Synthesis G. Evano et al. Review

Keteniminium Ions: Unique and Versatile Reactive Intermediates for Chemical Synthesis

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Dedicated to Prof. Herbert Mayr, a truly inspiring chemist, on the occasion of his 70th birthday

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Abstract Keteniminium ions have been demonstrated to be remarkably useful and versatile reactive intermediates in chemical synthesis. These unique heterocumulenes are pivotal electrophilic species involved in a number of efficient and selective transformations. More recently, even more reactive 'activated' keteniminium ions bearing an additional electron-withdrawing group on the nitrogen atom have been extensively investigated. The chemistry of these unique reactive intermediates, including representative methods for their in situ generation, will be overviewed in this review article.

Key words keteniminium ions, ketenimines, ynamines, ynamides, amides, reactive intermediates

1 Introduction

Most reactions in organic chemistry do not proceed through a single step but rather involve several elementary steps, in the course of which reactive intermediates are generated, to yield the desired products. These reactive intermediates are short-lived, high-energy, and highly reactive molecules. They are at the core of organic synthesis by enabling the conversion of reactants into the reaction product(s), the evolution of reactive intermediates into more stable molecules being one of the driving force of most transformations in chemical synthesis. Moreover, these reactive intermediates, whose evidence and structures can be proved by a set of experimental and theoretical methods, are especially useful to understand the underlying reaction mechanisms and selectivities of organic reactions and for the *de novo* design of innovative chemical transformations.[1]

Apart from neutral and metal-containing intermediates, these reaction intermediates can be roughly classified into four main categories: cationic, anionic, or radical species and carbenes. Among these intermediates, cationic species are of prime importance, the tremendous developments of chemical synthesis due to the chemistry of carbocations, which culminated in Olah's Nobel Prize in Chemistry in 1994, being the most representative and iconic examples. Besides 'pure' carbocations, cationic intermediates also include oxonium and iminium ions as well as their heterocumulene congeners, ketenium and keteniminium ions. While ketenium ions are still scarcely used in chemical synthesis, mostly due to difficulties associated with their generation, the chemistry of keteniminium ions **1** (Figure 1) has a rich history; these unique electrophilic heterocumulenes are pivotal reactive intermediates in a number of synthetic transformations. The chemistry of these intermediates, which has been extremely revisited lately with the discovery of new methods for their in situ generation and with the exploration of the reactivity of activated keteniminium ions **2** bearing an additional electron-withdrawing group on the nitrogen atom, will be overviewed in this review article. All reactions reviewed will be classified primarily based on the nature (activated or not) of the keteniminium ion and according to the reaction in which these reactive intermediates are involved (addition of a nucleophile, cycloaddition, etc.). Each section will start with an overview of the methods available for the in situ generation of keteniminium ions and the application of the chemistry of these reactive intermediates for the synthesis of natural and/or biologically relevant products will be overviewed at the end of this review article.

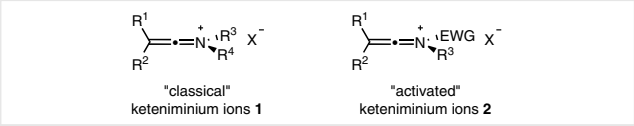


Figure 1 'Classical' and 'activated' keteniminium ions

As an important note, this review does not intend to be exhaustive, it will rather focus on the synthetically most relevant transformations, and the reader should refer to excellent review articles previously published on the chemistry of keteniminium ions.[2] Finally, it should to be mentioned that keteniminium ions in which R^3 and/or R^4 are a hydrogen atom do not fall within the scope of this manuscript since they are more properly described as protonated

Biographical Sketches

Gwilherm Evano was born in Paris in 1977 and studied chemistry at the Ecole Normale Supérieure. He received his Ph.D. from the Université Pierre et Marie Curie in 2002 under the supervision of Profs. François Couty and Claude Agami. After postdoctoral studies with Prof. James S. Panek at Boston University, he joined the CNRS as associate professor in 2004. He then moved to the Université libre de Bruxelles, where he is the head of the Laboratory of Organic Chemistry, in 2012. His research program currently focuses on natural/bioactive product synthesis, copper catalysis, the chemistry of hetero-substituted alkynes, and reactive intermediates.

Morgan Lecomte was born in Arlon, in the countryside of Belgium, in 1988 and studied chemistry at the Université libre de Bruxelles. In 2012, he joined the Laboratory of Organic Chemistry as a master student working under the supervision of Profs. Ivan Jabin and Gwilherm Evano on the use of hetero-substituted alkynes for the selective functionalization of calixarenes. He obtained a F.R.I.A. Ph.D. fellowship in 2013 to work in the group of Prof. Gwilherm Evano and his research focuses on the study of the reactivity of ynamides and activated keteniminium ions, and on the development of new reactions and processes from these building blocks.

Pierre Thilmany was born in Uccle (Belgium) in 1995 and studied chemistry at the Université libre de Bruxelles. He started his master thesis in 2017 in the Laboratory of Organic Chemistry under the supervision of Prof. Gwilherm Evano where his work focuses on the development of new reactions based on the reactivity of ynamide-derived keteniminium ions.

Cédric Theunissen was born in Brussels in 1989 and studied chemistry at the Université libre de Bruxelles. In 2012, he obtained his master thesis, under the supervision of Prof. Cécile Moucheron, which focused on the synthesis of new ruthenium complexes designed to interact with DNA in an anticancer approach. He then obtained a F.R.I.A. fellowship and joined the group of Prof. Gwilherm Evano as a Ph.D. student where his work focused on the development of new copper-mediated transformations and on the study of the reactivity of ynamides and keteniminium ions. After graduating in October 2016, he moved to Columbia University as a BAEF postdoctoral fellow in the group of Prof. Tomislav Rovis.

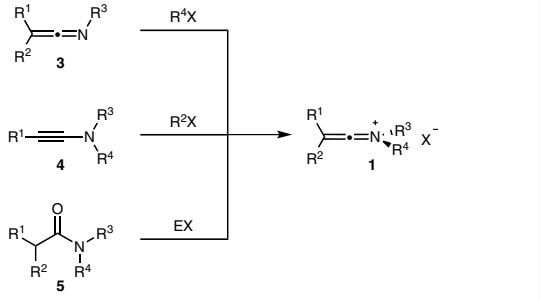
ketenimines than keteniminium ions. For clarity and simplicity, keteniminium and activated keteniminium ions are given the number **1** and **2**, respectively, regardless on the nature of their substituents and counteranions unless these substituents play a crucial role in further transformations.

2 The Chemistry of Keteniminium Ions

The chemistry of keteniminium ions was mainly initiated by the pioneering work of Viehe who reported efficient methods for their in situ generation and extensively studied their reactivity. The main methods that can be used for the formation of keteniminium ions, reactive intermediates that are rarely isolated and/or characterized due to their low stability,[3] will be briefly overviewed before focusing on reactions involving such species.

2.1 Main Methods for the Generation of Keteniminium Ions

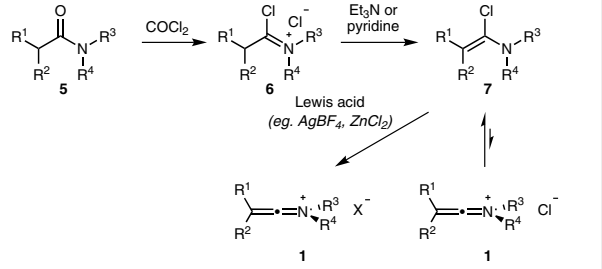
Keteniminium ions **1** can be mostly generated by three different routes relying on the direct alkylation of the corresponding ketenimines **3**,[3b,4] on the reaction of ynamines **4** with an electrophile,[2a,c,5] or on the electrophilic activation of an amide **5** followed by elimination (Scheme 1).



Scheme 1 Main routes for the generation of keteniminium ions

The first two routes rely on the use of starting materials **3** and **4** that are less attractive than amides **5** and are clearly less general than the third route which is definitely the most synthetically useful entry to keteniminium ions. The nature of the starting amide and the reagent(s) and/or additives used for this transformation have, however, been shown to have a dramatic impact on the outcome of the reaction.

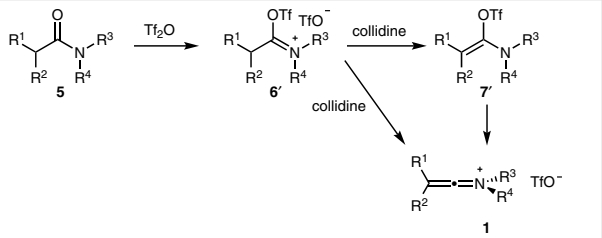
Several conditions and reagents have been indeed reported for the generation of keteniminium ions from amides, one of the first ones being Viehe's procedure relying on the use of phosgene in the presence of triethylamine or pyridine (Scheme 2).[6] Electrophilic activation of the starting amide **5** with phosgene produces an intermediate chloroiminium ion **6** which, upon addition of the base, yields chloro-enamine **7**, a compound that is in equilibrium with the corresponding keteniminium ion **1**. As an important note, chloro-enamines **7** can also be prepared by deprotonation of the starting amide **5** with LDA followed by reaction with diphenyl phosphoryl chloride, which avoids the isolation of the rather sensitive chloro-enamines.[7]



Scheme 2 Viehe's generation of keteniminium ions from enolizable amides with phosgene and a base

While this equilibrium is typically in favor of the chloro-enamine **7**, the use of Lewis acids such as silver tetrafluoroborate, zinc chloride, or titanium chloride favors the formation of the keteniminium ion **1**.[8] Besides the use of phosgene, which is not an ideal reagent, the main limitation of this route actually lies in its scope; while 'keto' keteniminium ions (R^1 and $R^2 \neq H$) are smoothly generated from the corresponding α-chloro-enamines, 'aldo' keteniminium ions (R^1 and/or $R^2 = H$) rapidly react with these precursors.[9]

Based on this limitation and capitalizing on the fact that this side reaction should not occur with non-nucleophilic precursors of the keteniminium salt, Ghosez reported in 1981 what would become the synthetically most useful method for the generation of keteniminium ions from the corresponding amides (Scheme 3).[9] Electrophilic activation of the starting amide **5** with triflic anhydride provides a transient *O*-triflyliminium triflate **6′**, which, upon reaction with collidine, gives the corresponding α-trifloyl-enamine **7′** that then undergoes elimination to the desired keteniminium triflate **1**, which could also result from direct elimination from **6**.

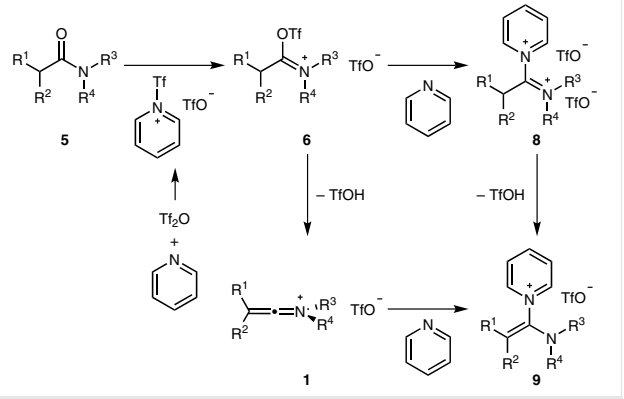


Scheme 3 Ghosez's generation of keteniminium ions from enolizable amides with triflic anhydride and collidine

While Ghosez's procedure is the one that is typically used nowadays for the generation of keteniminium ions from the corresponding enolizable amides, the nature of the pyridine used as the base was often shown to have a

dramatic impact on the outcome of the reaction. Based on extensive NMR studies, Charette has indeed proposed the mechanistic pathway depicted in Scheme 4 for the electrophilic activation of enolizable amides using pyridine as the base.[10] The triflating agent would be *N*-triflylpyridinium triflate, which would be formed by initial reaction of triflic anhydride with pyridine. Reaction of the starting amide **5** with this reagent would form an intermediate *O*-triflyliminium triflate **6** that could directly form the keteniminium triflate **1**. Pyridine is sufficiently nucleophilic to add to this reactive intermediate **1**, which would result in the formation of *N*-(aminoalkenyl)pyridinium triflate **9**, the main species that could be detected in the reaction mixture. Alternatively, the addition might proceed before the elimination through bis(cationic) intermediate **8**. A close examination of all reaction intermediates, which are all potentially in equilibrium, reveals the importance of the nature of the pyridine base used for the generation of keteniminium triflates from the corresponding enolizable amides via Ghosez's procedure. Indeed, the use of hindered and/or poorly nucleophilic pyridine derivatives such as collidine or 2-halopyridines avoids trapping the keteniminium ion and increases its proportion in the reaction mixture, a phenomenon that has been elegantly exploited in several reactions based on the generation of keteniminium triflates.[11,12]

As a direct consequence, which is of importance in the context of this review article, keteniminium ions, although potentially generated upon activation of amides, are not systematically drawn as reactive intermediates in reactions involving the electrophilic activation of enolizable amides.



Scheme 4 Possible intermediates generated upon reaction of enolizable amides with triflic anhydride and pyridine

After reviewing the most common methods for the generation of keteniminium ions, we will now focus on their chemistry and on reactions designed on the basis of their unique reactivity.

2.2 Reactions of Keteniminium Ions with Nucleophiles

The most trivial chemical transformation involving keteniminium ions is their reaction with a nucleophile. Depending on the nature of the nucleophile, the reaction can either stop at the addition step, yielding the corresponding substituted enamine, or initiate further transformations based on the reactivity of this newly installed enamine moiety. These processes will be overviewed in the following sections, starting with simple reactions of keteniminium ions with nucleophiles without further transformations.

2.2.1 Trapping Keteniminium Ions with Nucleophiles

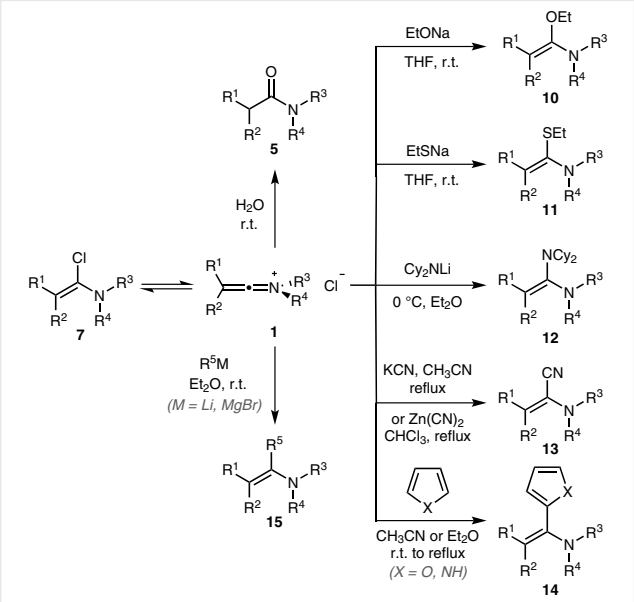
A broad range of nucleophiles have been used to trap keteniminium ions: most representative examples are shown in Scheme 5. As demonstrated in early studies by the Viehe[6] and Ghosez[13] groups, these include water, which yields the corresponding amide **5**, alkoxides, sulfides, lithium amides, and cyanides, the addition of all these nucleophiles to the keteniminium ion providing the corresponding substituted enamides **10**–**13** in excellent yields. Ethers can also be used to trap keteniminium ions, a strategy that has been used for the depolymerization of cellulose.[14]

Interestingly, keteniminium ions can also be used as electrophiles in Friedel–Crafts reactions with electron-rich arenes without the need for an acid catalyst.[13] Indeed, upon reaction with furan or pyrrole, a clean electrophilic aromatic substitution occurs to afford the corresponding C2-aminoalkenylated arenes **14**, a reaction that can also be performed with other electron-rich arenes such as *N*,*N*-dialkylanilines.

Finally, organolithium and Grignard reagents were also found to be suitable nucleophiles, providing an efficient entry to polysubstituted enamines **15** that can be obtained in fair to good yields.[6]

As an important note, the stereoselectivity of these reactions has not been addressed in most cases since they were mostly performed on symmetrical keteniminium ions ($R^1 = R^2$).

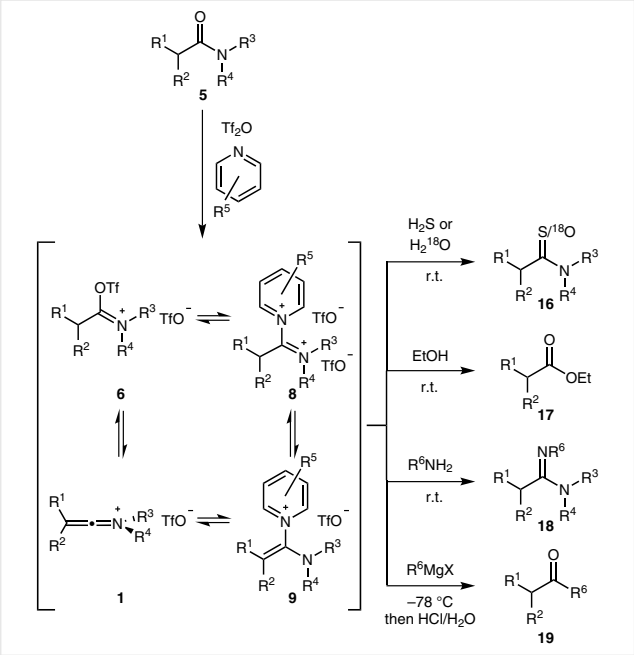
Since the 1990s, the groups of Charette and Huang have extensively revisited and modernized this chemistry based on Ghosez's method for the electrophilic activation of amides. While the reactions they developed, which usually work equally well with enolizable and non-enolizable amides, are typically described to proceed through *O*-triflyliminium triflates, the intermediacy of keteniminium ions cannot be ruled out starting from enolizable amides and these reactions will therefore be briefly overviewed.[15] Charette and Huang indeed reported a set of efficient methods enabling the direct transformation of amides to other synthetically useful building blocks such as thioamides or



Scheme 5 Trapping keteniminium chlorides with nucleophiles

^{18}O-labelled amides **16**,[16] esters **17**,[17] amidines **18**,[18] or ketones **19**[19] (Scheme 6). With nucleophiles such as hydrogen sulfide, $H_2{}^{18}O$, ethanol, or primary amines, activation of the starting amide **5** followed by trapping with the nucleophile and prototropy indeed provides an especially efficient entry to these building blocks with high levels of chemoselectivity and under especially mild reaction conditions. The addition of Grignard reagents, which provides after hydrolysis the corresponding ketones **19**, is probably the most remarkable example and represent an especially useful alternative to the use of Weinreb amides typically required for such a transformation. When switching to polyfunctional nucleophiles such as 1,2-aminothiols or triols, further condensation of the remaining nucleophilic moieties enables the direct synthesis of thiazolines[20] and bridged orthoesters,[21] respectively, from amides. Alternatively, the nucleophile can be embedded in the starting amide, as demonstrated by the Maulide group who reported in 2013 an efficient room-temperature lactonization of hydroxy- and *tert*-butyldimethylsiloxy-substituted amides.[22] It is noteworthy that this reaction might not, however, proceed through a keteniminium intermediate due to the absence of a base for the electrophilic activation of the starting amide.

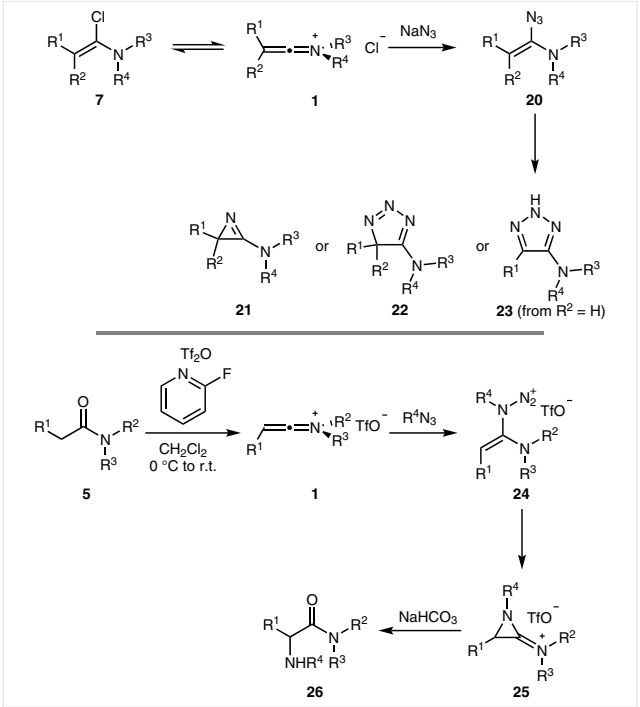
Other nucleophiles can be used to trap a transient keteniminium ion and initiate further chemical transformations. This strategy has proven over the years to be especially versatile and selected representative examples will be overviewed in Section 2.2.2.



Scheme 6 Trapping keteniminium triflates with nucleophiles

2.2.2 Trapping Keteniminium Ions with Nucleophiles and Subsequent Rearrangement

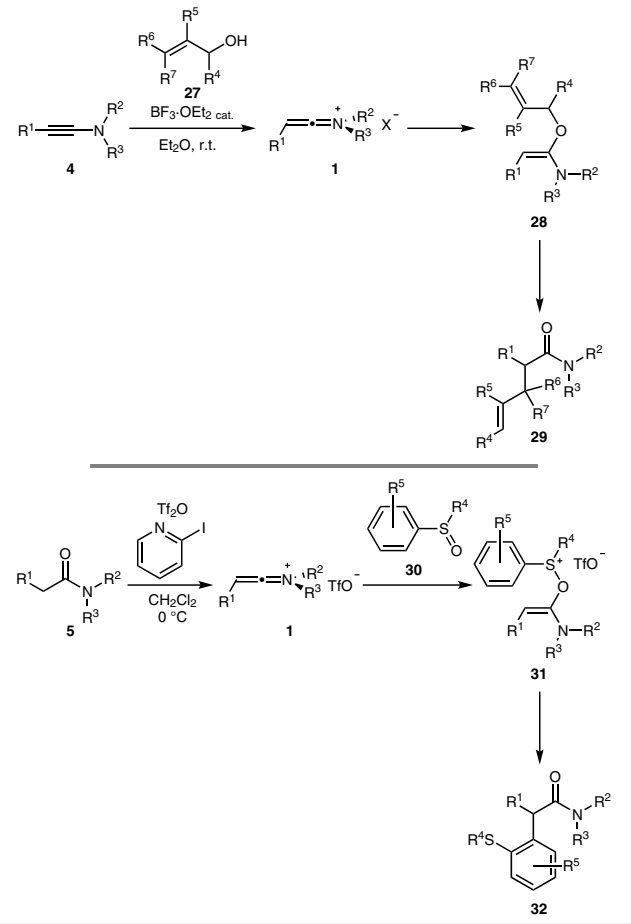
Some enamides formed after trapping a keteniminium ion with a nucleophile can indeed further react without the need for additional reactants, which provides excellent opportunities for the development of efficient and innovative processes. One of the simplest examples was reported in



Scheme 7 Trapping keteniminium ions with azides

1970 by Ghosez;[23] trapping keteniminium ions **1** generated from the corresponding α-chloro-enamines **7** with sodium azide yields intermediate vinyl azides **20**, which then rearrange to the corresponding 3-amino-2*H*-azirines **21**,[24] 5-amino-4*H*-1,2,3-triazoles **22**,[25] or 4-amino-2*H*-1,2,3-triazoles **23**[26] depending on the substitution pattern of the starting α-chloro-enamines (Scheme 7).

This reaction was revisited and extended to the direct amination of amides by the Maulide group some 46 years later.[27] In this case, the keteniminium ion was generated in situ by electrophilic activation of the corresponding amide **5** by triflic anhydride in the presence of 2-fluoropyridine and then trapped by an alkyl azide. Subsequent rearrangement of **24** with concomitant loss of dinitrogen would then afford an intermediate cyclic amidinium ion **25** whose facile hydrolytic ring opening would afford the aminated amide **26**. Remarkably, good levels of stereoinduction can be obtained starting from chiral amides, further increasing the synthetic potential of this procedure which compares well with others available for the direct amination of amides.



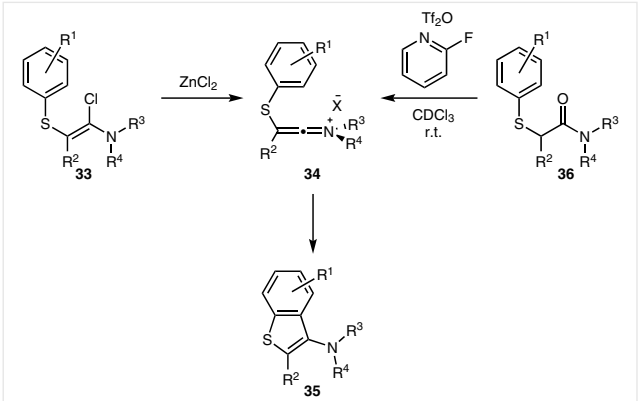
Scheme 8 Trapping keteniminium ions with allyl alcohols or aryl sulfoxides

Another interesting strategy relies on trapping a keteniminium ion with a nucleophile possessing an alkene or an arene at the β-position, which can be used to trigger a sigmatropic [3,3]-rearrangement, the most famous example being the Ficini–Claisen rearrangement initiated by condensation of an ynamine **4** with an allyl alcohol **27** in the presence of a Lewis acid which provides an efficient entry to α-allylamides **29** (Scheme 8).[28] This rearrangement proceeds equally well with propargyl alcohols, which provide β-allenylamides,[29] and was recently nicely extended by the Maulide group to the use of aryl sulfoxides **30**.[30] In this case, keteniminium ion **1** is generated by treatment of the corresponding amide **5** with triflic anhydride and 2-iodopyridine; trapping this reactive intermediate with an aryl sulfoxide **30** yields intermediate **31** which spontaneously rearranges upon warming the reaction mixture to room temperature to afford α-arylated amide **32**.

By using properly designed precursors of keteniminium ions embedded with an internal nucleophile, the intramolecular trapping can be used to trigger remarkably efficient processes enabling the conversion of readily available starting materials to useful cyclic building blocks. This strategy will be described in Section 2.2.3.

2.2.3 Intramolecular Trapping of Keteniminium Ions

One of the first examples of such a strategy was described by Ghosez in 1981 who reported an efficient entry to 3-aminobenzothiophenes **35** by an intramolecular Friedel–Crafts-type reaction from (arylthio)keteniminium ions **34** generated from the corresponding β-(arylthio)-α-chloro-enamines **33** (Scheme 9).[31] This reaction was extended in 2015 to the use of α-(arylthio)amides **36** by De Mesmaeker who in addition showed, by combined experimental/theoretical studies, that the cyclization proceeded through a 6π-electrocyclization,[32] and that replacing the aryl thioether by a styrene also enabled intramolecular trapping of a transient keteniminium ion yielding aminonaphthalene derivatives.[33]

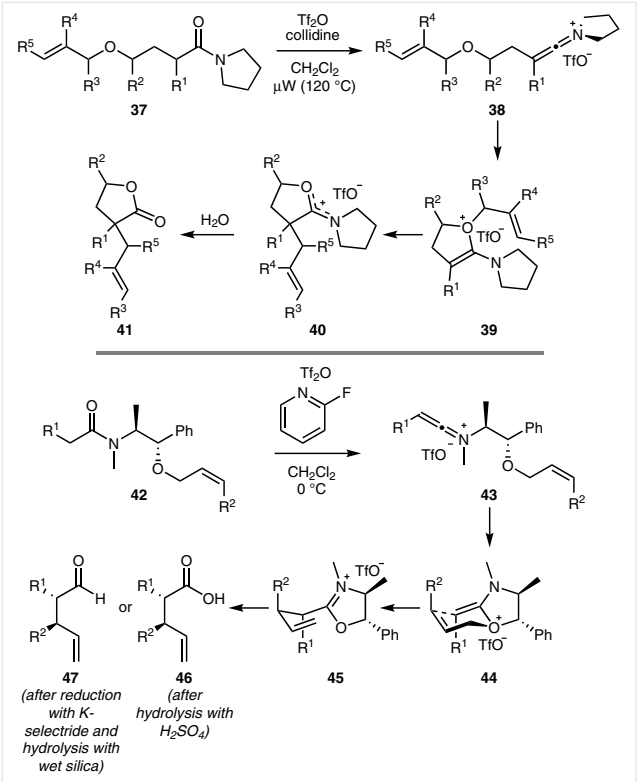


Scheme 9 Intramolecular trapping of keteniminium ions with arenes

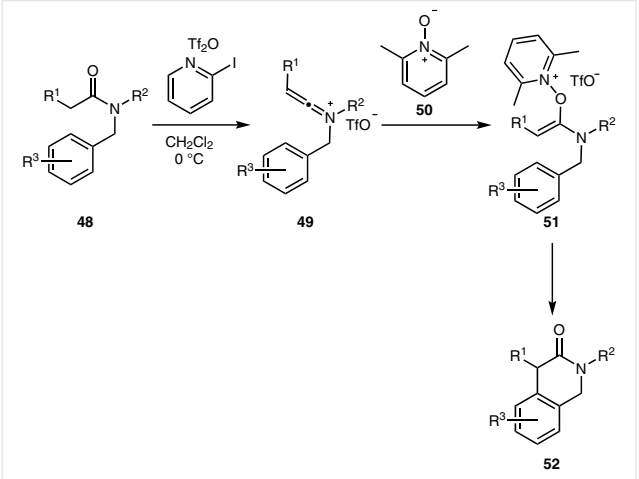
An interesting application of the intramolecular trapping of a keteniminium ion was reported in 2010 by the Maulide group. Attempting to initiate an intramolecular [2+2] cycloaddition between a keteniminium and an allylic ether (see Section 2.3 for this transformation), they noted the formation of a lactone, resulting from the initial trapping of the keteniminium ion by the ether, instead of the expected cyclobutanone cycloadduct.[34] This reaction was extensively studied and its generality unambiguously demonstrated. Mechanistic studies revealed that activation of the amide **37** generates the corresponding keteniminium triflate **38** which is then trapped intramolecularly by the ether moiety to generate an allylvinyloxonium ion **39** (Scheme 10). A Claisen-type sigmatropic [3,3] rearrangement transferring the allyl group from oxygen to carbon, followed by hydrolysis furnishes the final lactone **41**. Interestingly, good levels of stereoinduction were observed starting from *E*- or *Z*-alkenes or from chiral amides. Replacing the allyl ether in the starting amide **37** by a propargylic ether yields the corresponding α-allenyllactones and the intermediate iminium ether **40** can be opened by a nucleophile before hydrolysis.[35] Finally, placing an aromatic ring within the tether and/or switching to allylic amines provides interesting extensions of the electrophilic rearrangement of amides to the preparation of α-prenyl-hydrocoumarins, indoles, isoquinolines, and dihydroisoquinolinones.[36]

By capitalizing on this strategy and moving the allyl ether to the other side of the amide as well as adding a chiral tether between these two moieties, the Maulide group was next able to develop a remarkable traceless electrophilic α-allylation providing enantioenriched α-allylic carboxylic acids **46** or aldehydes **47**. Electrophilic activation of *O*-allylpseudoephedrine-derived amides **42** indeed triggers a highly diastereoselective sigmatropic rearrangement producing iminium ethers **45** which are finally transformed to the desired carboxylic acids **46** or aldehydes **47** by acidic hydrolysis and reduction/hydrolysis, respectively.[37,38]

While the electrophilic activation of amides such as **36**, **37**, or **42** to the corresponding keteniminium ions facilitates the addition of an internal nucleophile to the carbonyl group of the starting amides, an interesting switch to the α-position was recently designed by trapping the intermediate keteniminium ion first with an external nucleophile embedded with a masked leaving group.[39] A successful example of this strategy was reported in 2017 by the Maulide group who developed an efficient procedure for the intramolecular α-arylation of amides **48** based on an umpolung of their α-position (Scheme 11). This reversal of polarity was made possible by trapping an amide-derived keteniminium triflate **49** by 2,6-lutidine *N*-oxide (**50**) yielding an electrophilic enolium triflate **51** which, upon intramolecular addition of the arene and elimination of 2,6-lutidine, provides the cyclic amide **52**.



Scheme 10 Intramolecular trapping of keteniminium ions with ethers



Scheme 11 Trapping keteniminium ions with pyridine *N*-oxides and subsequent intramolecular arylation

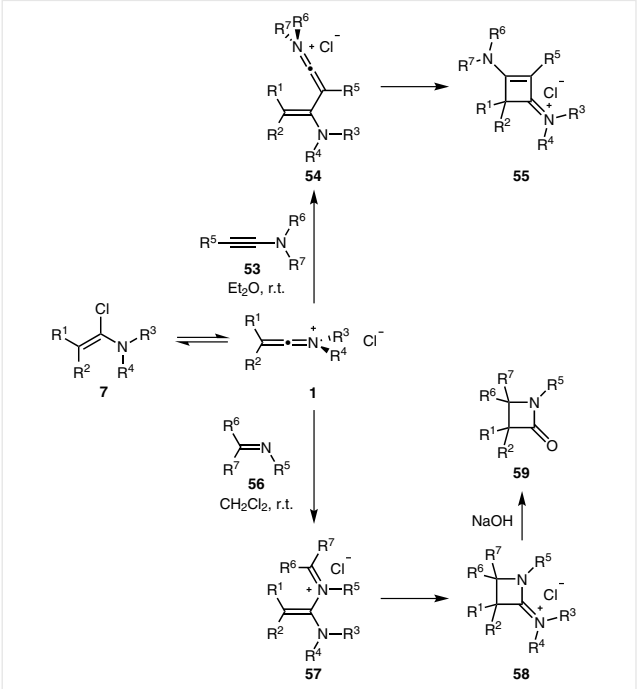
When reacted with keteniminium ions, some nucleophiles generate an electrophilic center that can be trapped intramolecularly with the newly installed enamine moiety, which enables a formal [2+2] cycloaddition with the keteniminium ion: such processes will now be briefly overviewed in Section 2.2.4.

2.2.4 Trapping Keteniminium Ions with Nucleophiles and Subsequent Ring Closure: Formal [2+2] Cycloaddition

Other nucleophiles which, after addition to keteniminium ions, initiate a subsequent transformation were indeed reported in 1969 by Viehe who described an interesting formal [2+2] cycloaddition of keteniminium chlorides **1** with ynamines **53** that readily proceeds at room temperature and furnishes cyclobutenecyanines **55** in high yields (Scheme 12).[6] This sequence actually involves two keteniminium ions, the second one, **54**, being generated upon addition of the ynamine to the starting keteniminium chloride **1** and then trapped intramolecularly by the enamine moiety in **54**.

In 1974, Ghosez reported that imines **56** are interesting nucleophiles that also react with keteniminium ions through a formal [2+2] cycloaddition, consisting of nucleophilic addition of the imine to the keteniminium ion followed by intramolecular addition of the resulting enamine to the iminium ion **57** to give **58**. Further hydrolysis of **58** provides the corresponding β-lactams **59** in excellent yields.[40] Computational analysis of this reaction indicates a stepwise mechanism in which the C–N bond is formed prior to the C–C bond.[41] The stereoselectivity of the reaction is determined by the second step: this step is subjected to torquoelectronic effects (a conrotatory electrocyclic ring closure for the transformation of **57** to **58** in combination with the preferential transition structure for an *E*-configured imine determines the stereochemical outcome of the formal cycloaddition) and was found to strongly depend on the nature of the counterion of the keteniminium ion, which is in turn related to the method used for its generation. Indeed, non-nucleophilic counterions such as a triflate favor a conrotatory electrocyclization, while nucleophilic anions such as a chloride favor a S_N2 reaction, which can account for the stereodivergence of reactions involving imines and keteniminium chlorides or triflates. An asymmetric variant of this reaction was reported by Ghosez in 1987 starting from chiral pyrrolidine-derived keteniminium ions, readily generated by electrophilic activation of the corresponding amides; while the corresponding lactams could be obtained with excellent optical purities, the yields were, however, rather modest in most cases.[42]

While they could be classified as reactions of keteniminium ions with nucleophiles and discussed in this section, their [2+2] cycloadditions with alkenes and alkynes, which is the most iconic transformation involving these reactive intermediates, clearly deserve a separate section; they will be overviewed in Section 2.3. As this chemistry has been thoroughly covered in previous reviews,[2b,f,h] only the main features and the most representative examples will be discussed.



Scheme 12 Trapping keteniminium ions with ynamines and imines

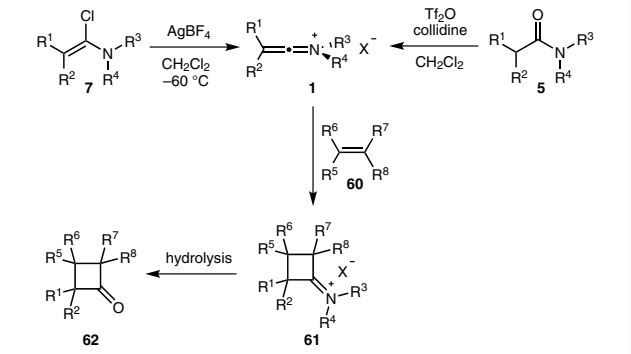
2.3 [2+2] Cycloaddition of Keteniminium Ions with Alkenes, Allenes, and Alkynes

2.3.1 Intermolecular [2+2] Cycloaddition of Keteniminium Ions with Alkenes

The use of keteniminium ions as an attractive alternative to ketenes for cycloaddition with alkenes was pioneered by Ghosez. Compared to ketenes, keteniminium ions do not dimerize or polymerize. As discussed in Section 2.1, they are easily prepared from readily available starting materials, they can be stored in solution, and they easily provide access to homochiral cycloadducts by introducing chiral substituents on the nitrogen atom.

The first examples of the cycloaddition of keteniminium ions with alkenes were reported in 1972 by Ghosez; upon reaction with alkenes **60** in the presence of silver tetrafluoroborate, α-chloro-enamines **7** reacted with exceptional ease to provide the corresponding cyclobutylideneiminium salts **61**, in situ hydrolysis of which gave the corresponding cyclobutanones **62** in excellent yields (Scheme 13).[8a,23b] Note, buffered solutions and short reaction times should be used for the hydrolysis to prevent epimerization if necessary. Alternatively, the keteniminium ion can be generated by direct electrophilic activation of the corresponding amide **5**,[9] the method that is now commonly used in most cases to promote Ghosez's cycloaddition. In addition to the formation of cyclobutanones by hydrolysis of the cyclobutylideneiminium cycloadducts, these intermediates can

also be trapped by various nucleophiles such as hydrides,[43] cyanides,[44] or various organometallic reagents,[44] which contribute to the versatility of the [2+2] cycloaddition of keteniminium ions with alkenes in organic synthesis.

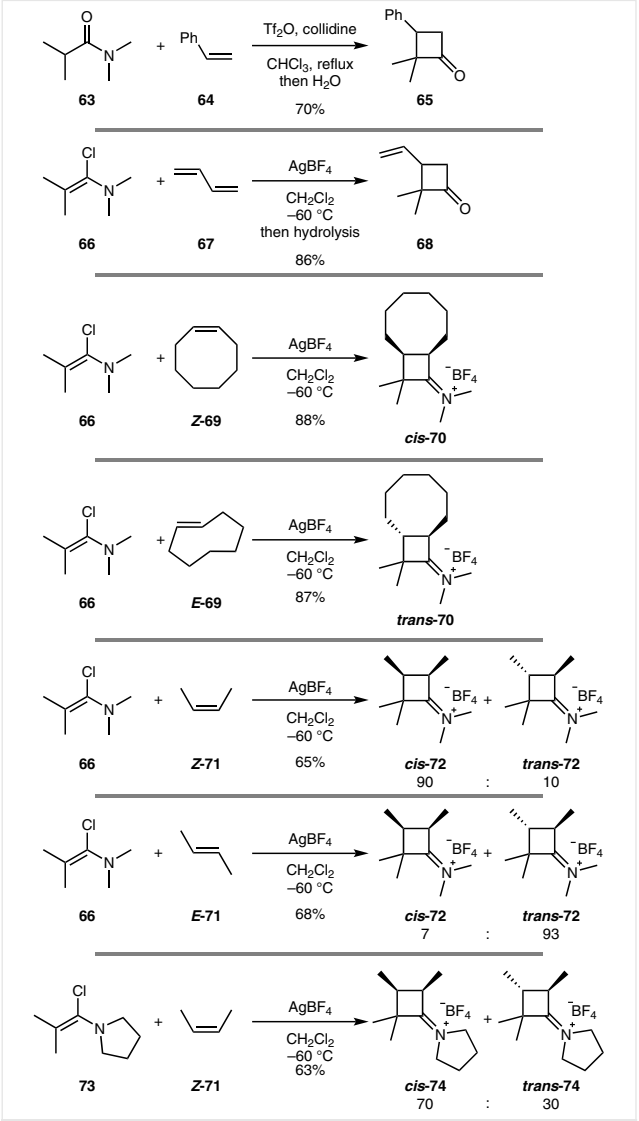


Scheme 13 [2+2] Cycloaddition of keteniminium ions with alkenes

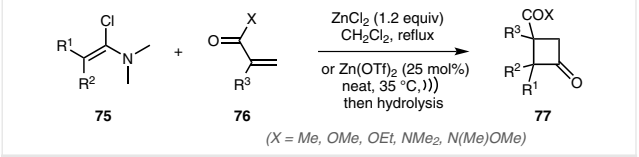
The main features of this [2+2] cycloaddition are summarized in Scheme 14. The reaction has been shown to be highly regioselective, as notably demonstrated with the use of styrene (**64**) or buta-1,3-diene (**67**)[8a] which yield cyclobutanones **65** and **68** with substituents at C2 and C3 only. These high levels of regioselectivity can be explained by the interactions between the LUMO orbital of the keteniminium ion and the HOMO orbital of the alkene. Importantly, the reaction with butadiene only gives the [2+2] cycloadduct without competing [4+2] cycloaddition, a selectivity that actually depends on the nature of the diene (see Section 2.4 for details). The stereospecificity of the reaction with regards to the stereochemistry of the alkene was found to be more subtle and to depend on the nature of both the alkene and the keteniminium ion.[8c] Indeed, while the reaction of α-chloro-enamine **66** with *Z*- and *E*-cyclooctene **69** was shown to be highly stereospecific, yielding the corresponding *cis*- and *trans*-cycloadducts **70**, respectively, lower levels of selectivity were observed when switching to *Z*- and *E*-but-2-ene **71**. The nature of the substituent on the nitrogen atom of the keteniminium ion was shown to have a stronger influence on the stereoselectivity of the reaction, as evidenced by the difference in selectivity observed in the reactions of α-chloro-enamines **66** and **73** with *Z*-but-2-ene *Z*-**71**, which was attributed to the contribution of a stepwise cationic mechanism.

The [2+2] cycloaddition was extended to the use of electron-poor alkenes, such as conjugated ketones, esters and amides **76** in the presence of stoichiometric amounts of zinc chloride or catalytic zinc triflate, the zinc salts activating both the starting α-chloro-enamines **75** and the conjugated alkenes **76** (Scheme 15).[45,46]

The mechanism of this (formal) [2+2] cycloaddition has been a matter of debate: initially proposed, by analogy to Woodward and Hoffmann's analysis of the related cycloaddition with ketenes,[47] as a concerted $[_{\pi}2_{s}+_{\pi}2_{a}]$ process,[8a] ample evidence for asynchronous or even stepwise cationic mechanisms are available. Indeed, the lack of stereospecificity observed in some cases (see Scheme 14) prompted Ghosez to formulate the mechanism depicted in Scheme 16 for the reaction of **78** with *Z*-but-2-ene *Z*-**71**. The least hin-



Scheme 14 Main features of the [2+2] cycloaddition of keteniminium ions with alkenes

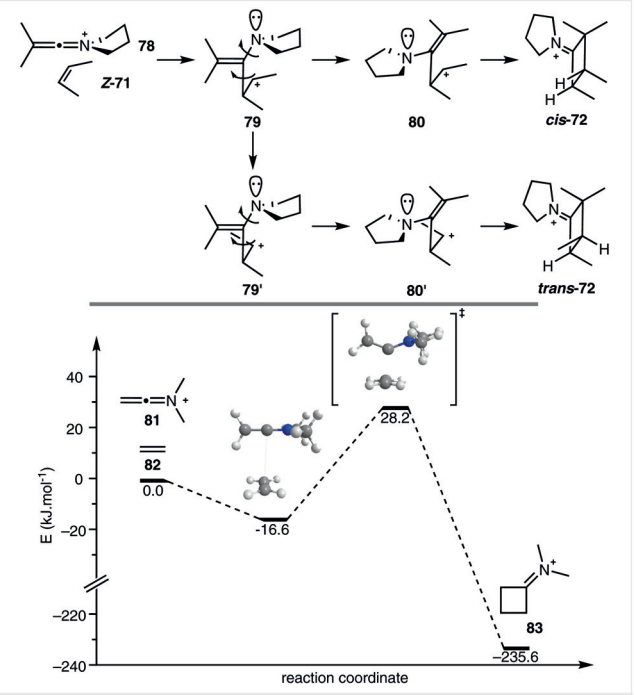


Scheme 15 [2+2] Cycloaddition of keteniminium ions with electron-deficient alkenes

dered approach between **78** and *Z*-**71** would initially lead to intermediate **79**. Rotation along the C–N and C–C bonds would enable conjugation of the nitrogen lone pair with the double bond, thereby 'creating' the enamine system in **80** and allowing for the formation of the second C–C bond yielding *cis*-**72**. Isomerization of **79** to **79′** prior to the cyclization would yield the *trans* isomer *trans*-**72**.

The mechanism of this cycloaddition was theoretically studied at BH and HLYP/6-31G* levels by Fang in 2001.[48] The reactions involving a keteniminium ion bearing hydrogens on the nitrogen atom were found to initially proceed by a hydrogen-bonded complex, one hydrogen being partially bonded to the alkene. This intermediate, which obviously could not be observed when the nitrogen atom bears substituents different from hydrogen, might not be relevant since keteniminium ions involved in [2+2] cycloaddition do not bear such hydrogens. The DFT analysis of the reaction of keteniminium ion **81** with ethene **82** is however closer to a real system and deserves some comments. When the two reactants **81** and **82** approach, a fairly loose complex resulting from a gauche approach is formed. This complex evolves to the cycloadduct **83** through a transition state in which the double bond lengths are lengthened and the C–C–N angle decreases. Interestingly, this geometry is in good agreement with the transition state proposed by Ghosez and reveals a concerted asynchronous reaction.

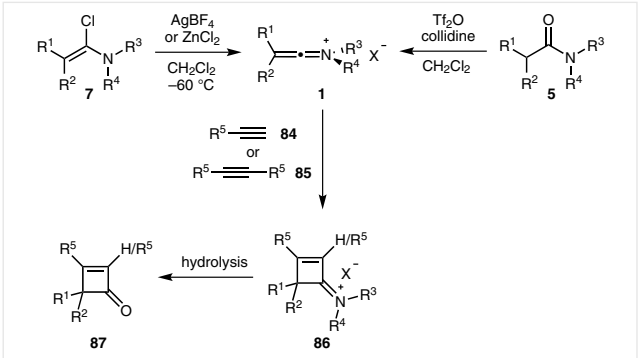
Compared to alkenes, the [2+2] cycloaddition of keteniminium ions with alkynes and allenes has been far less investigated: these reactions are discussed in Section 2.3.2.



Scheme 16 Stepwise and concerted asynchronous mechanisms proposed for the [2+2] cycloaddition of keteniminium ions with alkenes

2.3.2 Intermolecular [2+2] Cycloaddition of Keteniminium Ions with Alkynes and Allenes

In continuation of their studies, Ghosez and co-workers reported in 1981 the extension of their chemistry to acetylenes: keteniminium ions **1** readily react with a range of terminal **84** or symmetrical alkynes **85** to yield the corresponding cyclobutenylideneiminium ions **86** with excellent yields and selectivity, their further hydrolysis providing a remarkably useful route to cyclobutenones **87** (Scheme 17).[9] Here again, the keteniminium ions can be prepared either from the corresponding α-chloro-enamides **7**[49] or amides **5**.[9,50]



Scheme 17 [2+2] Cycloaddition of keteniminium ions with alkynes

Cyclobutenylideneiminium ions **86** were, in addition, found to be excellent substrates for Diels–Alder reactions[49,50b,c] or 1,4-addition,[50d] which further extend the synthetic usefulness of this [2+2] cycloaddition of keteniminium ions with alkynes, a reaction that is, however, still rarely used despite its efficiency.

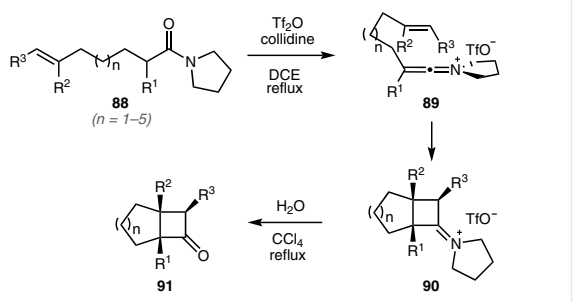
DFT studies of the reaction mechanism were reported in 2015 and revealed a two-step mechanism involving an initial rate-determining nucleophilic attack of the alkyne to the central carbon atom of the keteniminium ion yielding an intermediate cyclopropane followed by its conversion to the more stable cyclobutenylideneiminium ion.[51] This study, in addition, highlighted the strong electrophilic character of the keteniminium ion, which accounts for the feasibility of the cycloaddition.

Their cycloaddition with allenes have been even less-well investigated and therefore these reactions will not discussed here.[2a]

Since its discovery by Ghosez in 1972, this [2+2] cycloaddition has evolved as a remarkably powerful tool for the formation of cyclobutanes. Intramolecular versions of this reaction have been reported and they will be overviewed in Section 2.3.3.

2.3.3 Intramolecular [2+2] Cycloaddition of Keteniminium Ions with Alkenes

The intramolecular version of this cycloaddition offers straightforward routes for the regio- and stereocontrolled synthesis of polycyclic cyclobutanones.[2b] Ghosez reported the first systematic study of this reaction in 1985, demonstrating one more time the high efficiency of the [2+2] cycloaddition of keteniminium ions, notably compared to its analogous reaction involving ketenes.[52] This reaction, which is depicted in Scheme 18, was found to be rather general and provided polycyclic cyclobutanones **91** in yields generally superior to those obtained starting from acyl chlorides – generating the corresponding ketenes upon treatment with trimethylamine – instead of amides **88**. The reaction produces *cis*-fused cycloadducts in most cases, except if epimerization occurs during the hydrolysis of bicyclic iminium ion **90**, and the main limitation is the substitution pattern of the alkene: β,β-disubstituted alkenes favor intramolecular acylation rather than cycloaddition.

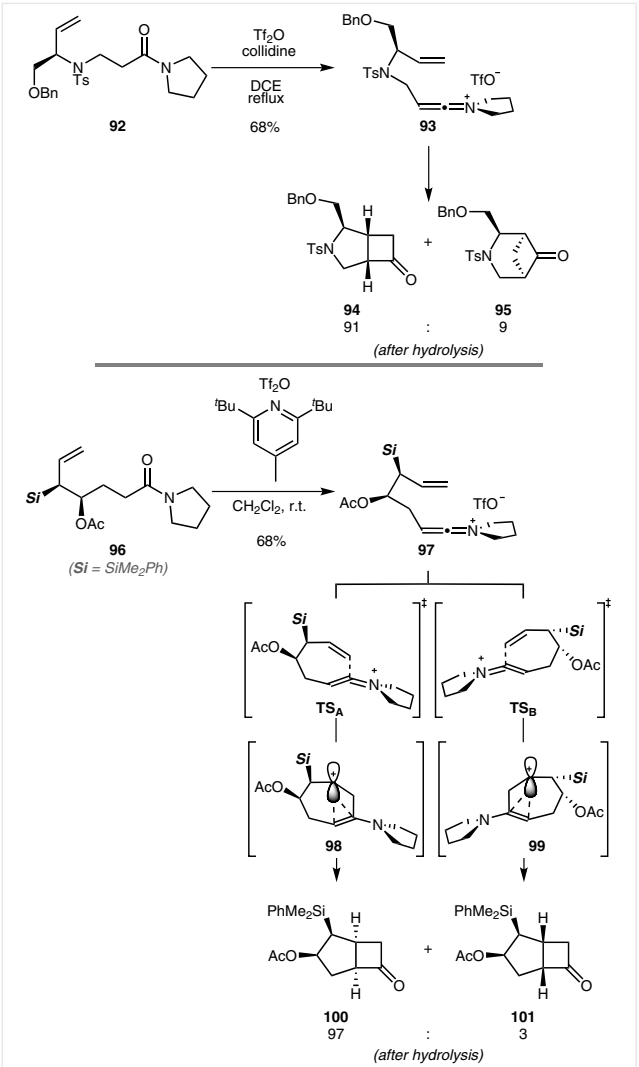


Scheme 18 Intramolecular [2+2] cycloaddition of keteniminium ions with alkenes

This intramolecular [2+2] cycloaddition of keteniminium ions with alkenes was later extended to alkoxyketeniminium ions[53] and other tethers[54] between the keteniminium and alkene moieties; these reactions typically proceed well unless a functional group within the tether can competitively trap the keteniminium ion[34,54] or interrupt the cycloaddition.[55] They were also extended to the synthesis of higher ring systems by using sequential ring expansion.[56] Applications of this reaction in natural product synthesis are described in Section 4.

To bring this reaction a step further, asymmetric induction starting from amido-alkenes linked through a chiral tether has been intensely studied. In this context, Zapia reported in 2000 a diastereoselective intramolecular [2+2] cycloaddition from vinylglycinol-derived substrate **92** (Scheme 19).[57] Upon reaction with triflic anhydride and collidine in refluxing dichloromethane, a 91:9 mixture of regioisomeric cycloadducts **94** and **95** were obtained in 68% yield and with high levels of diastereoselectivity. The diastereoselective formation of **94** was attributed to the most stable conformation of the intermediate keteniminium triflate **93**.

A higher level of asymmetric induction was obtained by placing a silyl substituent in the allylic position; this substituent not only controls the facial selectivity but also activates the alkene towards nucleophilic attack.[58] Indeed, keteniminium triflate **97** derived from amido-alkene **96** provided, after acidic hydrolysis, cycloadducts **100** and **101** in a 97:3 ratio. Computational analysis of this reaction leads to the lowest energy transition states $\mathbf{TS_A}$ and $\mathbf{TS_B}$ for the formation of **98** and **99** yielding **100** and **101**, respectively; $\mathbf{TS_A}$ is more stable than $\mathbf{TS_B}$ due to its nearly perfect staggered tether between the keteniminium and alkene moieties and the C–Si bond being aligned with the alkene π orbitals.



Scheme 19 Diastereoselective intramolecular [2+2] cycloaddition of keteniminium ions with alkenes

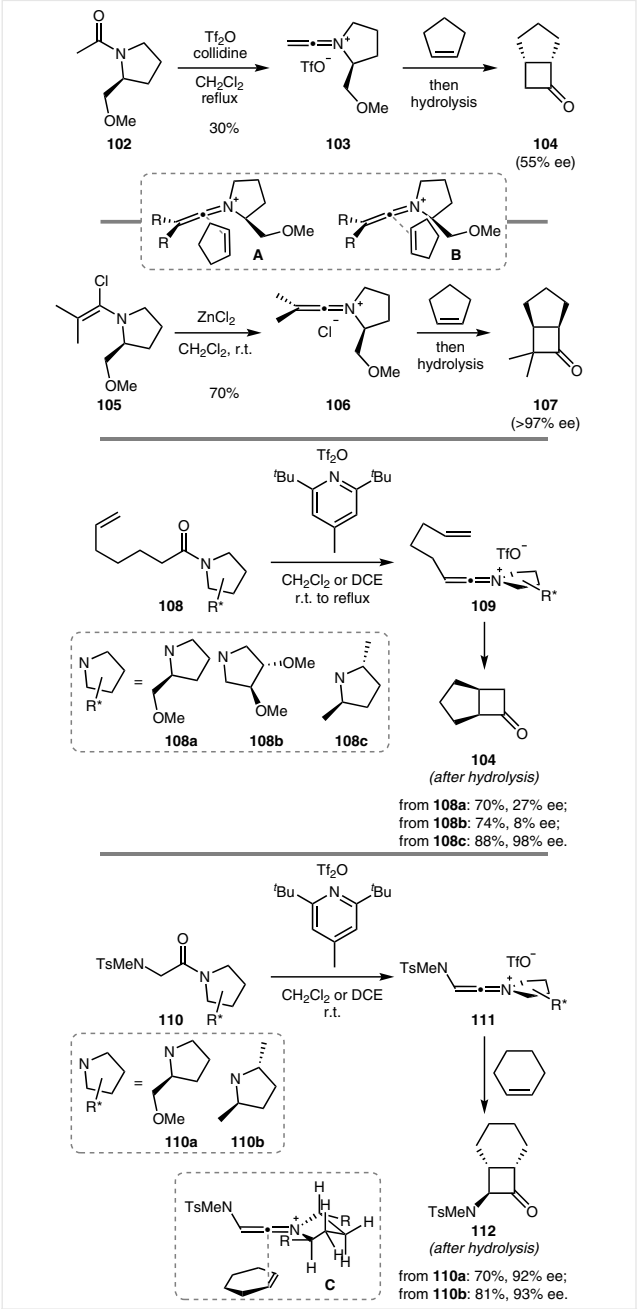
An even more appealing approach for the synthesis of enantioenriched cyclobutanones consists of the use of chiral pyrrolidine derivatives acting as chiral traceless auxiliaries. This strategy is discussed in Section 2.3.4.

2.3.4 Chiral Traceless Auxiliaries in [2+2] Cycloaddition of Keteniminium Ions with Alkenes

Another advantage associated with the use of keteniminium ions compared to ketenes lies in the possibility of using chiral keteniminium ions generated from chiral pyrrolidine-derived amides. This strategy was investigated in 1982 by Ghosez who demonstrated its feasibility and efficiency.[8c,59] *O*-Methyl-(*S*)-prolinol-derived keteniminium ions **103** and **106** were found to provide moderate to high levels of asymmetric induction, the corresponding cyclobutanones **104** and **107** being isolated with 55% and >97% ee, respectively (Scheme 20). An interesting reversal of selectivity was observed, which was attributed to a favored approach depicted as **A** in Scheme 20 with 'aldo' keteniminium ion **103** while the other approach **B** would be favored with 'keto' keteniminium ion **106** to avoid steric clash with the methyl groups. The counterintuitive approach of the alkene towards the methoxymethyl group was attributed to a stabilizing interaction between the oxygen lone pair and the developing positive charge on the olefinic carbon atom.

Moving to keteniminium ions bearing two different substituents on the β-carbon atom could be expected to be problematic due to the possible formation of diastereoisomers of this reactive intermediate. Indeed, attempts at a diastereoselective intramolecular [2+2] cycloaddition starting from *O*-methyl-(*S*)-prolinol-derived amidoalkene **108a** gave the corresponding cycloadduct **104** with only 27% ee.[60] To avoid the problematic formation of diastereoisomeric keteniminium triflates, C_2-symmetrical amides **108b** and **108c** were used; when the two stereocenters are sufficiently close to the keteniminium, such as when starting from **108c**, excellent levels of chiral induction were obtained.[60]

Further studies on the extension of this reaction involving unsymmetrical keteniminium intermediates to an intramolecular version by the Ghosez group actually revealed that non-C_2-symmetrical chiral auxiliaries can provide the corresponding cycloadducts with enantiomeric excesses that compare well with those obtained with C_2-symmetrical pyrrolidines. This is nicely exemplified in Scheme 20 by the cycloaddition from sarcosine-derived amides **110a** and **110b** with cyclohexene yielding bicyclic cyclobutenone **112** in similar yields and enantioselectivities.[61] These comparable results, which enable the use of readily available and cheap prolinol derivatives as traceless chiral auxiliaries rather than C_2-symmetrical pyrrolidines, has been rationalized by a twisted conformation of the pyrrolidine ring in the intermediate keteniminium ion **111** placing the 2- and 5-substituents in pseudoequatorial positions. Minimization of the steric interactions of the incoming alkene, which approaches, as depicted in **C** (Scheme 20), on the opposite side of the bulky sulfonamide, with the pseudoaxial hydrogen atoms of the pyrrolidine ring would account for the stereoselectivity observed.



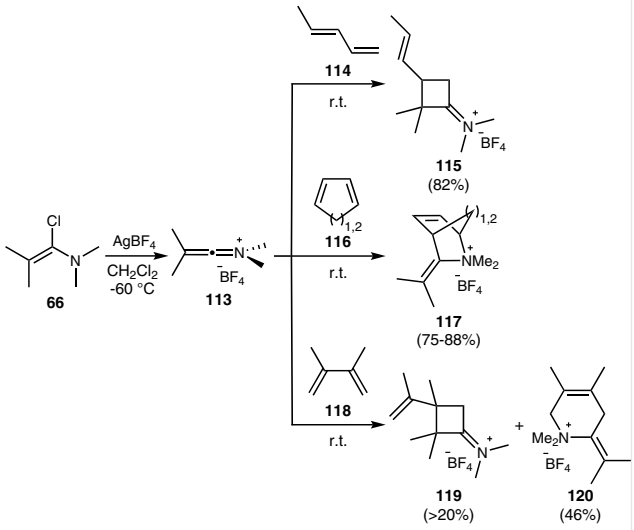
Scheme 20 Chiral traceless auxiliaries in [2+2] cycloaddition of keteniminium ions with alkenes

While the scope of this reaction was extensively studied with α-amino-amides and a broad variety of alkenes, its extension to the use of other unsymmetrical keteniminium intermediates has not been, to the best of our knowledge, reported.

As evidenced by all results overviewed in this section, the [2+2] cycloaddition of keteniminium ions with alkenes has become a powerful synthetic tool enabling the synthesis of a variety of cyclobutane derivatives, even in an asymmetric manner. As previously described, the reaction can even be extended to dienes such as butadiene (Scheme 14) without competing [4+2] cycloaddition. This actually depends on the nature of the starting diene and some of them predominantly undergo a Diels–Alder-type cycloaddition, which will be briefly described in Section 2.4.

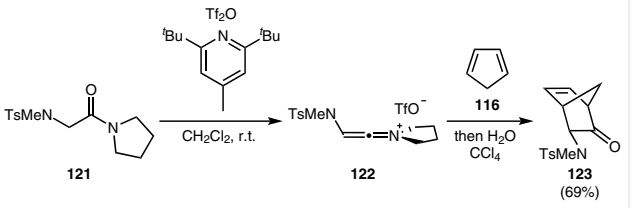
2.4 [4+2] Cycloaddition of Keteniminium Ions with Dienes

The competition between the [2+2] and [4+2] cycloadditions indeed depends on the nature of the diene used: while acyclic dienes such as penta-1,3-diene (**114**) generally undergo [2+2] cycloaddition with keteniminium ions at the less substituted double bond, cyclic dienes such as cyclopentadiene or cyclohexadiene **116** that are locked in an s-*cis* conformation exclusively provide the [4+2] cycloadducts **117** (Scheme 21).[62] Originally assigned as a product involving the C=C bond of the keteniminium ion, it was later shown that it was actually the C=N bond that participated in the [4+2] cycloaddition, which is not surprising in view of the dienophilic properties of iminium ions. With an acyclic diene with a low energy barrier between the s-*cis* and s-*trans* conformations such as 2,3-dimethylbuta-1,3-diene (**118**), a mixture of [2+2] **119** and [4+2] **120** cycloadducts are formed.



Scheme 21 [4+2] Cycloaddition involving the C=N bond of keteniminium ions with s-*cis* dienes

A dramatically different outcome was observed with aminoketeniminium triflate **122**, which also underwent [4+2] cycloaddition with cyclopentadiene **116**, but now involving the C=C bond of the keteniminium ion yielding **123** (Scheme 22).[63] This reaction, which is still limited to keteniminium ions derived from *N*-tosylsarcosinamides, was extended to an asymmetric version relying on the use of chiral pyrrolidines.



Scheme 22 [4+2] Cycloaddition involving the C=C bond of keteniminium ions with s-*cis* dienes

From the discussion so far, the synthetic utility of keteniminium ions should be evident at this point. They clearly are more than stable synthetic equivalents of ketenes and their rich chemistry has found many applications.

The chemistry of even more reactive heterocumulenes in which one of the substituents on the nitrogen atom of the keteniminium ions is replaced by an electron-withdrawing group has been intensively explored recently, mostly due to the development of efficient methods for their generation. The reactivity of these activated keteniminium ions is reviewed in Section 3.

3 The Chemistry of Activated Keteniminium Ions

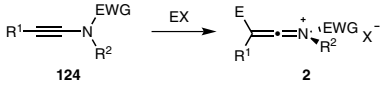
As described and extensively exemplified in Section 2, the chemistry of keteniminium ions is mostly based on their electrophilicity, which even accounts for their successful use in cycloaddition reactions. More recently, even more reactive intermediates containing an electron-withdrawing group on the nitrogen atom, which will be referred to as 'activated keteniminium ions' in this review, have been extensively studied and used for the design of a series of remarkably efficient transformations, the success of which is due, in most cases, to their exceptional reactivity. Methods for the in situ generation of these reactive intermediates and reactions based on such species will be the focus of this section.

3.1 Main Methods for the Generation of Activated Keteniminium Ions

Such activated keteniminium ions **2** are mostly generated by reaction of an ynamide **124**[2c,e,g] with an electrophile (Scheme 23). The choice of the electrophile is crucial for

two main reasons: it must react selectively at the nucleophilic carbon atom of the starting ynamide and not with the electron-withdrawing group, which would result in a loss of stabilization of the ynamine moiety, and its counteranion must be a weak nucleophile in order to avoid trapping the keteniminium ion, a side reaction commonly observed, even with poorly nucleophilic counteranions.

The electrophiles used for the generation of keteniminium ions from the corresponding ynamides can be classified into five main categories: acids (strong acids are typically used although not strictly required), halogenium ions, chalcogenyl halides,[64] C-electrophiles, and electrophilic metal complexes/organometallic reagents; the use of these reagents will be discussed throughout Section 3. Activated keteniminium ions have also been postulated as intermediates resulting from the cyclopropenation[65] and epoxidation[66] of ynamides followed by ring opening, although they are more properly described as 'push-pull' carbenes in the latter case.



Scheme 23 Main route for the generation of activated keteniminium ions

The development of efficient and broadly applicable methods for the synthesis of ynamides,[67] some of which are now commercially available, clearly contributed to the tremendous developments reported in the chemistry of activated keteniminium ions. Their exceptional reactivity was, indeed, used to design a series of innovative and efficient chemical transformations in which non-activated keteniminium ions often fail. The number and structures of nucleophiles that can trap such reactive intermediates gives a rather good illustration of their high electrophilicity.

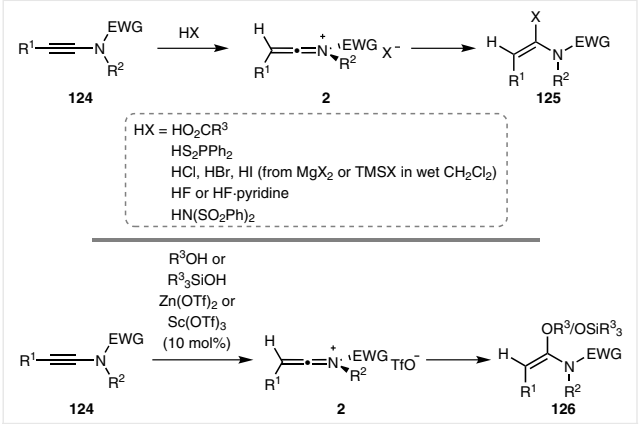
3.2 Reactions of Activated Keteniminium Ions with Nucleophiles

As with simple keteniminium ions, the most trivial chemical transformation involving activated ones is their reaction with a nucleophile. Depending on its nature, it can either be trapped by the counteranion of the electrophilic species used for the generation of the activated keteniminium ion or by a more nucleophilic reactant present in the reaction mixture, which can initiate further transformations. We will first overview the most simple case in which the reaction stops after trapping the keteniminium ions with the nucleophile.

3.2.1 Trapping Activated Keteniminium Ions with Nucleophiles

A range of acids have been reported for the generation of activated keteniminium ions by protonation of the corresponding ynamides **124** and their subsequent trapping by the conjugated base providing polysubstituted enamides **125** (Scheme 24). They include: carboxylic acids,[68] HCl, HBr, and HI (which are best generated in situ from the corresponding magnesium[69] or trimethylsilyl[70] halides in wet dichloromethane),[71] HF,[72] sulfonates,[73] or diarylsulfonimides.[74] The successful reactions with these last three acids, which readily proceed at room temperature or below, clearly highlights the remarkable electrophilicity of the transient keteniminium ion which is easily trapped by poor nucleophiles such as a fluoride, sulfonates, or a bis-sulfonamidate. This can actually be especially problematic in some cases since such side reactions can be difficult to avoid. As a note, some of the corresponding adducts, notably with sulfonates, have been shown to be poorly stable, which can be used for their further in situ transformation[73a,c] or result in a formal hydrolysis of the starting ynamide, a commonly encountered side reaction which is often tricky to suppress.

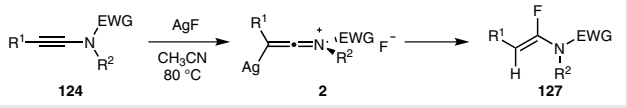
Such additions are usually found to be highly stereoselective and to proceed in a *syn* fashion, which can be rationalized by nucleophilic addition of the incoming nucleophile from the less hindered side of the keteniminium ion **2**. While alcohols and silanols are not sufficiently acidic to protonate an ynamide, Gaunt demonstrated that the addition of catalytic amounts of zinc or scandium triflate generates traces of triflic acid which protonates the ynamide, therefore generating the corresponding activated keteniminium ion **2** that undergoes selective addition of the alcohol or silanol over the C–H bond to form the *E*-enol/silyl enol ether derivative **126**. A subsequent Mukayama aldol reaction involving the latter furnished the corresponding



Scheme 24 Generation of activated keteniminium ions by protonation of ynamides with acids and subsequent trapping with the conjugated base

anti-aldol products with moderate to good levels of diastereoselectivity, this reaction being catalyzed by the Lewis acid present in the reaction mixture.[75]

An interesting way to reverse the stereoselectivity of such reactions involves the activation of the starting ynamide with a π-electrophilic metal generating a metalated keteniminium ion that can be trapped by a nucleophile, which adds to the opposite side of the metal, followed by hydrolysis of the resulting metalated enamide. The *trans* hydrofluorination of ynamides to **127** with silver fluoride[76] (Scheme 25) is representative of this strategy and nicely complements the *cis* selectivity obtained with HF.[72]

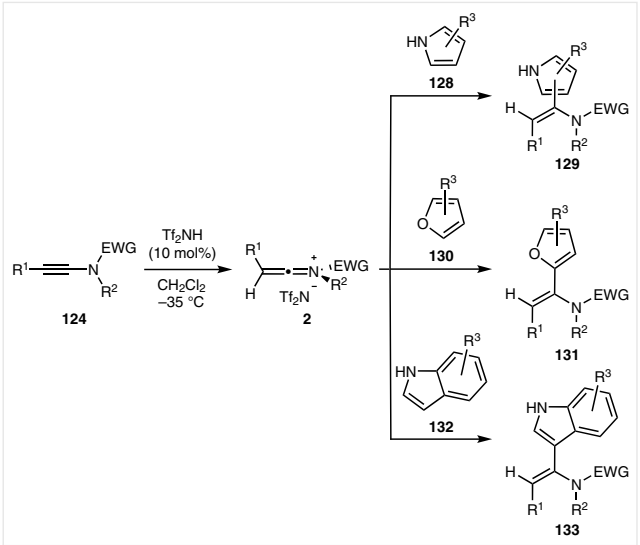


Scheme 25 *trans* Hydrofluorination of ynamides by activation with a π-electrophilic metal and subsequent trapping with fluoride and hydrolysis

While the hydrofunctionalization of ynamides with acids is of limited synthetic utility in some cases, it does, however, provide crucial information on the nature of the acid that can be used for the generation of keteniminium ions from ynamides and, more importantly, on the ease with which they can be trapped by its conjugated base. If the keteniminium ion must react with another reactant or functional group, a strong acid, therefore, must be used. An interesting example was reported by Zhang in 2005 who described an efficient intermolecular reaction between pyrroles **128**, furans **130**, and indoles **132** with keteniminium ions **2** yielding the corresponding vinylpyrroles **129**, furans **131**, and indoles **133** (Scheme 26).[77] The nature of the acid used for the generation of the activated keteniminium ion was found to have a dramatic influence and catalytic amounts of bistriflimide, whose conjugated based is sufficiently poorly nucleophilic to avoid its reaction with **2**, were found to efficiently promote the reaction.

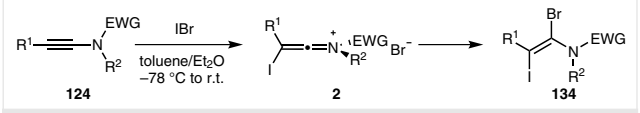
Besides acids and π-electrophilic metals, the use of which for the generation of activated keteniminium ions will be discussed later, other electrophiles have also been reported to efficiently and selectively react with ynamides to generate the corresponding functionalized keteniminium ions which can then be trapped by a nucleophile. As an important note, the stereoselectivity of this last step is too often overlooked since the nucleophile should trap the keteniminium ions from its less hindered face, which therefore depends on the relative size of the substituent of the starting ynamide and the electrophile: care should therefore be taken when looking at such reactions.

Halogenium ions have been shown to be excellent reagents for the generation of activated keteniminium ions from the corresponding ynamides. As an example, iodine



Scheme 26 Generation of activated keteniminium ions by protonation of ynamides with bistriflimide and subsequent trapping with heteroarenes

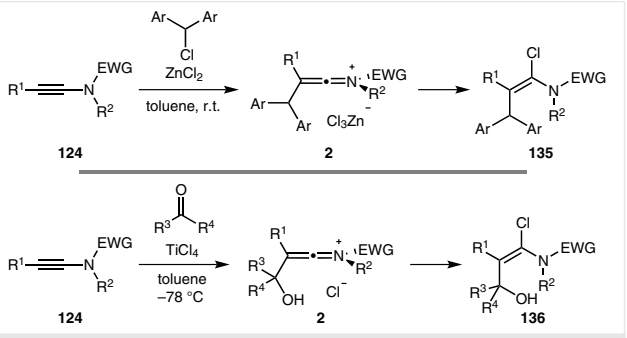
monobromide was shown to selectively react with ynamides **124** to generate iodinated keteniminium bromide **2** which then gives α-bromo-β-iodo enamide **134** with excellent levels of regioselectivity (Scheme 27).[78] Other electrophilic halogenation reagents, such as iodine,[78,79] *N*-iodosuccinimide,[80] Barluenga's reagent,[81] or bromine,[78] have been reported for the generation of halogenated keteniminium ions from the corresponding ynamides, and various nucleophiles, including halides,[78] amines,[79b] pyridines,[81] water,[79a] or DMSO,[80] were shown to efficiently trap these reactive intermediates. In addition to providing an efficient and stereoselective entry to halogenated enamides, the combination of the correct electrophilic halogenation reagent and nucleophile can be used to trigger efficient transformations via a transient halogenated keteniminium ion.



Scheme 27 Generation of activated keteniminium ions by iodination of ynamides and subsequent trapping with bromide

In sharp contrast, the use of carbon-based electrophiles for the generation of keteniminium ions is much less documented, despite its clear synthetic potential. Indeed, besides benzhydryl halides[82] and aldehydes/ketones[83] activated with a strong Lewis acid highlighted in Scheme 28 (intramolecular versions using such electrophiles will be described in Section 3.2.4), the use of other C-electrophiles is rarely discussed.[81] While many of such electrophiles are sufficiently electrophilic to react with ynamides, as evi-

denced by examination of the nucleophilicity parameters of ynamides[84] and the electrophilicity parameters of C-electrophiles on Mayr's reactivity scale,[85,86] the low efficiency of these reactions is most certainly due to competing reactions of these electrophiles with the electron-withdrawing group rather than with the alkyne.



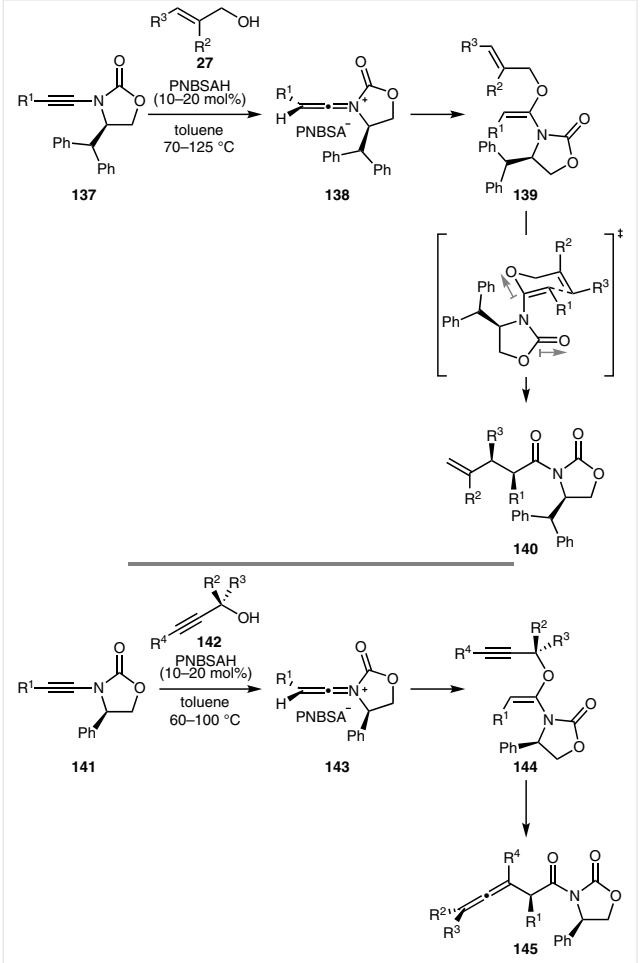
Scheme 28 Generation of activated keteniminium ions by reaction of ynamides with C-electrophiles and subsequent trapping

As discussed, π-electrophilic metals such as gold, silver, and zinc are also especially suitable reagents that can be used for the generation of metalated keteniminium ions from ynamides. This strategy is especially appealing when the nucleophiles that are used to trap the intermediate keteniminium ions are not compatible with an acid,[87] when a metal catalyst is more efficient than an acid,[88] or simply when the metalated keteniminium ion displays a reactivity that could not be achieved with its protonated equivalent. Examples of the peculiar and remarkable reactivity of such intermediates, notably as carbenoid species, will be overviewed in Section 3.2.3, after describing reactions involving the trapping of activated keteniminium ions with nucleophiles initiating a tandem transformation that will be overviewed in Section 3.2.2.

3.2.2 Trapping Activated Keteniminium Ions with Nucleophiles and Subsequent Rearrangement

As with amide- or α-chloro-enamine-derived keteniminium ions, the use of nucleophiles that, after nucleophilic addition to an activated keteniminium ion generate an enamine that can undergo a tandem skeletal rearrangement, has been extensively studied due to the extraordinary synthetic potential of this strategy. The development of efficient methods for the synthesis of ynamides in addition facilitated the design and study of an impressive and ever-growing number of processes based on trapping an activated, ynamide-derived keteniminium ion followed by subsequent rearrangement.

One of the first successful example was reported by the Hsung group in 2002 who developed an interesting diastereoselective extension of the Ficini–Claisen rearrangement (Scheme 8) based on the use of chiral keteniminium ions **138** (Scheme 29).[89] This reactive intermediate was generated by activation of a chiral ynamide **137** by catalytic amounts of *p*-nitrobenzenesulfonic acid (PNBSAH) and subsequently trapped by an allylic alcohol **27** yielding *E*-ketene *N*,*O*-acetal **139**. The latter underwent a sigmatropic [3,3]-rearrangement to give **140** with excellent levels of diastereoselectivity resulting from a chairlike transition state in which the dipole and steric interactions are minimized. This reaction was later shown to be efficiently catalyzed by zinc or scandium triflate (in the presence of additional substoichiometric pivalic acid or not)[75] and the use of *N*-bromosuccinimide to generate a brominated keteniminium ion was shown to initiate a sigmatropic rearrangement followed by dehydrobromination yielding dienamides instead of brominated Claisen products.[90] Finally, it should be mentioned that non-Claisen pathways have been reported in the gold-catalyzed reaction between enynamides and highly activated allylic and propargylic alcohols.[91]



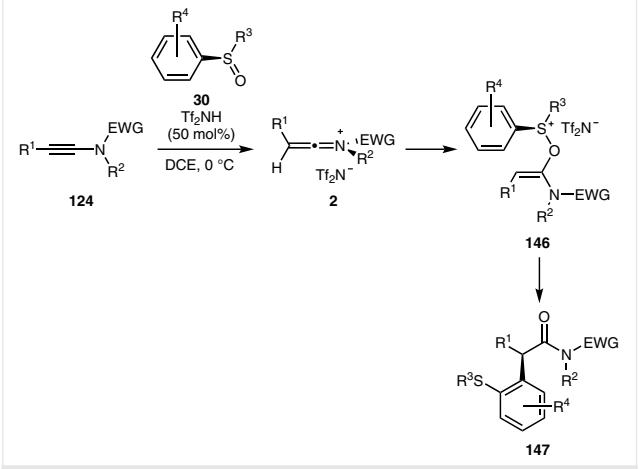
Scheme 29 Trapping activated keteniminium ions with allyl/propargyl alcohols and subsequent sigmatropic rearrangement

The extension of this reaction to propargyl alcohols **142** was also found to be efficient and this version of the Saucy–Marbet rearrangement provides an efficient entry to chiral, optically enriched homoallenylamides **145** in which both the central and axial chirality are controlled.[92] In this case, the use of homochiral propargyl alcohols had a strong influence on the diastereoselectivity of the rearrangement due to match and mismatched pairs. Starting from *N*-sulfonyl-ynamines, the rearrangement was promoted by stoichiometric zinc bromide[93] or catalytic silver triflate.[94]

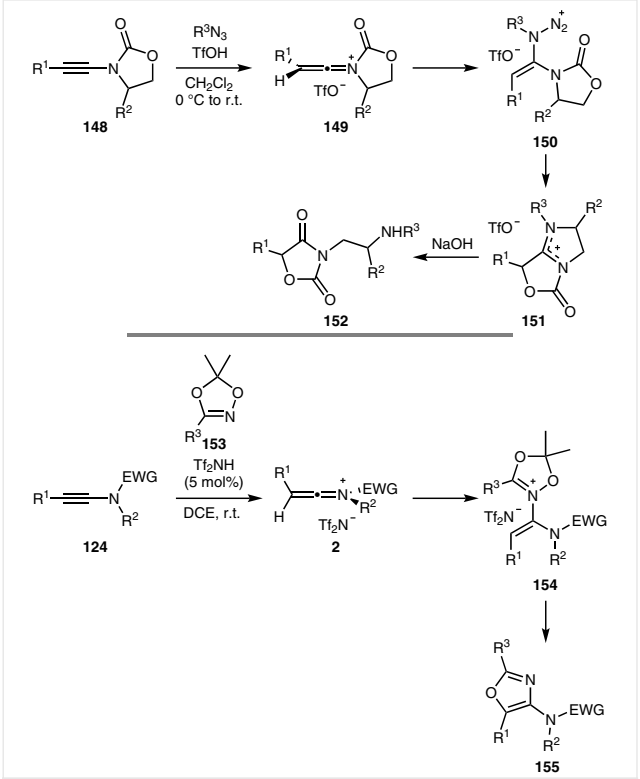
While all attempts to extend these rearrangements to benzylic alcohols failed, the Maulide group, in continuation of their studies of sigmatropic rearrangements involving non-activated keteniminium ions,[37] reported in 2014 and 2017 an interesting extension of their work involving activated keteniminium ions and aryl sulfoxides. First they demonstrated the feasibility and efficiency of such a process. Compared to the analogous reaction with non-activated keteniminium ions that required activation of the starting amides with stoichiometric amounts of triflic anhydride and 2-iodopyridine (Scheme 8), this reaction indeed only necessitated mixing the starting ynamide and aryl sulfoxide with catalytic amounts of an acid.[95] They then described an interesting use of chiral aryl sulfoxides **30** providing, after nucleophilic addition to keteniminium ion **2** and sigmatropic rearrangement, the optically enriched α-arylamides **147** resulting from chirality transfer from sulfur to carbon (Scheme 30).[96]

Besides sigmatropic [3,3]-rearrangement, other types of skeletal rearrangements consecutive to the trapping of activated keteniminium ions with various nucleophiles have been reported. Such nucleophiles include alkyl azides, which were previously shown to react with non-activated keteniminium ions (Scheme 7),[27] whose reaction with yne-oxazolidinone-derived keteniminium triflates **149** yield transient aminovinyltriazinium triflates **150** that undergo, after extrusion of nitrogen, a series of ring-closure and ring-opening reactions yielding, after hydrolysis, oxazolidine-2,4-diones **152** (Scheme 31).[97] Starting from sulfonyl-protected ynamines and benzylic azides, a concerted deprotonation/protonation yielding 2-azabuta-1,2-dienes occurs after the extrusion of nitrogen.[98] Switching to dioxazoles, **153** promotes another rearrangement from aminovinyldioxazolium ions **154** affording 4-aminooxazoles **155** resulting from a formal [3+2] cycloaddition.[99]

The successful outcome of these two reactions in which an activated keteniminium ion is trapped with azides or dioxazoles is actually based on the electrophilic character of ketene acetals cations **150** and **154**. An interesting and particularly relevant extension of this reactivity was reported in 2017 by the Shin group, who devised a remarkable oxidative intermolecular Friedel–Crafts-type coupling of electron-rich arenes or silyl enol ethers (Scheme 32).[100] The design of this reaction, which is closely related to the intramolecular version reported by the Maulide group (Scheme 11),[39] is actually based on the trapping of keteniminium bistriflimidate **2** with 2-chloropyridine *N*-oxide (**156**) generating an electrophilic enolium ion **157** which can then be efficiently trapped by indoles **132**, pyrroles **128**, phenols/anisoles/anilines **160** or silyl enol ethers **162** to give the corresponding substituted amides **158**, **159**, **161**, and

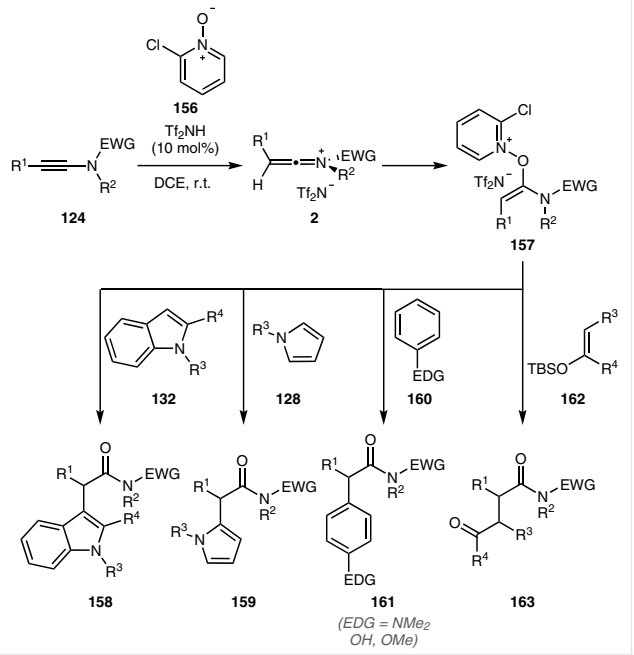


Scheme 30 Trapping activated keteniminium ions with aryl sulfoxides and subsequent sigmatropic rearrangement.



Scheme 31 Trapping activated keteniminium ions with azides and dioxazoles and subsequent rearrangement

163 with high efficiency. This reaction was also shown to be efficiently catalyzed by gold complexes and the use of chiral, C_2 symmetric bipyridine *N,N′*-dioxides provided good levels of enantio-induction.



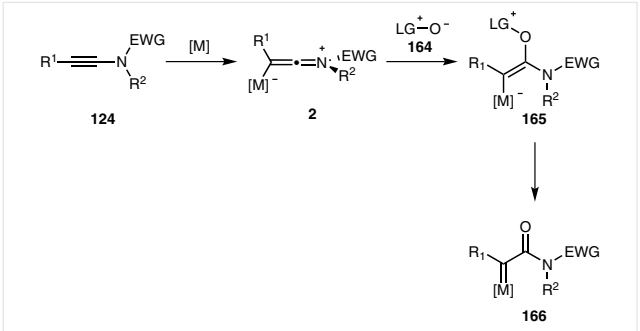
Scheme 32 Trapping activated keteniminium ions with pyridine *N*-oxides and subsequent intermolecular arylation

As highlighted with these examples, the generation of enolium ions from activated keteniminium ions provides an efficient method for the synthesis of a wide range of α-arylated amines. This strategy was later extended to the preparation of α-aryloxy-, α-arylthio-, α-azido-, α-thiocyanato-, and α-haloamides by using the correct nucleophile/pyridine *N*-oxide combination.[101]

The reactions of enolium ion **157** with indoles and pyrroles is actually reminiscent of a carbenoid reactivity, a concept which has been extensively explored and which will be overviewed in Section 3.2.3.

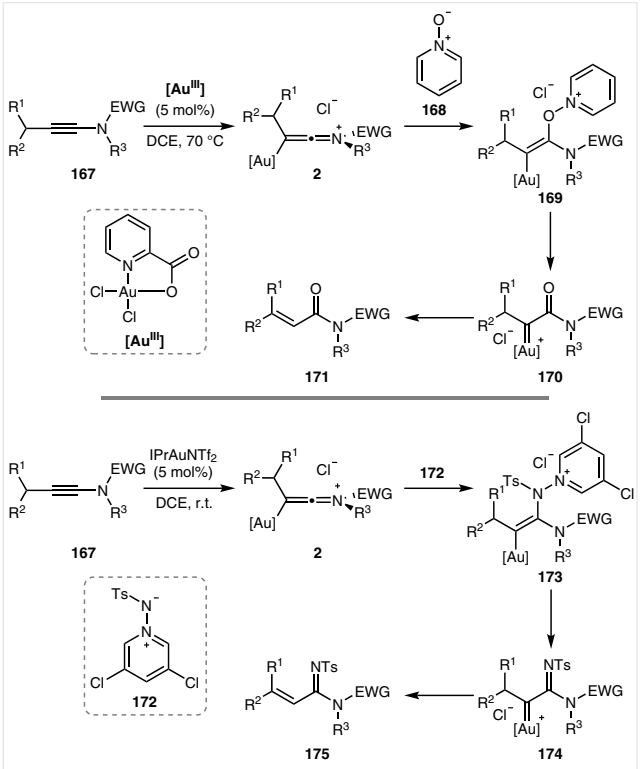
3.2.3 Trapping Activated Metalated Keteniminium Ions with Nucleophiles Yielding α-Oxo/Imido-carbenes/carbenoids

Trapping metalated keteniminium ions **2**, which are conveniently generated in situ by reaction between an ynamide **124** with a π-electrophilic metal complex, with nucleophilic mild oxidants $LG^+–O^-$ **164** indeed yields a transient metalated ketene *N,O*-acetal **165** which can further evolve to α-oxo-carbenoid species **166** (Scheme 33). Compared to the classical route to such carbenes involving metal-promoted decomposition of the corresponding potentially hazardous diazo derivatives, this strategy only requires mild oxidants and readily available ynamides and is therefore strongly appealing.



Scheme 33 Generation of α-oxo-carbenoids by trapping activated keteniminium ions with mild oxidants

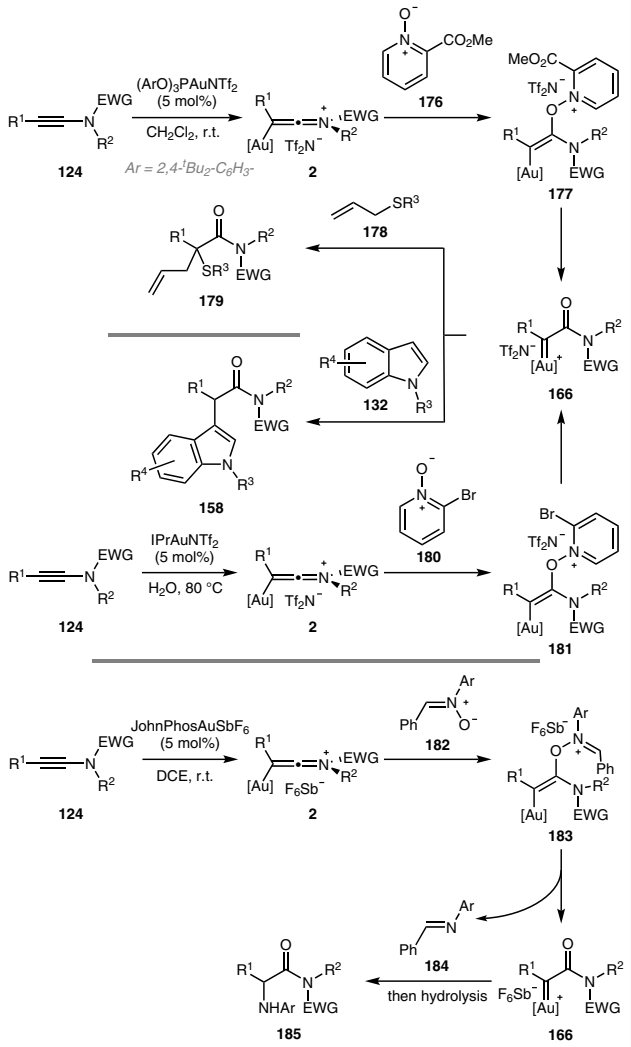
An early example of this strategy was reported in 2011 by the Davies group who described the in situ generation of α-oxo-gold carbenoids **170** initiated by trapping ynamide-derived gold keteniminium ion **2** with pyridine *N*-oxide (**168**) and elimination of pyridine (Scheme 34).[102] Subsequent 1,2-CH insertion then provided the corresponding α,β-unsaturated amides **171**. This strategy was later ex-



Scheme 34 Generation of α-oxo/imido-carbenoids by trapping activated keteniminium ions with pyridine *N*-oxide or an iminopyridinium ylide and subsequent 1,2-CH insertion

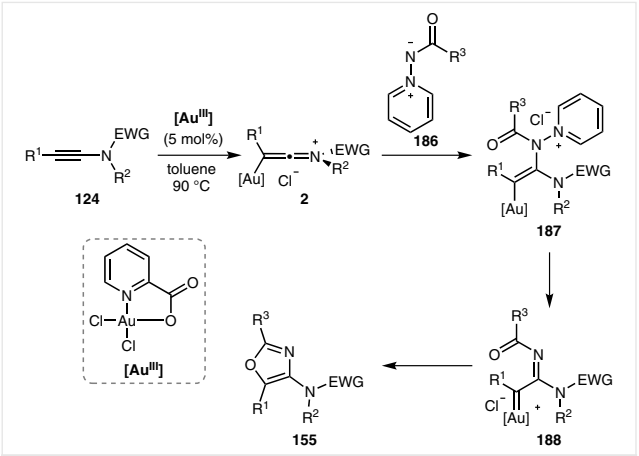
tended to the generation of α-imido-gold carbenoids **174** by the Zhang group by replacing pyridine *N*-oxide with an iminopyridinium ylide **172**[103] while the use of diphenyl sulfoxide was shown to give α-keto-imides[104a] or cyclobutenecarboxamides starting from cyclopropyl-substituted keteniminium ions (Scheme 34).[104b]

The full potential of this strategy was later demonstrated by trapping the α-oxo-carbenoid **166** with, for example, allylic sulfides **178**, which promotes the formation of sulfur ylides followed by a [2,3]-sigmatropic rearrangement to **179**,[105] or indoles **132**, giving the corresponding α-arylated amides **158** (Scheme 35).[106] While efficient, it should however be noted that the exact same transformation yielding **158** can be performed using catalytic amounts of bistriflimide instead of the gold catalyst (Scheme 32).[100] The use of other oxidants such as nitrones **182** also highlights the synthetic usefulness of this method for the generation of α-oxo-carbenoids, the imine **184** released in this case upon generation of carbenoid **166** trapping this reactive intermediate to give, after hydrolysis, α-amino-amides **185**.[107] Note, the use of nitrosoarenes in place of the nitrone was also found to be efficient and promoted an efficient oxoimination instead of the oxoamination observed with nitrones.[107,108]



Scheme 35 Generation of α-oxo-carbenoids by trapping activated keteniminium ions with mild oxidants and subsequent transformation

In the last example, the nitrone plays a dual role, first oxidizing the gold keteniminium ion and then trapping the resulting gold carbenoid. With other reagents that allow intramolecular trapping of this metal carbenoid, such dual reactivity can actually be used to promote efficient cyclizations. This was exemplified by the Davies group who reported in 2011 an interesting and original entry to 4-aminooxazoles **155** (Scheme 36).[109] Upon activation of ynamide **124** with a gold(III) catalyst and nucleophilic addition of *N*-acyliminopyridinium ylide **186** followed by elimination of pyridine, gold carbenoid **188** is generated and its further cyclization yields the desired 4-aminooxazole **155**.



Scheme 36 Generation of α-imido-carbenoids by trapping activated keteniminium ions with *N*-acyl-iminopyridinium ylides and subsequent cyclization

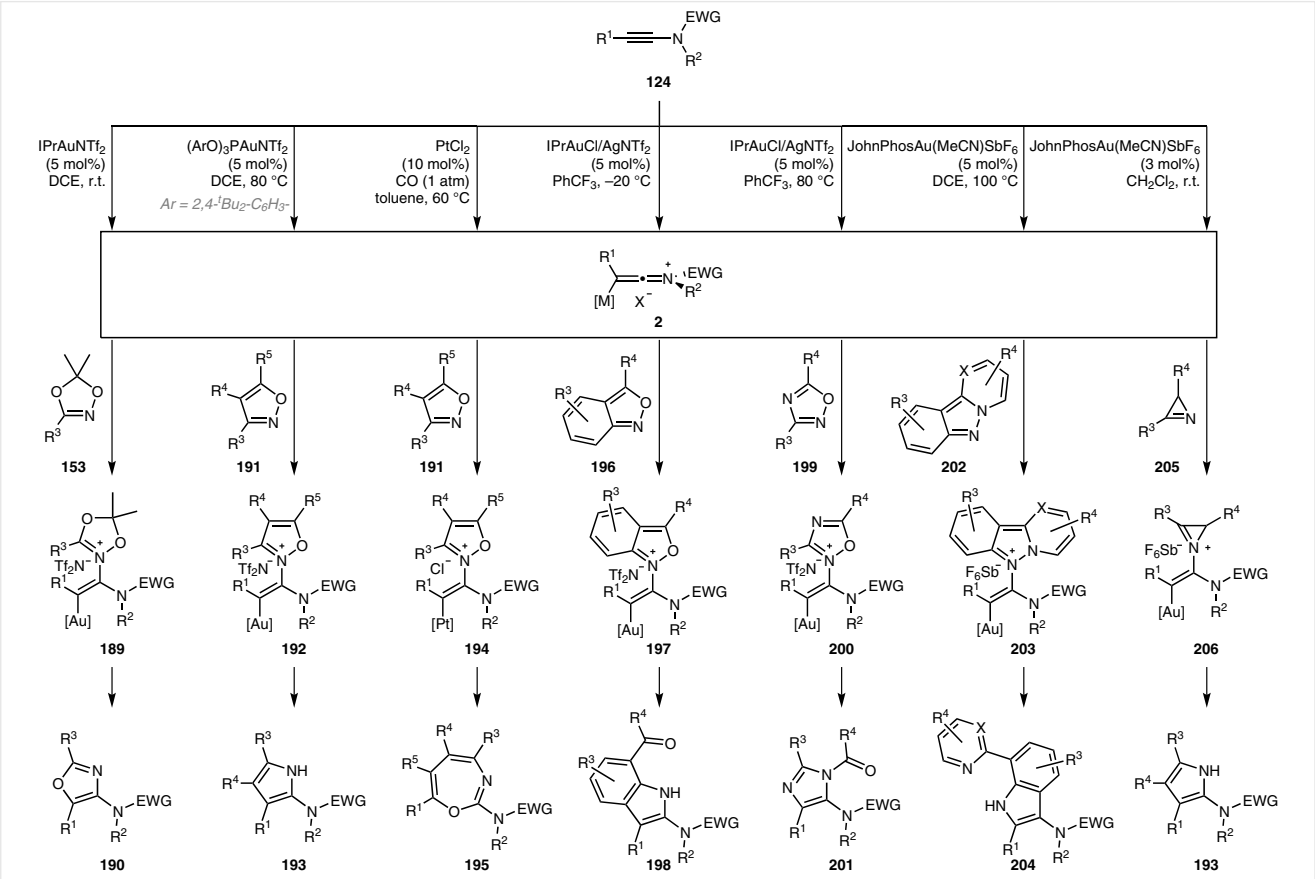
In addition to pyridine *N*-oxides, *N*-acyliminopyridinium ylides or nitrones, which release pyridines or imines after reacting with the gold keteniminium ion, other reagents, in which the leaving group is revealed after this step, can be used for the generation of gold–carbenoids and promote cyclization yielding various heterocyclic systems. Such reactions have been extensively studied since 2015 and representative examples are summarized in Scheme 37: they include the use of dioxazoles **153**,[110] isoxazoles **191**,[111] anthranils **196**,[112] oxadiazoles **199**,[113] pyridoindazoles **202**,[114] or azirines **205**[115] which result in the formation of various heterocyclic scaffolds. It is important to note that some reactions were also shown to be efficiently catalyzed by an acid instead of a gold catalyst (e.g., reaction of ynamides and dioxazoles **153** in Schemes 31[99] and 37[109]), and both the nature of the metal catalyst and the starting

ynamide can result in the formation of different heterocyclic systems. Indeed, while gold complex **192** gives 2-aminopyrrole **193**,[111a,b] the analogous platinum complex **194** gives 2-amino-1,3-oxazepines **195**,[111c] and the presence of a TBS-protected propargylic ether in the starting ynamide **124** shifts their gold-catalyzed reaction with anthranils **196** to the formation of 2-aminoquinolines.[116] Finally, it should be mentioned that some reagents, whose availability can greatly vary, can actually provide the exact same heterocycles, 2-aminopyrroles **193** being, for example, obtained after trapping the intermediate gold keteniminium ion with isoxazoles **191**,[111a,b] azirines **205**,[115] or vinyl azides.[115,117]

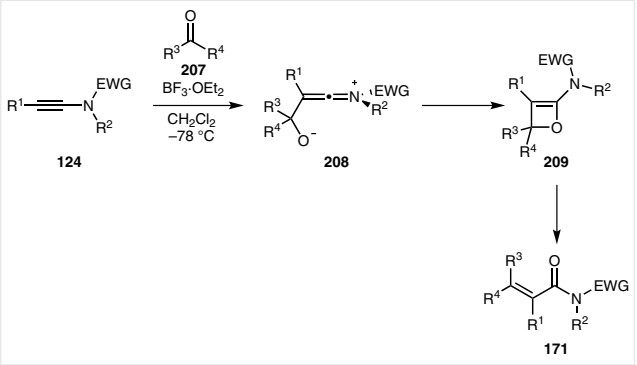
As demonstrated with selected examples overviewed in Sections 3.2.1 and 3.2.2, ynamide-derived activated keteniminium ions can be simply trapped with a nucleophile, which yields the corresponding enamides or more complex building blocks if a subsequent rearrangement occurs. As highlighted in Section 3.2.3, metalated keteniminium ions are in addition shown to be remarkably useful precursors of carbenoid species when trapped with suitable nucleophiles. When the electrophilic reagent used for the generation of the activated keteniminium ions is embedded with an internal nucleophilic center, which is revealed after its reaction with the starting ynamide, a subsequent ring closure occurs yielding an overall formal [2+x] cycloaddition from the starting ynamide. Selected examples of such reactions will now be reviewed in Section 3.2.4.

3.2.4 Intramolecular Trapping of Activated Keteniminium Ions with Nucleophiles: Formal [2+2], [2+3], [2+4], and [2+2+2] Cycloadditions of Ynamides with Bifunctional Electrophiles

One of the first example of such an intramolecular nucleophilic addition to an activated keteniminium ion was reported in 2007 by the Hsung group who designed a remarkably efficient [2+2] cycloaddition between ynamides and aldehydes and ketones (Scheme 38).[118] This formal cycloaddition is initiated by addition of ynamide **124** to an aldehyde or a ketone **207** activated by a Lewis acid yielding keteniminium ion **208**. Intramolecular addition of the resulting alkoxide to this keteniminium ion then generates a transient oxetene **209** whose electrocyclic ring opening results in the formation of an α,β-conjugated amide **171**. This reaction was later extended to an intramolecular version[119] and to the synthesis of α,β-conjugated amidines by replacing the starting aldehyde or ketone with an imine.[120]



Scheme 37 Generation of α-imido-carbenoids by trapping activated keteniminium ions with N-heterocycles and subsequent cyclization

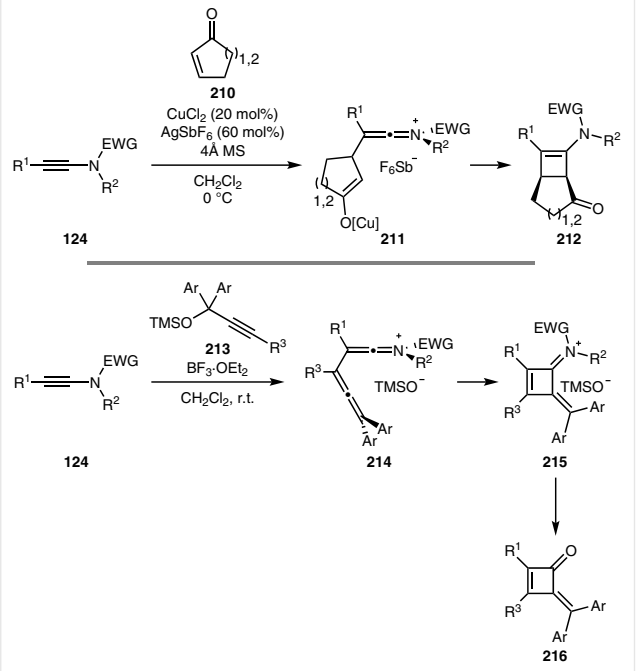


Scheme 38 Intramolecular trapping of activated keteniminium ions with alkoxides; formal [2+2] cycloaddition of ynamides and aldehydes/ketones

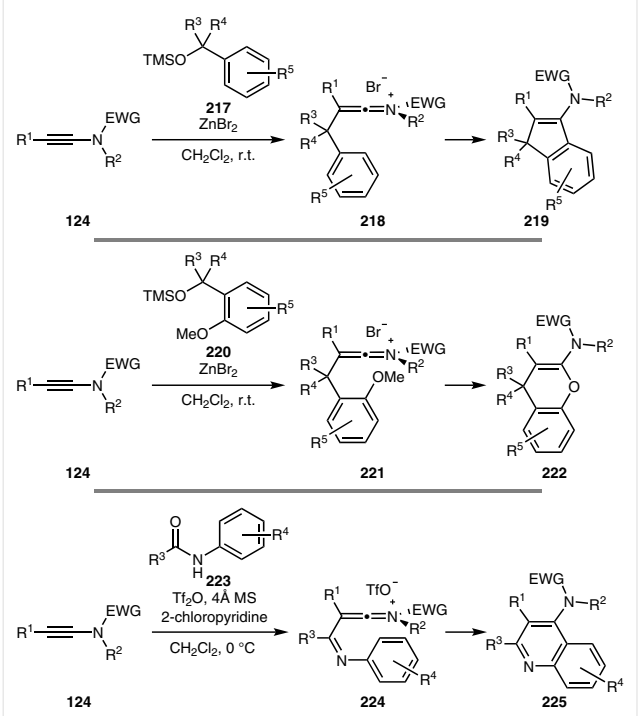
Other electrophiles, when reacted with an ynamide, generate keteniminium ions that can be trapped intramolecularly by the newly formed nucleophilic center include cyclic enones **210** and propargyl silyl ethers **213** (Scheme 39). In the first case, the enone **210** was found to be smoothly activated with catalytic amounts of copper(II) chloride; nucleophilic 1,4-addition of ynamide **124** to this activated enone generates keteniminium ion **211** whose intramolecular condensation with the copper enolate affords Ficini's *cis*-cycloadduct **212**.[121] Starting from acyclic enones, the *trans*-cycloadducts are formed. The strong synthetic potential of this reaction has attracted the attention of various research groups; it was indeed shown in 2015 to be efficiently catalyzed by silver bistriflimide[122] and enantioselective versions catalyzed by chiral ruthenium[123] or copper complexes[124] have been reported.

As for propargyl silyl ethers **213**, their activation with boron trifluoride generates an intermediate allenyl carbocation whose reaction with ynamide **124** gives keteniminium ion **214**.[125] Further intramolecular addition of the allene to the keteniminium moiety in **214** yields cyclobutenylideneiminium ion **215**, precursor of cyclobutenone **216**.

Reaction of ynamide **124** with benzyl silyl ethers **217** activated by zinc bromide was shown to promote a formal cationic [2+3] cycloaddition to give 1-amino-3*H*-indenes **219** through keteniminium ions **128** (Scheme 40).[126] In contrast, the presence of an additional methoxy group in **221** provided 2-aminochromenes **222** from a formal [2+4] cycloaddition,[126] a reaction that was also shown to proceed starting from 2-methoxyaroyl chorides,[127a] oxetanes, and aziridines.[127b] From a similar perspective, a modular synthesis of 4-aminoquinolines **225**, an especially relevant scaffold for the design of antimalarial drugs, was recently reported by the Bräse group.[128] The key to the design of this synthesis was the cyclization of keteniminium ion **224**, smoothly generated by condensation of acetanilide **223**, pre-activated with triflic anhydride in the presence of 2-chloropyridine, and ynamide **124**.



Scheme 39 Intramolecular trapping of activated keteniminium ions with enolates and allenes; formal [2+2] cycloaddition of ynamides with enones and allenyl cations

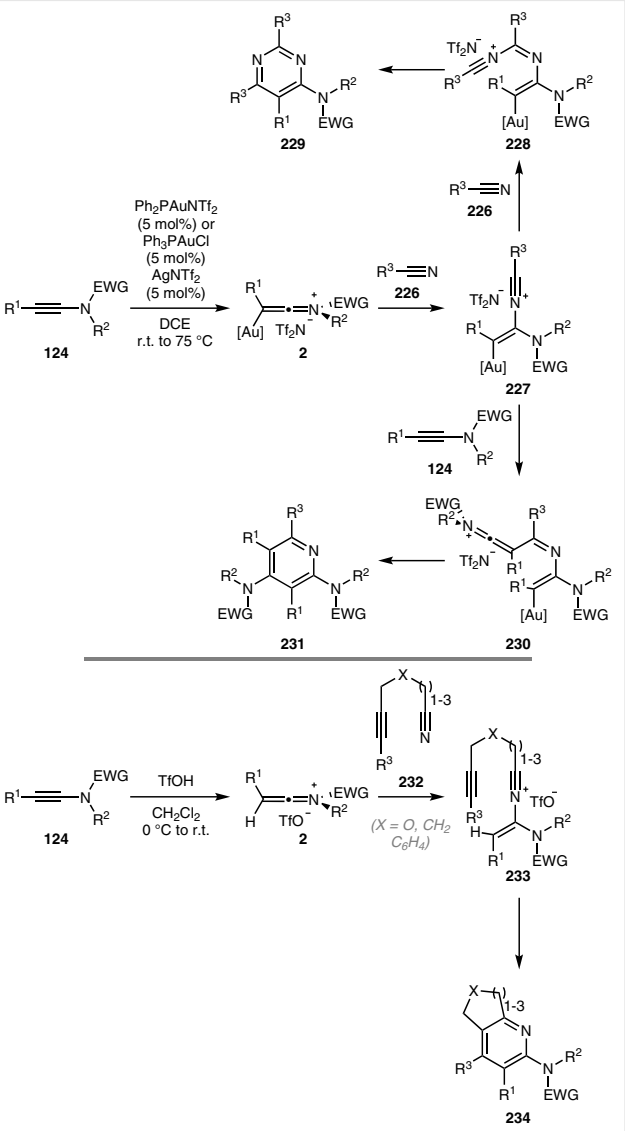


Scheme 40 Intramolecular trapping of activated keteniminium ions with arenes and anisoles; formal [2+3] and [2+4] cycloaddition with ynamides

Other electrophiles, such as nitriles **226**, can be used to trap an activated keteniminium ion **2** in a Ritter-type process. The subsequent 4-*endo*-*dig* cyclization of the resulting aminovinyl nitrilium ion **227** being disfavored for geometrical and electronical reasons, it can then be trapped either by a second equivalent of nitrile **226** yielding nitrilium **228** whose cyclization provides 4-aminopyrimidines **229** (Scheme 41).[129] Alternatively, a second ynamide **124** can react with aminovinyl nitrilium ion **227** to yield keteniminium intermediate **230** whose cyclization now provides 2,4-diaminopyridines **231**.[130] Although less favorable, alternative pathways accounting for the formal [2+2+2] cycloadditions to **229** and **231** involve the dimerization of nitrile **226** or ynamide **124** prior to their reaction with **124** or **226**, respectively. These reactions, which were shown to be efficiently catalyzed by gold complexes as shown in Scheme 41[129,130] were also found to be efficiently mediated by triflic acid in the case of 4-aminopyrimidines **229**,[131] and by bistriflimide[132] and TMSOTf[133] in the case of 2,4-diaminopyridines **231**. Besides nitriles, enol ethers have also been shown to participate in a formal [2+2+2] cycloaddition involving an intermediate gold keteniminium ion.[134]

Alkynes clearly cannot be used to trap an aminovinyl nitrilium ion such as **227** because of their limited nucleophilicity, as indicated by comparing Mayr's nucleophilicity parameters of phenylacetylene (*N*: –0.04, S_N: 0.77)[84] with those reported for acetonitrile (*N*: 2.23 S_N: 0.84),[135] *N*-benzyl-*N*-tosylbut-1-ynylamine (*N*: 5.16, S_N: 0.85),[84] or 1-(phenylethynyl)pyrrolidin-2-one (*N*: 3.12, S_N: 0.85).[84] However, intramolecular trapping was shown to be possible by the Maulide group who reported in 2016 an interesting entry to bicyclic 2-aminopyridines **234** by trapping ynamide-derived keteniminium ions with alkynylnitriles **232**.[136] The resulting nitrilium ion **233** was efficiently trapped in an intramolecular fashion by the tethered alkyne to provide the formal [2+2+2] cycloadduct **234**.

As shown in this section, the development of formal cycloaddition processes relying on the generation of activated keteniminium ions with bifunctional electrophilic reagents containing internal nucleophiles that can be revealed after their reaction with the starting ynamide has been an especially prolific area which has resulted in the design of efficient processes for the synthesis of a variety of (hetero)cyclic systems. A complementary strategy, which has been extensively studied, relies on the use of bifunctional ynamides rather than bifunctional electrophilic reagents. Representative examples will be at the core of Section 3.2.5.



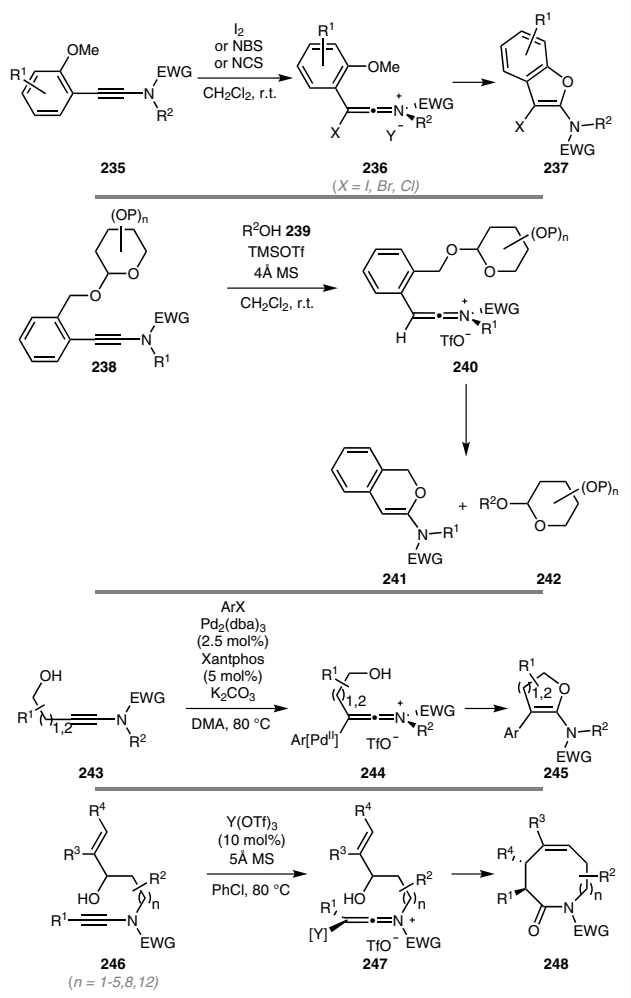
Scheme 41 Trapping activated keteniminium ions with nitriles and subsequent reaction with nitriles, ynamides and alkynes: formal [2+2+2] cycloadditions of ynamides with nitriles and alkynes

3.2.5 Intramolecular Trapping of Activated Keteniminium Ions with Nucleophiles: Cyclizations Involving Bifunctional Ynamides

One of the simplest application of such a strategy involves the generation of *o*-anisyl-haloketeniminium ions **236**, readily generated upon electrophilic activation of the corresponding ynamide **235** with iodine, NBS, or NCS (Scheme 42).[137] A fast intramolecular addition of the methoxy onto the keteniminium moiety of **236** follows, yielding 2-aminobenzofurans **237**. An ethoxyethyl ether in place of the methoxy group gives a similar outcome[138] while a methyl thioether provides the corresponding 2-aminobenzothiophenes.[137] The keteniminium ion was also found to be readily generated upon activation of **235** with stabilized carbocations[139] or by reaction with a gold catalyst.[140] In this last case, the introduction of an allyl ether in the gold keteniminium ion induces a shift of the allyl group from the oxygen to the C3 position of the final benzofuran. Note that

the intermediacy of keteniminium ions in these reactions is not obvious since they might actually involve concerted processes. This will actually be the case with most reactions overviewed in this section, but we felt that they clearly could not be left out of this review article.

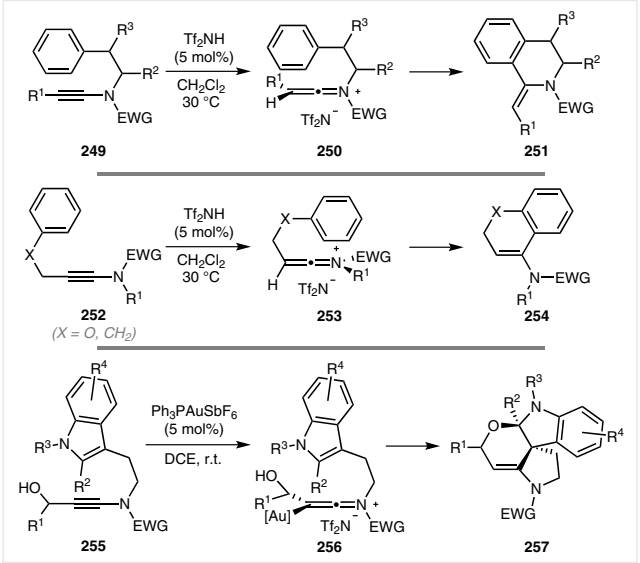
Benzyl acetals also efficiently trap activated keteniminium ions, such as **240**, in an intramolecular fashion, as nicely utilized by the Yu group who developed new glycosyl donors **238** for the latent glycosylation of a wide range of alcohols **239** including protected glucose and galactose derivatives, oligosaccharides, adamantanol, and cholesterol.[141] Related benzyl ether-substituted gold keteniminium species were also shown to undergo intramolecular trapping by the ether group, which initiates a ring-opening/ring-closing sequence yielding unique α-hemiaminal ether gold carbenes which finally undergoes a 1,2-N-migration to indenes.[142]



Scheme 42 Intramolecular trapping of activated keteniminium ions with O-nucleophiles and illustrative consecutive transformations

Cyclizations of keteniminium ions containing an unprotected alcohol have also been reported and utilized for the design of remarkably efficient processes. In this context, the Yorimitsu group developed an elegant regioselective arylative cyclization of hydroxy-ynamide **243** to **245** proceeding through the intramolecular addition of the alcohol to the keteniminium moiety in **244**, this intermediate being generated by electrophilic palladation of **243** with an arylpalladium(II) complex.[143] An even more impressive and especially useful sequence proceeding through cyclization and [3,3] sigmatropic rearrangement from yttrium keteniminium species **247** was reported in 2017 by the Ye group.[144] This intramolecular Ficini–Claisen rearrangement affords an especially efficient entry to medium- and large-sized lactams **248**.

Other internal O- and N-nucleophiles including alkoxides,[119] esters/amides,[145] and sulfinamides/sulfonamides[146] have also been shown to efficiently trap activated keteniminium ions intramolecularly. Arenes are equally efficient, Hsung's keteniminium Pictet–Spengler cyclization from keteniminium ions such as **250** being the most representative example (Scheme 43).[147] The use of arenes as internal nucleophiles is especially relevant for the synthesis of polycyclic heterocycles, and has therefore been extensively exploited.[148] Tethering the arene and the keteniminium moieties through the nitrogen or carbon atoms of the latter leads to totally different heterocyclic systems as exemplified in Scheme 43 with the cyclization of **250** and **253** leading to **251** and **254**, respectively.[147] Compared to the intermolecular version of this reaction (Scheme 26),[77] which is restricted to the use of electron-rich heteroarenes such as furan, pyrrole, or indole derivatives, it should be noted that simple, non-activated arenes can be used in this case. The



Scheme 43 Intramolecular trapping of activated keteniminium ions with arenes

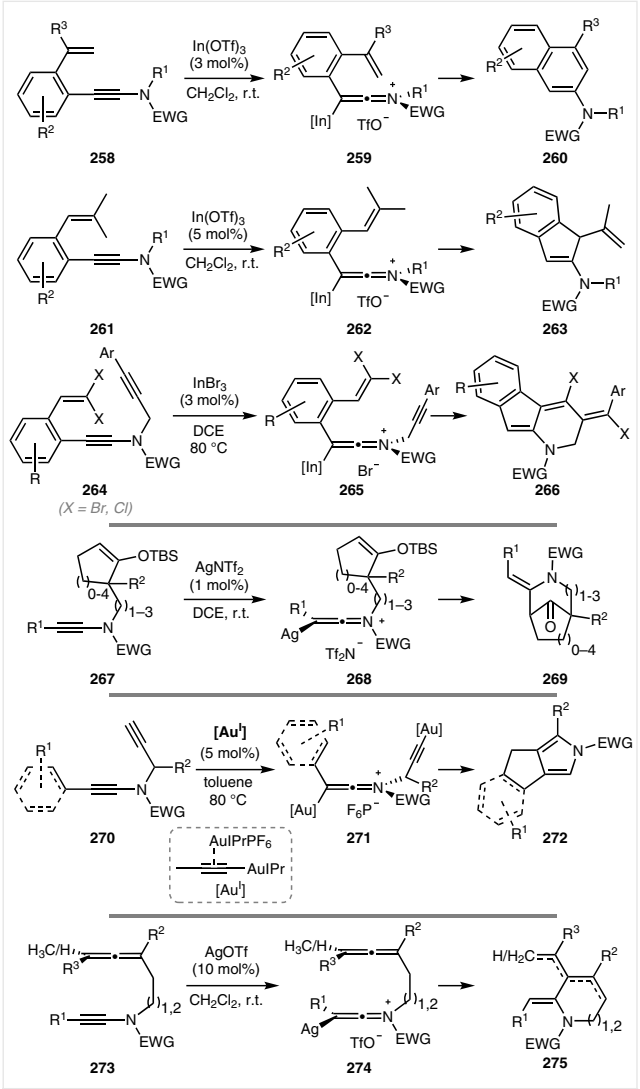
use of such arene-keteniminium cyclizations combined with a tandem cyclization provides unique opportunities for the synthesis of remarkably complex and intricate molecular scaffolds, as demonstrated by the gold-catalyzed cyclization of **255** to **257** via gold keteniminium intermediate **256**.[149]

Alkenes, alkynes, and allenes are also excellent reaction partners for the intramolecular trapping of activated keteniminium ions. Except in some rare peculiar cases, the keteniminium ion is best generated from the corresponding ynamide with an electrophilic metal rather than with a strong acid, the overall process corresponding to a cycloisomerization of the starting alkenyl-,[150] alkynyl-,[151] or allenyl-substituted[152] ynamide. As with arene-keteniminium cyclizations, these reactions offer innovative entries to various (hetero)cyclic systems from readily available starting materials. In this perspective, the Yeh group reported a series of divergent alkene-keteniminium cyclizations depending on the nature of the alkene (Scheme 44).[150d] Upon generation of indium keteniminium **259**, **262**, and **265** by activation of the starting ynamides **258**, **261**, and **264** with indium triflate or indium bromide, cyclization of **259** to the more stabilized carbocation yields 2-aminonaphthalenes **260**, while preferred pathways from **262** and **265** result in the formation of a 5-membered ring, followed by a further cyclization starting from **265**, yielding 2-aminoindenes **263** or dihydroindenopyridines **266**, respectively.

A remarkably elegant and efficient enol ether-keteniminium cyclization from **268** was reported in 2016 by Miesch and co-workers.[150f] This cyclization, which readily proceeds at room temperature, provides a straightforward entry to bridged azabicyclic frameworks **269** in excellent yields. The stereochemistry of the enamide formed in the process was rationalized by a more favorable addition of the silyl enol ether on the less shielded face of the keteniminium ion, i.e. opposite to the R^1 group.

In contrast to arene- and alkene-keteniminium cyclizations, there are only rare examples of related processes involving alkynes and allenes. Ohno and Hashmi reported in 2015 a cycloisomerization of alkynyl-ynamides **270** relying on a dual activation of both the ynamide and terminal alkyne in **270** to the gold keteniminium and acetylide moieties in **271**, respectively.[151] Addition of the latter to the former and further Friedel–Crafts-type reaction or formal C(sp^3)–H activation yields the corresponding bicyclic and tricyclic pyrroles **272**. In a similar perspective, intramolecular trapping of silver keteniminium triflate **274** by an internal allene followed by subsequent demetalation and loss of a proton yields unsaturated piperidines **275**, the substitution pattern of the allene in **274** dictating the positions of the double bonds.[152]

As an important note, other metals such as iron(II) chloride or bromide, used in stoichiometric amounts, smoothly generate *N*-allyl-iron keteniminium halides from the corresponding *N*-allyl-ynamides.[153] Intramolecular activation of the alkene by the electrophilic iron center induces its iron-chlorination which is followed by a reductive elimination, highlighting again the dramatic influence of the metal on such processes.



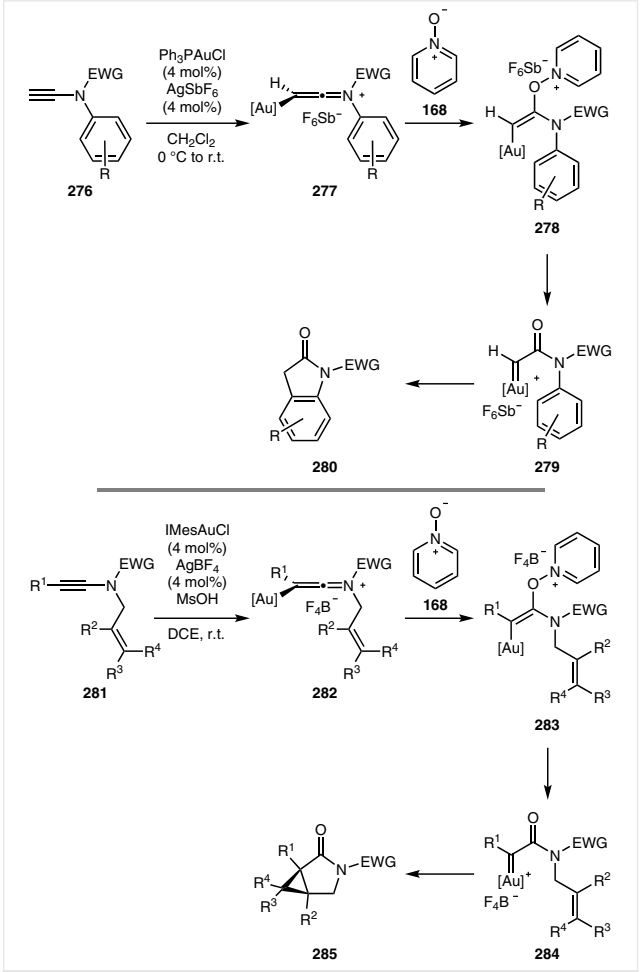
Scheme 44 Intramolecular trapping of activated keteniminium ions with alkenes, alkynes, and allenes

3.2.6 Trapping Metalated Activated Keteniminium Ions with Nucleophiles Yielding α-Oxo/Imido-carbenes/carbenoids and Further Cyclization

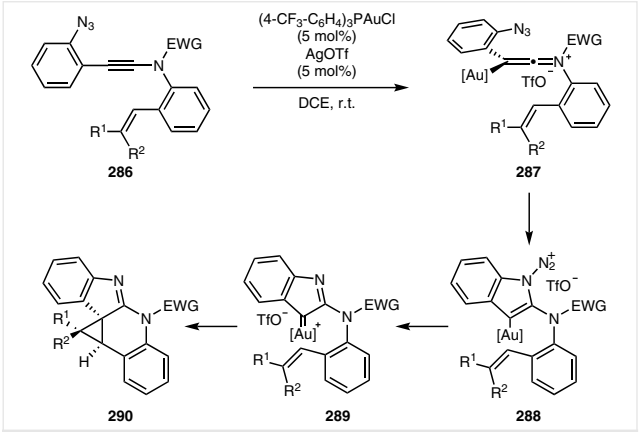
As described in Section 3.2.3, trapping metalated keteniminium ions with nucleophilic pyridine *N*-oxides or azides yields transient metalated ketene acetals which further react to α-oxo- or α-imido-carbenoid species that can then undergo a broad range of transformations. This strategy has also been utilized with keteniminium ions containing a reactive group susceptible to intercept this transient carbene, such as an arene or an alkene. One of the first example was

reported in 2013 by the Li group who designed an interesting entry to oxindoles **280** relying on trapping *N*-aryl-gold keteniminium species **277** with pyridine *N*-oxide (**168**) followed by extrusion of pyridine leading to carbenoid **279** and C–H insertion (Scheme 45).[154] Incorporating one carbon atom between the keteniminium and the arene provides isoquinolinones and replacing the benzene ring by an indole gives β-carbolines.[155] The carbenoid reactivity can also be exploited starting from *N*-allyl-gold keteniminium species **282**, a precursor of carbenoid **284** whose intramolecular cyclopropanation provides an efficient entry to azabicyclohexanones **285**.[156] As in previous cases, tethering the keteniminium and the arene/alkene through the nitrogen provides nitrogen heterocycles such as **280** and **285** while C-tethered precursors yield substituted carbocycles.[157]

Azides can be used in place of pyridine *N*-oxides to generate α-imido-carbenoids, instead of α-oxo-carbenoids, which can also be trapped intramolecularly by arenes and alkenes, as exemplified by the synthesis of 2-aminoindoles[158] and -pyrroles[159] by gold-catalyzed reactions between azides and *N*-aryl-ynamides and enynamides, respectively. One major interest in the use of azides for the generation of carbenoids from keteniminium ions is their stability and limited reactivity. They can therefore be embedded within the ynamide used for the generation of the activated keteniminium ion and trap this reactive intermediate in an intramolecular fashion. In the presence of an additional internal functional group able to react with the carbene, fully intramolecular versions can, therefore, be developed,[160] as illustrated by the impressive gold keteniminium initiated cyclization of **286** to **290** which proceeds in excellent yields (Scheme 46).[160a]

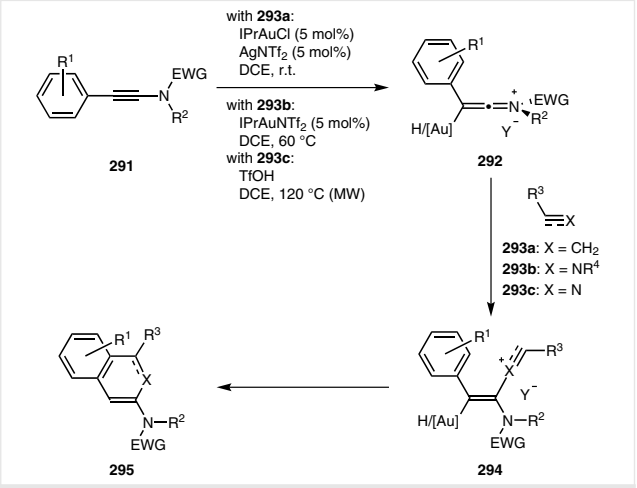


Scheme 45 Generation of α-oxo-carbenoids by trapping bifunctional activated keteniminium ions with pyridine *N*-oxide and subsequent intramolecular reaction with arenes and alkenes



Scheme 46 Generation of α-imido-carbenoids by intramolecular trapping trifunctional activated keteniminium ions with azides and subsequent intramolecular cyclopropanation

All examples discussed in this section involve the cyclization of bifunctional keteniminium ions, or even trifunctional ones, which are simply generated by electrophilic activation of the corresponding ynamides. Related processes involve the addition of nucleophiles to bifunctional keteniminium ions – aryl-substituted keteniminium ions, such as **292** in most cases – followed by cyclization. These reactions correspond to formal [4+2] cycloadditions from the starting ynamides (Scheme 47). Nucleophiles that can successfully participate in such processes include styrenes **293a**,[134] imines **293b**,[161] and nitriles **293c**;[131a] addition of these nucleophiles to keteniminium ions **292** yields cationic intermediates **294** whose intramolecular Friedel–Crafts-type reaction provides 2-amino-dihydronaphthalenes, 2-amino-dihydroisoquinolines, and 2-aminoquinolines **295**. Formal [4+3] cycloadditions involving epoxides have also been reported.[162]



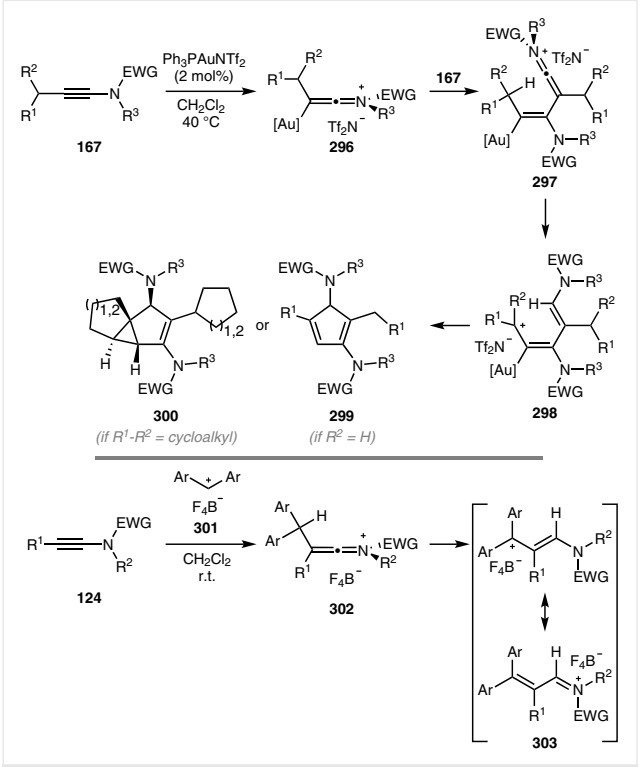
Scheme 47 Tandem intermolecular trapping of arylketeniminium ions and cyclization- formal [4+2] cycloadditions of aryl-ynamides

The synthetic usefulness of keteniminium ions, which have been used for the design and development of an array of efficient and innovative chemical transformations, should be quite evident at this point of this review article. An additional testimony of the exceptional reactivity of these intermediates is their ability to promote sigmatropic shifts of hydrogen or hydride shifts; reactions involving such a step will be overviewed in Section 3.3.

3.3 Keteniminium-Induced [1,3]- and [1,5]-H Shifts

The high electrophilicity of ynamide-derived activated keteniminium ions can indeed be used to promote sigmatropic shifts of hydrogen or hydride shifts, even from unactivated positions, reactions that cannot be promoted with less reactive amide- or α-chloro-enamide-derived keteniminium ions.

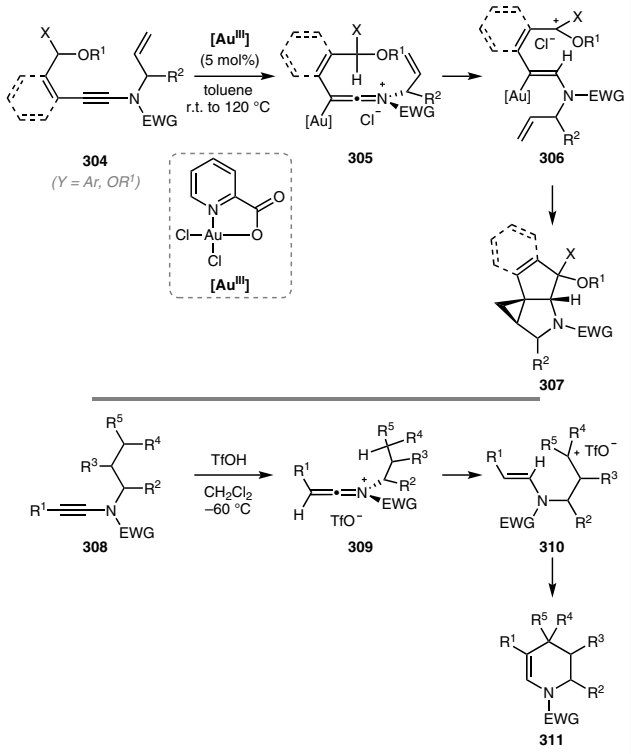
This was actually first noted in 2011 by Gagosz, Skrydstrup and co-workers who, during some studies on the addition of nucleophiles onto ynamide-derived activated gold keteniminium ions **296**, noted that they could in fact be trapped by the starting ynamide **167**, yielding a second keteniminium intermediate **297** (Scheme 48).[163] A [1,5]-hydride shift follows, yielding stabilized carbocation **298**, in resonance with a conjugated iminium ion, whose metalla-Nazarov cyclization followed by [1,2]-hydride shift or C–H insertion, depending on the nature of the substituents, afford **299** and **300**, respectively. The electron-withdrawing group has a dramatic influence on the [1,5]-hydride shift; while *N*-sulfonyl-keteniminium ions **297** undergo the hydride shift, analogous species containing a carbamate did not. [1,3]-Hydride shifts are also possible, as demonstrated by the formation of conjugated iminium ion **303** from keteniminium tetrafluoroborate **302**.[84]



Scheme 48 Keteniminium-induced [1,5]- and [1,3]-hydride shifts

The synthetic potential of keteniminium-initiated hydride shifts was demonstrated later on, first by the Davies group who designed a remarkably efficient synthesis of polycyclic nitrogen heterocycles initiated by a [1,5]-hydride shift from gold keteniminium chloride **305** (Scheme 49).[164] This hydride shift provides stabilized carbocation **306** whose electrocyclic ring closure followed by intramolecular cyclopropanation of the internal alkene yields **307**. In 2016, we reported that ynamide-derived keteniminium ions were sufficiently nucleophilic to initiate [1,5]-hydride shifts from non-activated positions. Indeed, the generation of keteniminium triflates **309** by protonation of the corresponding ynamides **308** promotes a [1,5]-hydride shift from a non-activated side chain yielding carbocations **310**, the intramolecular trapping of which by the newly installed enamide affords tetrahydropyridines **311**.[165] Importantly, all attempts at initiating this cyclization from a non-activated, amide-derived keteniminium ion failed, therefore highlighting the unique and higher reactivity of activated ynamide-derived keteniminium species.

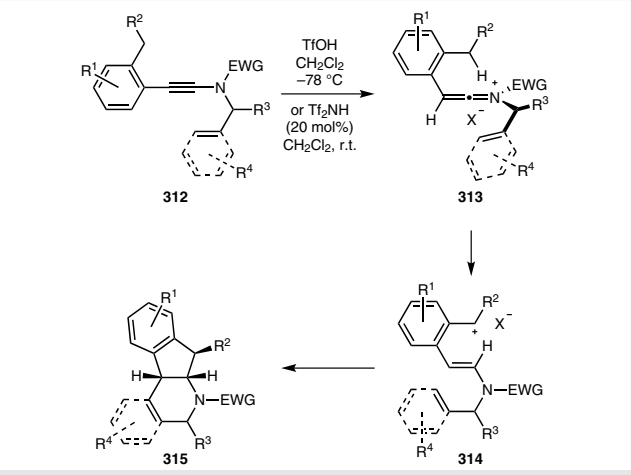
Keteniminium ions can also initiate [1,5]-sigmatropic hydrogen shifts which can trigger further cyclizations to polycyclic nitrogen heterocycles as shown in Scheme 50.[73b,81] We indeed reported in 2014 a novel keteniminium-initiated cationic polycyclization from key intermediate **313**, readily generated by protonation of the starting



Scheme 49 Cyclizations based on a keteniminium-induced [1,5]-hydride shifts

ynamide **312** by triflic acid or bistriflimide. The generation of this activated keteniminium ion triggers a [1,5]-sigmatropic hydrogen shift yielding **314** and subsequent electrocyclization and intramolecular Friedel–Crafts-type reactions afford **315**. The nature of the counteranion of keteniminium ion **313** was found to have a dramatic influence on the outcome of the polycyclization since a chloride immediately trapped **313** prior to the hydrogen shift and only the poorly nucleophilic bistriflimidate enabled a catalytic process. A comparison of the structures of the starting ynamide and the final polycyclic products clearly highlights the usefulness of the chemistry of keteniminium ions for the synthesis of complex molecular architectures.

The synthetic utility of these reactive intermediates will be further highlighted in the Section 4 of this review article dealing with the use of the chemistry of keteniminium ions for the synthesis of natural and/or biologically relevant molecules.

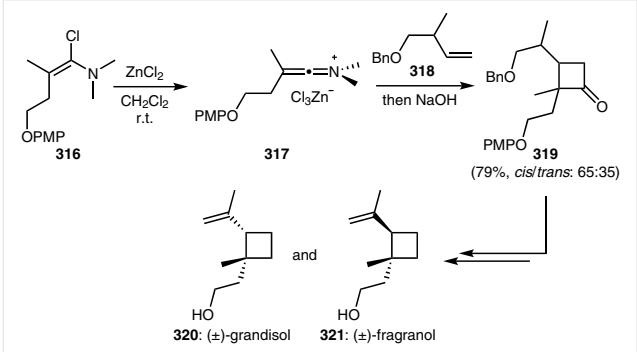


Scheme 50 Keteniminium-induced [1,5]-sigmatropic hydrogen shift and subsequent polycyclization

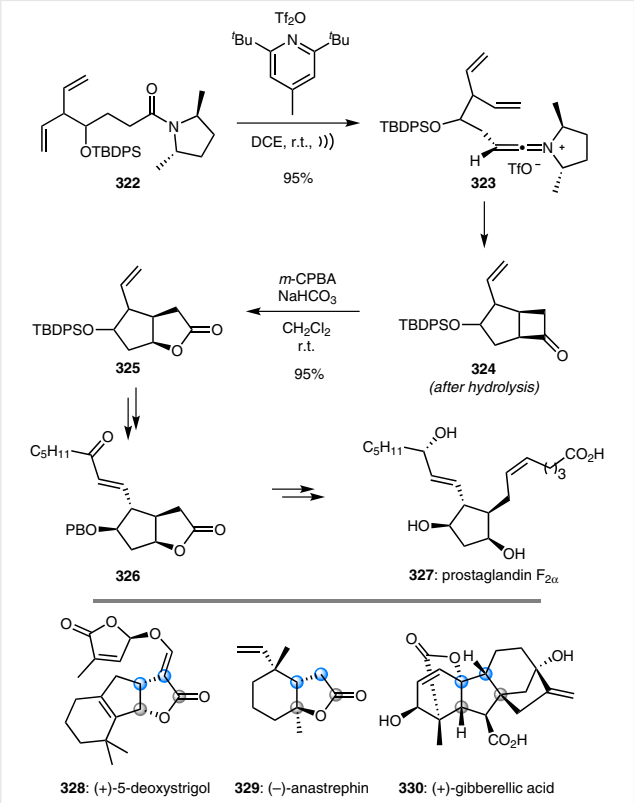
4 Keteniminium Ions: Pivotal Intermediates for the Synthesis of Natural and/or Biologically Relevant Molecules

The chemistry of keteniminium ions has been indeed used for the preparation of various natural products, even if the number of synthetic applications is still limited compared to the synthetic potential of reactions involving these reactive intermediates.

The main applications of keteniminium ions in natural product synthesis rely on their [2+2] cycloaddition with alkenes, even if the cyclobutane formed in the process is rarely found in the target molecules but rather used as a synthetic handle for the formation of larger ring systems. Indeed, one of the only synthesis of a naturally occurring cyclobutane using Ghosez's cycloaddition was reported in 1991 by Granguillot and Rouessac (Scheme 51).[166] With the aim of developing a practical and scalable synthesis of grandisol (**320**) (a monoterpenic pheromone of the cotton boll weevil *Anthonomus grandis* from which it gets its name), which is the main component of a mixture known as 'grandlure' used to protect cotton crops from the boll weevil, they envisioned that the cyclobutane ring could be installed by a [2+2] cycloaddition between a properly substituted keteniminium and a suitable alkene. The best combination found relied on keteniminium ion **317**, readily



Scheme 51 Total synthesis of (±)-grandisol and (±)-fragranol featuring an alkene/keteniminium [2+2] cycloaddition

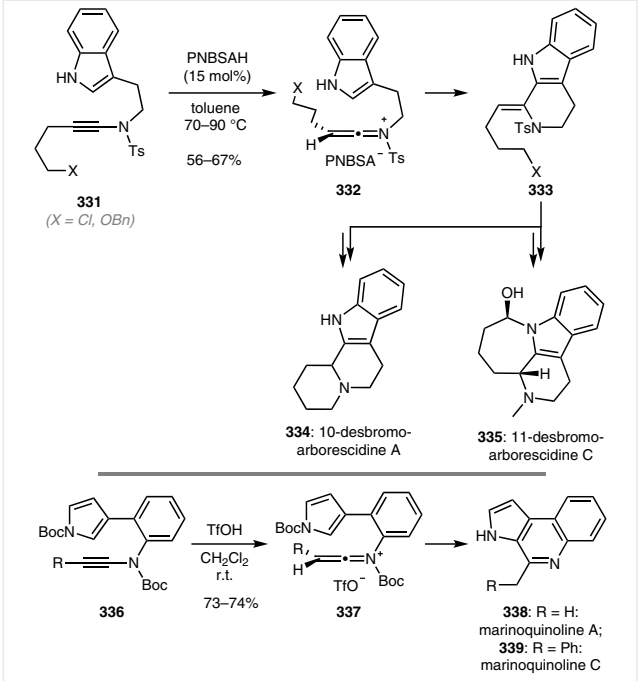


Scheme 52 Formal total synthesis of prostaglandin $F_{2\alpha}$ featuring an asymmetric alkene/keteniminium [2+2] cycloaddition and other natural products prepared via this reaction (grey circles indicate the carbon atoms originating from the keteniminium, blue circles those from the alkene)

prepared by reacting the corresponding α-methyl-γ-butyrolactone-derived α-chloro-enamine **316** with zinc chloride, and alkene **318** providing, after basic hydrolysis, cycloadduct **319** obtained as a mixture of diastereoisomers in which the *cis* isomers are formed predominantly. Wolff–Kishner reduction of the ketone followed by simple functional group manipulations and separation of the diastereoisomers finally gave racemic grandisol (**320**) and fraganol (**321**).

Apart from this example, most uses of this cycloaddition for the preparation of naturally occurring and/or biologically relevant molecules actually rely on the combination of an intramolecular cycloaddition with a subsequent Baeyer–Villiger oxidation of the cyclobutanone cycloadduct.[167] This strategy was found to be especially relevant for the preparation of prostaglandins, prostanoids, and analogues, the stereochemical outcome of the cycloaddition relying on the use of either stereocenters incorporated within the tether or on the amine which then acts as a traceless auxiliary, or both. Ghosez's synthesis of bicyclic lactone **325**,[167c] an advanced intermediate in Corey's synthesis of prostaglandins $F_{2\alpha}$ (**327**) and E_2, depicted in Scheme 52 is illustrative of this strategy. Other (formal) total syntheses relying on a key alkene/keteniminium [2+2] cycloaddition include de De Mesmaeker's synthesis of (+)-5-deoxystrigol (**328**),[167g] Shishido's formal synthesis of (–)-anastrephin (**329**),[167d] and Kim's formal synthesis of (+)-gibberellic acid (**330**).[168] In this last case, a ring enlargement of the cyclobutanone adduct with diazomethane was used in place of the Baeyer–Villiger oxidation.

In comparison, the use of ynamide-derived, activated keteniminium ions in total synthesis has been much less exploited to date, which is actually fairly logical since their chemistry has been thoroughly investigated only recently. The two total syntheses relying on activated keteniminium ions essentially involve an arene-keteniminium cyclization. The first example was reported by the Hsung group who further demonstrated the synthetic potential of their keteniminium Pictet–Spengler cyclization by using it as a key step for the synthesis of 10-desbromoarborescidine A (**334**) and 11-desbromoarborescidine C (**335**) (Scheme 53).[147] They indeed demonstrated that the common tricyclic tetrahydropyridoindole core of these natural products could be efficiently installed by an indole-keteniminium cyclization from **332**. A related strategy was utilized later by the Yamaoka and Takasu group for the preparation of marinoquinoline A (**338**) and C (**339**) as well as aplidiopsamine A (not shown) using a pyrrole-keteniminium cyclization from **337**, in situ deprotection of the Boc groups, and aromatization directly providing the target molecules.[148b]



Scheme 53 Applications of the intramolecular arene-keteniminium cyclization in total synthesis

5 Conclusions and Perspectives

Since the pioneering work of Viehe in the late 1960s, the chemistry of keteniminium ions has been considerably studied, which resulted in the development of a series of remarkably efficient synthetic procedures enabling the preparation of a broad diversity of building blocks, from the simplest to the most sophisticated ones. They can be easily generated in situ from readily available starting materials such as amides under mild conditions and their high electrophilicity has been elegantly exploited in chemical synthesis; many research groups worldwide being especially active in this area which has undergone a clear renaissance recently.

Recent developments in the chemistry of ynamides, which can now be easily prepared from an array of reagents, have also clearly contributed to the chemistry of keteniminium ions, the presence of an electron-withdrawing group on the nitrogen atom in this case considerably increasing their reactivity and allowing for the development of reactions in which simple, unactivated keteniminium fail.

There is little doubt that the chemistry of these highly reactive intermediates will continue to find various synthetic applications in the years to come and will attract more and more research groups. In this perspective, a better understanding of their electrophilicity and of the influence of the substituents of the cationic heterocumulene will be crucial; the measurement of the electrophilicity parameters *E* of a set of representative keteniminium ions would represent a major step forward and we hope to see these remarkable reactive intermediates included in the Mayr reactivity scale in the near future.

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