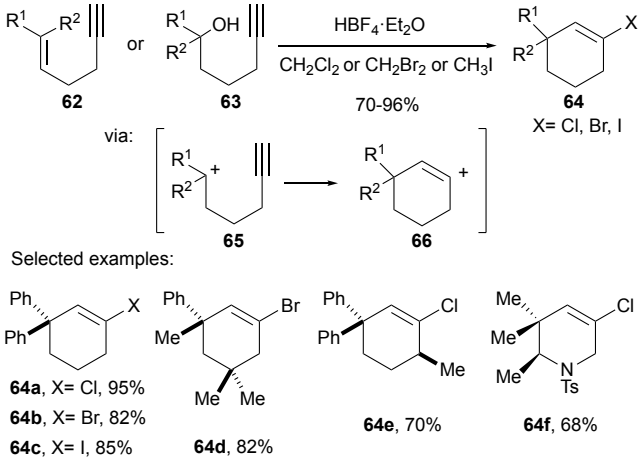
Cationic cyclizations involving alkynes as precursors of alkenyl halides

In 1972, during their studies on the participation of alkynes in cationic biomimetic cyclization reactions, W. S. Johnson and co-workers reported the transformation of the dienynol derivative **58** into the decalin **59** containing in its structure an alkenyl chloride moiety (Scheme 14).[26] Formation of this product was explained by the initial formation of the 6/5 fused bicycle **60**. The cationic cyclization reaction leading to this product implies the participation of the alkyne through a 5-exo cyclization process to form an exocyclic alkenyl cation. This cation suffers a Wagner-Meerwein shift to deliver the new 6/6 fused bicyclic intermediate **61** containing an endocyclic alkenyl cation that is able to abstract a chloride ion from the solvent (dichloromethane) to produce the final product **59**.



Scheme 14 W. S. Johnson's pioneer work on the use of alkynes in cationic cyclizations as precursors of alkenyl halides (year 1972, single example).

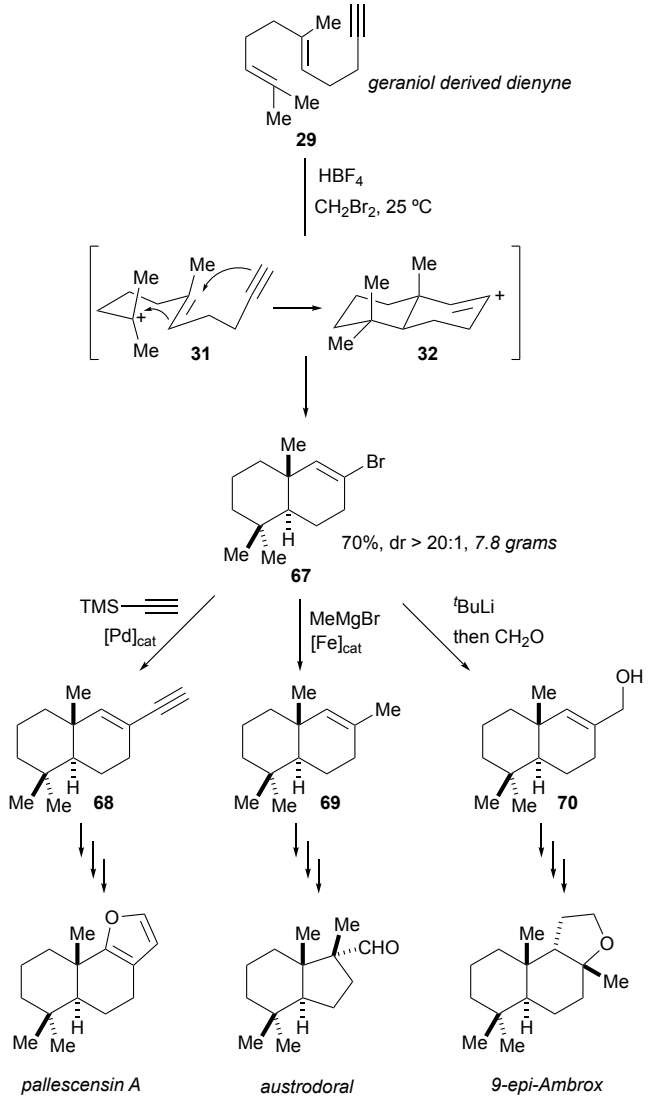
It is important to note that only one example of this remarkable transformation was reported in the article. Despite the wide synthetic opportunities that this transformation seems to offer, this work passed somewhat unnoticed by the synthetic community. However, this single reaction called our attention and we became interested into further investigate it. More precisely, it was believed that a general method to synthesize cyclic alkenyl halides could be developed. In fact, we were able to transform simple enyne (**62**) or alkynol (**63**) derivatives into cyclic alkenyl chlorides, bromides or iodides **64** by treatment with tetrafluoroboric acid in the presence of a halogenated solvent (dichloromethane, dibromomethane or iodomethane respectively; Scheme 15).[27] As expected, the use of terminal alkynes favours the cyclization through the terminal carbon of the triple bond and endocyclic alkenyl halides were exclusively obtained through alkenyl cation **66**. As shown, the initiating group could be an alkene or an alcohol and so, the initial alkyl cation **65** may be formed by protonation of the alkene or dehydration of the alcohol.[28]



Scheme 15 A general method to synthesize cyclic alkenyl halides by a cationic cyclization of enyne or alkynol derivatives.

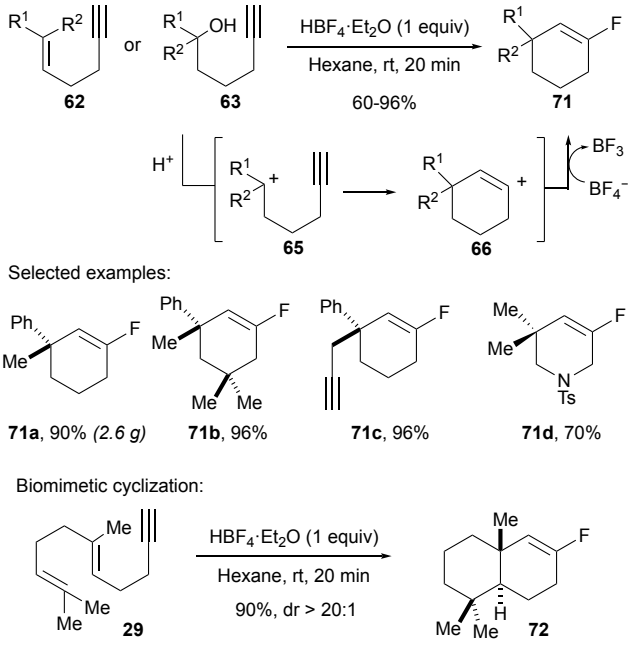
Interestingly, this reaction could be extended to biomimetic cyclization processes. For example, the geraniol-derived dienyne (*E*)-6,10-dimethylundeca-5,9-dien-1-yne **29** was efficiently transformed into the corresponding bicyclic alkenyl bromide derivative **67** by treatment with tetrafluoroboric acid in dibromomethane as solvent and source of the bromide ion (Scheme 16). The *trans*-fused 6/6 bicycle is selectively obtained in high yield through cationic intermediates **31** and **32**. Moreover, this biomimetic transformation could be performed on a multigram scale without problems. The synthetic opportunities offered by the carbon-bromine bond were clearly demonstrated in the transformation of the above mentioned bicyclic alkenyl bromide into some other interesting molecules (Scheme 16). Thus, a Sonogashira-type cross coupling reaction was used to access an alkyne derivative intermediate **68** further converted into the natural product pallescensin A. Alternatively, a Kumada-type coupling of the alkenyl bromide with methylmagnesium bromide led to a decaline derivative **69** that

was used for the synthesis of the terpene austrodoral. Apart from those typical cross-coupling reactions above mentioned, the alkenyl bromide functionality could be used for other interesting transformations. Thus, taking advantage of the easy bromine-lithium interchange, an allyl alcohol derivative **70** was easily synthesized and further transformed into the amber odorant 9-*epi*-Ambrox (Scheme 16).[29]



Scheme 16 Biomimetic cationic cyclization of a geraniol derived dienyne derivative. Applications in the synthesis of terpenes and other interesting molecules.

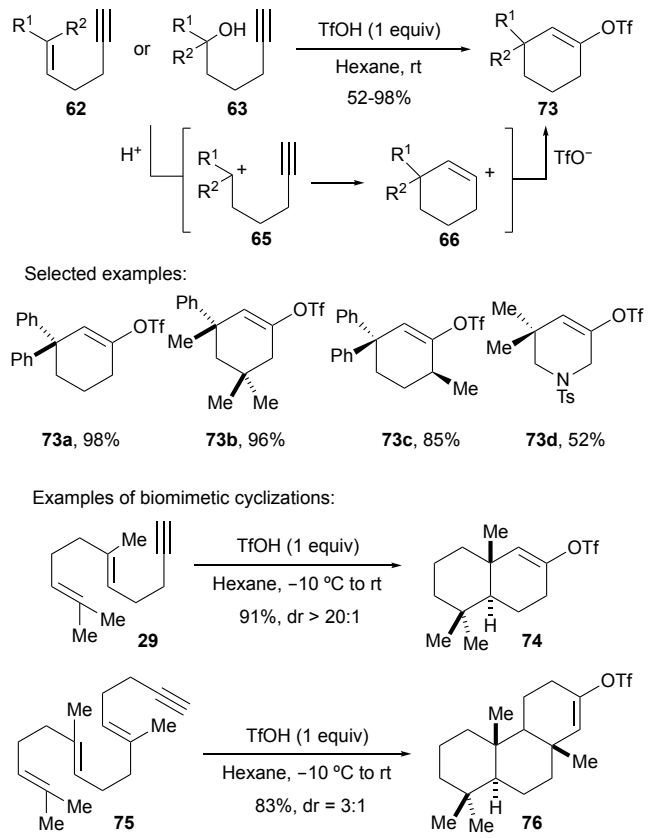
In the above-described method for the synthesis of cycloalkenyl halides **64**, the solvent is the source of the halide (see Scheme 15). This strategy allows the synthesis of the corresponding chlorides, bromides or iodides but it cannot be used for the synthesis of cycloalkenyl fluorides because the strength of the carbon-fluorine bond prevents the transfer of a fluorine atom from a fluorinated solvent to the alkenyl cation intermediate. However, it was found that the tetrafluoroborate anion could act as a source of fluoride when the cationic cyclization reaction was performed with tetrafluoroboric acid in an inert, non-nucleophilic solvent such as hexane. Thus, simple enyne (**62**) or alkynol (**63**) derivatives were easily converted into cyclic alkenyl fluorides **71** by treating them with tetrafluoroboric acid in hexane at room temperature (Scheme 17).[30,31] Interestingly, the time required for the conversion of the starting material into the fluorinated product is usually short (20 min). This fact, along the efficiency of the process, makes this method attractive for the synthesis of 18F-radiotracers for positron emission tomography (PET) imaging. The biomimetic version of the process that allows the transformation of polyenyne derivatives into the corresponding polycyclic alkenyl fluoride derivative was also developed (Scheme 17). For example, the geraniol-derived dienyne (*E*)-6,10-dimethylundeca-5,9-dien-1-yne **29** was efficiently transformed into the corresponding bicyclic alkenyl fluoride derivative **72** by treatment with tetrafluoroboric acid in hexane at room temperature.



Scheme 17 A general method to synthesize cyclic alkenyl fluorides by a cationic cyclization of enyne or alkynol derivatives.

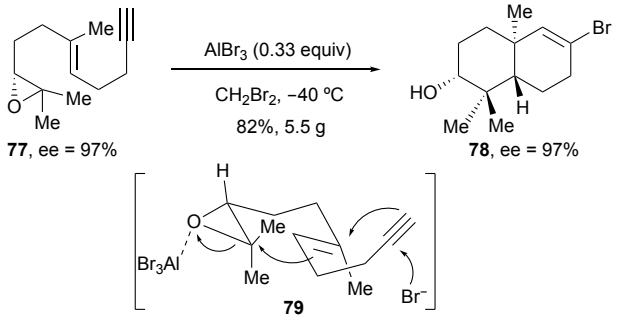
It is important to remark that in the fluorination process above presented, the acid (HBF_4) acts not only as a promoter of the cationic cyclization (proton source) by favouring the formation of the initial cation **65** but also as source of the final anion (fluoride) that traps the alkenyl cation **66**. In this context, it was believed that the use of acids with a different anion counterpart could serve for the synthesis of other interesting compounds. More precisely, cyclic alkenyl triflates **73** were easily synthesized from simple enyne (**62**) or alkynol (**63**) derivatives by treatment with one equivalent of triflic acid (TfOH) in hexane as solvent (Scheme 18).[32] As before, the triflic acid provides both, the proton that facilitates the formation of the initial cation **65**, and also the anion (triflate) that reacts with the alkenyl cation intermediate **66**. It is important to remark that this protocol complements and challenges conventional methodologies of synthesis of alkenyl triflates. In this regard, it

should be noted that the traditional way of accessing alkenyl triflates is the protocol developed by McMurry and Scott that employs ketones as starting materials.[33] This process involves the enolization of the ketone by treatment with a base followed by trapping of the ketoenolate with a triflating agent [usually *N*,*N*-bis(trifluoromethanesulfonyl)aniline]. In many cases, this method suffers from regiochemical and racemization problems that may be avoided by using the cationic cyclization strategy shown in Scheme 18. The concept behind this method of synthesis of alkenyl triflates was extended to biomimetic cationic cyclization reactions of polyenyne derivatives (e.g. **29** or **75**) to yield interesting triflate-containing polycyclic compounds (e.g. **74** or **76**; Scheme 18). The rich reactivity of the C-OTf bond in the context of cross coupling reactions offers wide synthetic opportunities in the field of total synthesis of natural products.



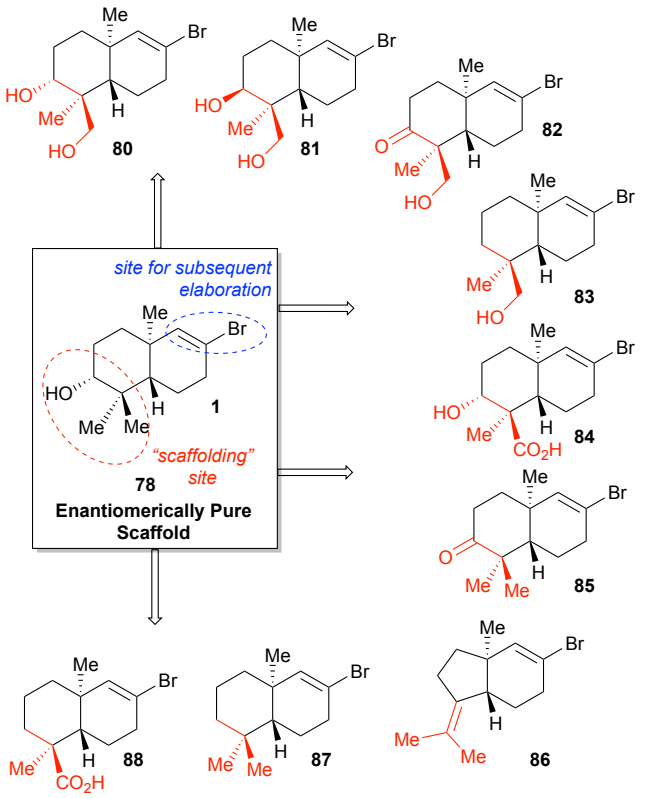
Scheme 18 A general method to synthesize cyclic alkenyl triflates by a cationic cyclization of enyne or alkynol derivatives.

As noted along this section, the biomimetic cationic cyclization reaction of polyenyne derivatives to get polycyclic alkenyl halide (or pseudohalide) derivatives is a powerful synthetic tool. In all the examples shown before in this context, the cyclization reaction is triggered by protonation of an initial alkene. Our group became interested in the extension of these reactions to biomimetic processes initiated by the ring opening of an epoxide. The possibility of accessing the epoxide in an enantiomerically pure form by conventional asymmetric epoxidation reactions is one of the main advantages that this initiating group offers. Thus, considering that the biomimetic cyclization process occurs in a stereoselective way, the final products may also be obtained in enantiopure form. More precisely, we developed the cationic cyclization reaction of the alkyne-containing geraniol-derived epoxide **77**, promoted by aluminium bromide and performed in dibromomethane as solvent, to obtain the decalin derivative **78** (Scheme 19).[34] The stereoselectivity of this cationic cyclization reaction can be explained by a model like that shown in **79**.



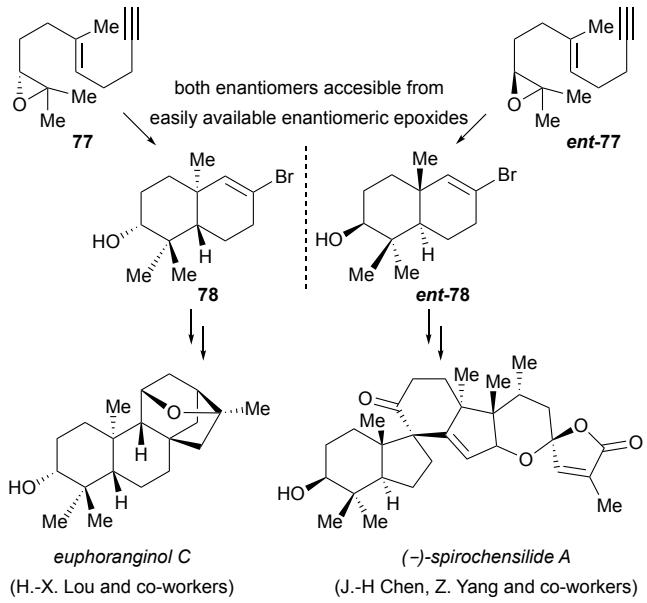
Scheme 19 Cationic cyclization of an alkyne-containing geraniol-derived epoxide to get an enantiomerically pure terpenoid decalin subunit.

Interestingly, the structure of the decalin derivative **78** comprises all the features of an enantiomeric scaffold. In fact, its structure overlaps many common motifs in target molecules, both enantiomers are easily available in a scalable way in a minimum number of synthetic steps, and it contains additional functionalities for subsequent elaborations. The enantiomerically pure decalin derivative **78** thus synthesized contains an alcohol in one of the rings and an alkenyl bromide in the other one. Interestingly, these two functionalities can be orthogonally transformed. In fact, the left-side cycle containing the alcohol was easily transformed, through conventional reactions, into a series of new molecules **80**-**88** with structural motifs widespread found in terpenoids (Scheme 20).[34]



Scheme 20 Structurally diverse decalin derivatives constructed from a common enantiomerically pure scaffold.

In the other hand, the synthetic versatility of the alkenyl bromide functionality offers the opportunity of further elaboration of the decalin core. In this context, H-X. Lou and co-workers have recently reported the total synthesis of euphoranginol C and other related natural products through a synthetic sequence that implies the modification of the alkenyl bromide contained in the right-side cycle of the decalin derivative (Scheme 21).[35] Further demonstration of the utility of this decalin derivative is found in the total synthesis of (–)-spirochensilide A described by J.-H. Chen, Z. Yang and co-workers (Scheme 21).[36] The possibility of easily synthesize both enantiomers of the starting epoxide (**77** and ***ent*-77**) is relevant because it allows the construction of both enantiomers of the final decalin derivative (**78** and ***ent*-78**). This is an important issue because many terpenoid natural products have similar structural motifs, but they differ on the absolute configuration of their sterocentres. This is clearly demonstrated in the total synthesis of euphoranginol C and of (–)-spirochensilide shown in Scheme 21 that require different enantiomers of the initial epoxide.



Scheme 21 Applications of the cationic cyclization of an alkyne-containing geraniol-derived epoxide in total synthesis of natural products.

Conclusions and outlook

The use of alkynes as terminating groups in cationic cyclization reactions offers wide synthetic possibilities due to the flexibility of this group to act as precursor of different functionalities. Cationic cyclization reactions with alkynes as terminating groups, firstly reported in the 1960s, rapidly found synthetic application in the context of biomimetic synthesis of natural products. However, the use of the alkyne as precursor of a ketone functionality remained as the main application of this type of reactions till recently. The interest on these type of cationic cyclization reactions suffered a renascent in the last years when it was found that the alkyne could be used as precursor of other synthetically useful functionalities such as alkenyl halides and pseudohalides. The innate power of these reactions in assembling useful and complex frameworks in a single chemical operation has been outlined.

Future research directions in this field includes the development of cationic cyclizations with different initiating groups. This could be particularly interesting in the context of biomimetic cyclizations where we have already shown that alkenes and epoxides are appropriate initiating groups to get useful molecules. However, the development of biomimetic polycylization processes with alkynes as terminating groups with other initiating groups seems very attractive and is a field where we are devoting our efforts. In the context of cyclization reactions with alkenes as initiating groups, it would be interesting to develop processes promoted by reagents different from protons. In this context, we are particularly interested in halonium-promoted cationic cyclization reactions to get halogen-containing products that may find wide applications in different areas. Also, the development of catalytic asymmetric biomimetic cyclizations from prochiral alkyne-containing starting materials is an appealing goal that is

strongly pursued in our group. Finally, application of the concept in the total synthesis of natural products or other useful compounds is being considered and results from our group and others are expected to appear in the near future.

Conflicts of interest

There are no conflicts to declare.

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Olaya García-Pedrero was born in Oviedo (Asturias, Spain) in 1996. She graduated in Chemistry at the University of Oviedo in 2018. Then, she moved to the University Jaume I for her Master studies and in 2019 she came back to the University of Oviedo where she is performing her PhD studies under the supervision of Professor Félix Rodríguez. She works on the development of new cationic cyclization reactions and their application to the synthesis of natural products.