

Keteniminium Ion-Initiated Cascade Cationic Polycyclization

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Supporting Information

ABSTRACT: A novel and efficient keteniminium-initiated cationic polycyclization is reported. This reaction, which only requires triflic acid or bistriflimide as promoters, affords a straightforward entry to polycyclic nitrogen heterocycles possessing up to three contiguous stereocenters and seven fused cycles. These complex, polycyclic molecules can be obtained in a single operation from readily available ynamides which were shown to be remarkable building blocks for multiple, consecutive cationic transformations.

The development of efficient and straightforward methods for the synthesis of complex, polycyclic molecular scaffolds in a single operation is fueled by the strong and growing demand for such processes in most areas of chemical synthesis. In this context, cationic polycyclization reactions, mostly inspired by the biosynthesis of natural products such as steroids and alkaloids,¹ have emerged as valuable tools for the generation of diverse polycyclic skeletons with unmatched efficiency. Among the cationic intermediates involved in such reactions, carbocations² and iminium ions³ are the most frequently encountered, the cyclization of polyprenoids and sequences involving multiple Mannich reactions being iconic processes for the construction of polycyclic structures from remarkably simple starting materials.⁴ Surprisingly, and to the best of our knowledge, keteniminium ions have never been used in polycyclization reactions despite the possibility to use these highly reactive intermediates as strong electrophilic anchors for multiple consecutive cationic transformations, which might provide a straightforward access to complex heterocycles.^{5–7} Herein, we disclose an unprecedented keteniminium ion-initiated cascade polycyclization based on a Brønsted acid-mediated reaction from suitably functionalized ynamides yielding to polycyclic nitrogen heterocycles.⁸

Based on our interest in the chemistry of ynamides,^{9,10} we recently investigated their reactivity under fluorinating superacidic conditions.^{7b} While most ynamides studied were found to be smoothly transformed to the corresponding fluorinated enamides in pure fluorhydric acid upon generation of highly reactive *N*-acyl-keteniminium ions followed by nucleophilic addition of the fluoride ion, we were surprised to note a completely different reaction outcome starting from ynamide **1a**.

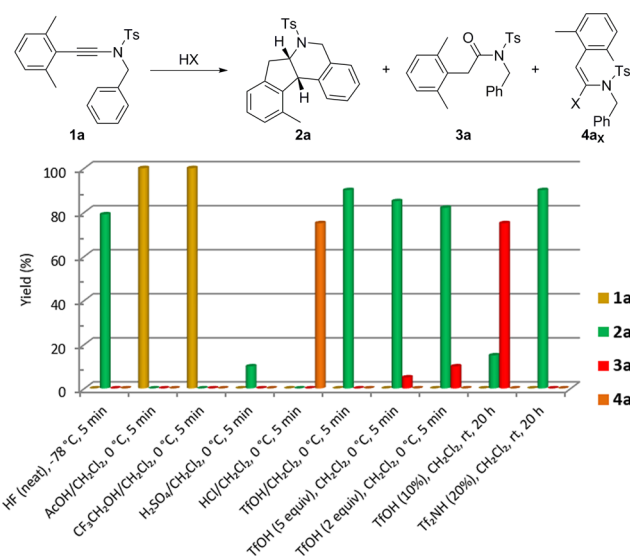


Figure 1. Influence of the acid promoter for the polycyclization.

Indeed, after reaction in HF, **1a** gave tetracyclic compound **2a**¹¹ as a single diastereoisomer and in 79% yield (Figure 1). To explore the possibility to generalize this process, we focused our efforts in the first instance toward the use of other acids, used in excess, as promoters to avoid the use of HF; results of these studies are shown in Figure 1. While no reaction was observed with mild acids such as acetic acid or trifluoroethanol, the use of stronger acids such as sulfuric or hydrochloric acids did not allow for a clean reaction due to competitive hydrolysis or hydrochlorination^{7b} yielding to **3a** or **4a_{Cl}**, respectively, and to extensive degradation. A clean and fast reaction was observed when switching to triflic acid, which smoothly promoted the polycyclization. The best conditions were found to rely on an excess of this reagent in order to avoid the competitive formation of the hardly separable amide **3a** which was still formed when using 0.1 to 5 equiv of TfOH. We envisioned that the formal hydrolysis of the ynamide, which most certainly results from trapping of the intermediate keteniminium ion by the triflate

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counterion followed by hydrolysis of the intermediate unstable *N,O*-ketene acetal **4a_{OTf}**,^{7i,12} could be avoided by using a weakly nucleophilic counterion such as bistriflimidate that should enable a polycyclization under catalytic conditions.¹³ To our delight, the use of 20 mol% of bistriflimide indeed promoted a clean polycyclization yielding to **2a** in 90% yield, provided that the reaction was performed at room temperature for 20 h. As an important note, π -acid metal catalysts including gold and copper complexes were found to be totally inefficient to promote the reaction and mostly gave hydrolysis or extensive decomposition.

With a set of conditions for the polycyclization based on the use of excess triflic acid (Conditions A) or catalytic bistriflimide (Conditions B), we next evaluated the generality of our procedure in a series of cascade bicyclizations. To this end, a set of *N*-benzyl-ynamides **1a–m** possessing representative substitution patterns, readily prepared using our previously reported procedure,¹⁴ were submitted to the cationic polycyclization (Figure 2). The cyclization proceeded smoothly in

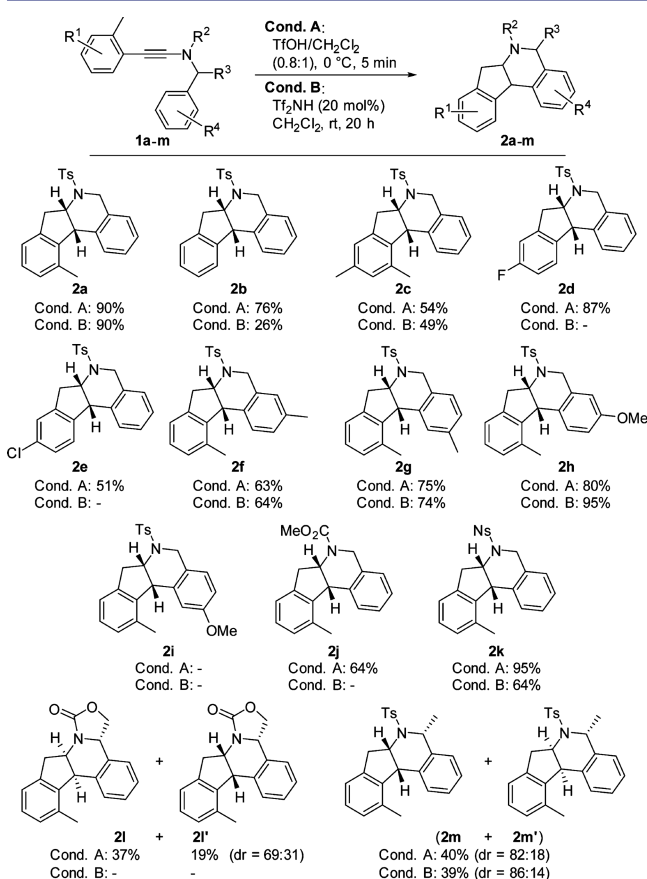


Figure 2. Scope of the polycyclization of *N*-benzyl-ynamides.

most cases and with full diastereoselectivity (exclusive formation of the *cis* isomers) under both stoichiometric and catalytic conditions, the former being more efficient in the most challenging cases (**2b,d,e,j,l**). A variety of tolyl groups on the starting ynamide were found to be suitable for the polycyclization, including deactivated ones (**1d,e**) which however required the use of triflic acid. The nature of the aromatic ring on the benzyl moiety in **1**, which must act as the terminal nucleophile in the polycyclization, had a stronger impact on the reaction. Indeed, the desired polysubstituted indenotetrahydroisoquinolines **2** could be readily obtained starting from simple *N*-benzyl-ynamides (**2a–e**, **2j–m**) and in the case of electron-donating

group suitably placed in the *meta* position to direct the terminal cyclization (**2f,h**). Moving this electron-donating substituent to the *para* position (**2g,i**) resulted in a more substrate-dependent cyclization which was found to still be operative with a methyl substituent (**2g**) but inefficient with a more donating methoxy group (**2i**). Other electron-withdrawing groups on the starting ynamide were equally well tolerated, including a carbamate (**2j**) and an easily deprotected nosyl group (**2k**), the cyclization being however a bit more sluggish and less efficient with the former. Finally, we briefly evaluated the possibility of diastereoselective polycyclizations yielding to enantiopure nitrogen polycyclic compounds by reacting 4-phenyl-oxazolidinone- and α -methylbenzylamine-derived ynamides **1l** and **1m**. Although moderate levels of diastereoselectivity were observed with these substrates (69:31 to 86:14), these chiral ynamides were however readily transformed to the corresponding enantiopure highly substituted tetra- and pentacyclic products **2l/2l'**¹¹ and **2m/2m'**¹⁵ which could therefore be obtained in a single operation from readily available starting materials.

Importantly, the cyclization is not limited to the small scale used for the scope and limitation studies as it could be conveniently performed on a 1.3 g scale from **1a** in 90% yield using catalytic amounts of bistriflimide.

We next envisioned the replacement of the arene by a suitably functionalized alkene as the terminal nucleophile in the polycyclization, which could provide a remarkably straightforward entry to tricyclic indenotetrahydropyridines **6**, compounds that are at the core structure of complex alkaloids such as haouamine A **7**.¹⁶ Ynamides **5a,b**, bearing a substituent on the internal carbon of the alkene in order to stabilize the carbocation that would be formed at this position during the second cyclization, were therefore subjected to the acid-mediated cascade cationic cyclization (Figure 3). To our delight, the cyclization, which was definitely more audacious in the allyl series than in the benzyl one, provided the desired tricyclic nitrogen heterocycles **6** in moderate to good yields. In both cases, mixtures of polycycles **6a,b** and **6a',b'** were obtained, the former being formed predominantly. For the sake of curiosity, the reaction of unsubstituted *N*-allyl-ynamide **5c** was also evaluated and was found, as expected, to be reluctant to undergo the cyclization, therefore demonstrating the requirement for the substitution of the alkene for the cyclization to occur.

Encouraged by the successful acid-mediated bicyclization of ynamides, we then tested the possibility of increasing the level of structural complexity of the polycyclic products by introducing an additional substituent. Ynamide **8** was therefore treated with either excess triflic acid at 0 °C for 5 min or catalytic bistriflimide

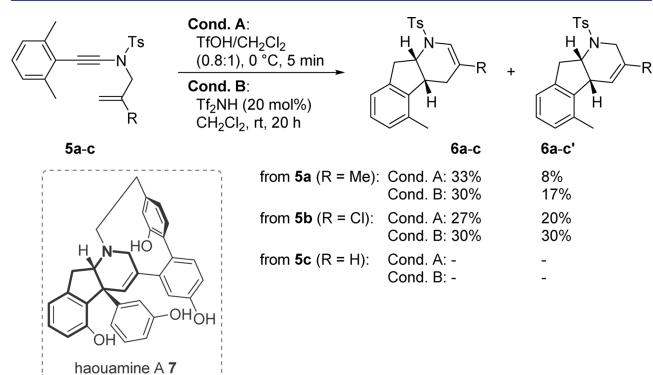
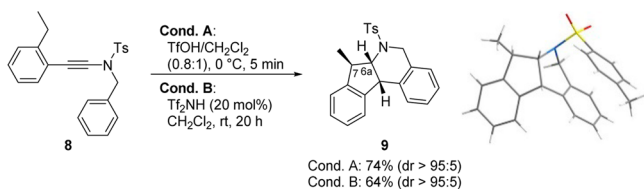


Figure 3. Polycyclization of *N*-allyl-ynamides.

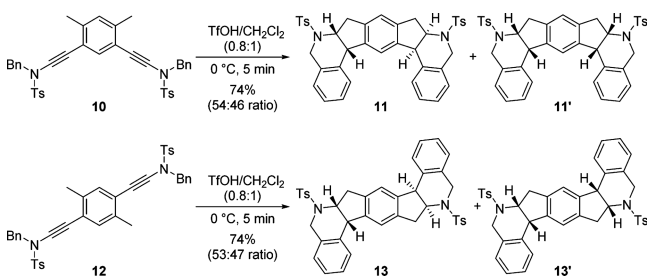
at rt for 20 h and was found to be smoothly transformed to the corresponding polycycle **9**¹¹ in excellent yields (Scheme 1). Importantly, complete diastereoselectivity was observed in both cases, the polycyclization therefore establishing three contiguous stereocenters in a single step.

Scheme 1. Double Diastereoselective Polycyclization



All these results set the stage to the more challenging case of a double cationic cascade cyclization. We indeed finally evaluated the possibility of performing a double cyclization from bis-ynamides **10** and **12**, which could hopefully provide a remarkably straightforward access to heptacyclic nitrogen heterocycles from structurally simple “flat” starting materials (Scheme 2). To our delight, the polycyclization was found to be quite robust since, upon treatment of substrates **10** and **12** with triflic acid, the corresponding polycyclized targets **11/11'** and **13/13'** were found to be readily formed within 5 min at 0 °C and could be isolated in 74% yield in both cases.

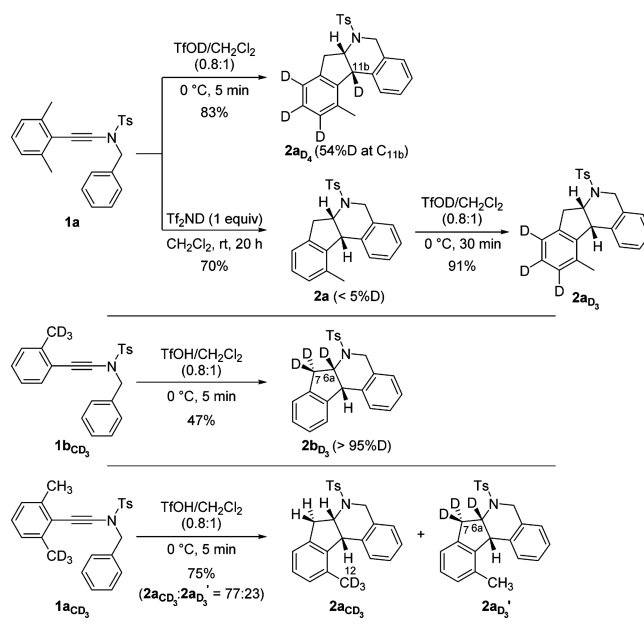
Scheme 2. Double Polycyclization from Bis-Ynamides



Having demonstrated the efficiency of our new cationic polycyclization, we next focused our efforts on gaining insights into its mechanism. To this aim, a series of experiments shown in Scheme 3 were performed starting from deuterated ynamides and acids. Upon treatment of **1a** with a large excess of TfOD, the resulting polycycle **2a_D** was shown to only partially incorporate a deuterium atom at the benzylic ring junction (C_{11b}) in addition to the expected full deuteration of the electron-rich trisubstituted aromatic ring, a reaction that was also shown to occur after the polycyclization as demonstrated with the conversion of **2a** to **2a_D** under the standard reaction conditions. The use of 1 equiv of Tf₂ND for the polycyclization of **1a** resulted in no deuteration of the polycyclic product, demonstrating a strong kinetic isotopic effect for the initial protonation of the ynamide.

To gain insights on the activation of the benzylic C–H bond, the cyclization of **1b_{CD3}** was performed and complete deuteration at C_{6a} and C₇ was observed in the resulting polycyclized product **2b_{D3}**, indicating that a shift of deuterium had occurred during the polycyclization. An intramolecular competition experiment was finally performed by studying the cyclization of ynamide **1a_{CD3}**, which possesses both CH₃ and CD₃ groups. A mixture of deuterated polycycles **2a_{CD3}** (deuterated at C₁₂) and **2a_{D3}**

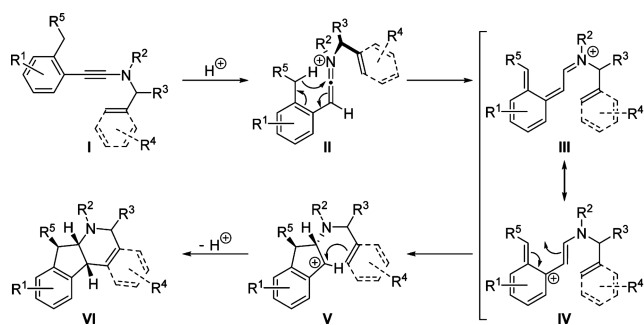
Scheme 3. Deuteration Studies



(deuterated at C_{6a} and C₇) was formed in a 77:23 ratio, showing that the hydrogen was preferentially transferred over the deuterium and also suggesting a kinetic isotopic effect for the shift of hydrogen.

Based on these experiments, and notably on the position of the deuterium atoms in **2a_D** and **2b_{D3}**, the mechanism shown in Scheme 4 can be proposed to rationalize our cationic polycyclization. The reaction would be initiated by protonation of the electron-rich alkyne of the starting ynamide **I** yielding a highly reactive *N*-tosyl- or *N*-acyl-keteniminium ion **II**. A [1,5]-sigmatropic hydrogen shift would then occur, generating conjugated iminium **III** (in resonance with the bis-allylic carbocationic form **IV**). The first cycle would then be formed by a 4π conrotatory electrocyclic yielding to **V** (in the manner of the Nazarov reaction), which is in accordance with the observed stereochemical outcome of the double diastereoselective polycyclization in which three stereocenters are formed (Scheme 1).¹⁷ A second cyclization between this intermediate benzylic carbocation **V** and the arene/alkene subunit would finally account for the formation of polycycle **VI** as well as its *cis* ring junction. Importantly, two key parameters can account for the success of this transformation. First, the use of a strong acid promoter such as TfOH or Tf₂NH is essential to avoid trapping the intermediate keteniminium ion by the conjugated base, i.e.,

Scheme 4. Proposed Mechanism for the Cationic Polycyclization



the weakly nucleophilic anions TfO^- or Tf_2N^- . Second, the nature and the high reactivity of this key *N*-acyl-keteniminium ion intermediate is also crucial since switching to a less reactive *N,N*-dialkyl-keteniminium ion,¹⁸ which can be generated from the corresponding amide under Ghosez's conditions,¹⁹ was shown to be detrimental and no cyclization occurred in this case.

In conclusion, we have developed a highly efficient keteniminium-initiated cationic polycyclization. This reaction, which just requires an acid as the promoter, affords a straightforward entry to nitrogen heterocycles possessing up to three contiguous stereocenters and seven fused cycles that can be obtained in a single operation from readily available ynamides. The broad availability of the starting ynamides implies that an extensive range of substituents can be selectively incorporated on the polycyclic products. In addition to its use in heterocyclic chemistry, medicinal chemistry, and natural product synthesis, this new polycyclization extends the chemistry of ynamides which were shown to be excellent building blocks for multiple, consecutive cationic transformations.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (12) The formation of an intermediate *N,O*-ketene acetal related to **4a_{OTf}** could be evidenced by NMR upon reacting an ynamide with triflic acid in CD_2Cl_2 at $-20\text{ }^\circ\text{C}$; see SI for details.

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