Cyclization Reactions

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Synthesis of Cyclic Alkenyl Triflates by a Cationic Cyclization Reaction and its Application in Biomimetic Polycyclizations and Synthesis of Terpenes

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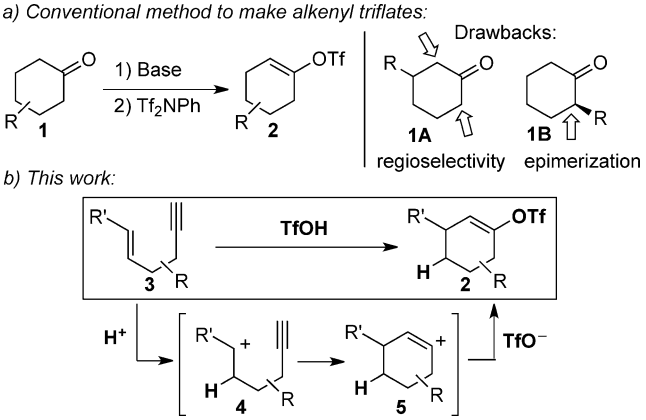
Dedicated to Professor José Barluenga on the occasion of his 75th birthday

Abstract: *Cyclic alkenyl triflates are useful intermediates in organic synthesis usually synthesized from ketones through a reaction involving enolization and trapping with a triflating agent. This sequence suffers from some stereochemical drawbacks owing to the basic conditions required. Herein, we describe a new acid-mediated cationic cyclization reaction of enyne derivatives (or alkynols) to access cyclic alkenyl triflates. This new atom-economical process is high yielding, scalable, technically very simple, proceeds without the need of any metallic reagent or catalyst, and more importantly, it complements and challenges conventional methodologies. We have also developed new biomimetic cationic cyclization reactions to yield interesting polycyclic compounds. As a demonstration of the potential of this method in the context of total synthesis, we have synthesized two terpenes: austrodoral and pallescensin A. Using the cationic cyclization in the key step of the synthetic routes allowed the synthesis of these natural products in a very simple, concise, scalable, and efficient way.*

Cyclic alkenyl triflates are ubiquitous intermediates in organic chemistry because they can be further derivatized using a plethora of cross-coupling reactions.[1–3] The protocol developed by McMurry and Scott more than forty years ago could be considered the only reliable strategy to synthesize these interesting compounds (Scheme 1 a).[4] This process involves the enolization of a cyclic ketone **1** by treatment with a base (usually lithium amides), followed by trapping of the ketoenolate with a triflating agent [usually *N*,*N*-bis(trifluoromethanesulfonyl)aniline]. A severe limitation of this sequence is found when both α- and α′-positions of the initial ketone are very similar (ketone **1A**). In this situation, complete control of the regiochemistry of the enolization reaction is basically impossible. Along with this regiochemical issue, enantiopure ketones possessing a stereogenic center at the α-position (ketone **1B**) suffer from further problems with base-promoted racemization. All these aspects call for the development of different approaches to the synthesis of these target molecules. Thus, we present a method for the synthesis of cyclic alkenyl triflates. This method is suitable for practical organic synthesis, and it has been utilized to prepare some relatively complex natural products.



Scheme 1. Conventional synthesis of cyclic alkenyl triflates and our approach.

For the development of this new reaction, we found inspiration in some excellent works on biomimetic cationic cyclizations of polyenyne derivatives developed some decades ago.[5] These works showed that alkynes could serve as the terminating group of polycyclization processes. We reasoned that this concept could be exploited in a much simpler way for the development of a method for the synthesis of cyclic alkenyl triflates. Thus, we assumed that enyne derivatives such as **3** should react with triflic acid (TfOH) to give the cation **4** (Scheme 1 b). This cation could be intercepted by the alkyne to furnish the alkenyl cation **5**. Finally, the reaction of the triflate anion with intermediate **5** should lead to the desired cyclic alkenyl triflates **2**. Surprisingly, this simple approach to cyclic alkenyl triflates, which could serve as a complementary method to the McMurry procedure, has not been developed to date.

Proof-of-concept was first established after a brief screen of solvents by mixing equimolecular amounts of enyne derivative **3a** and triflic acid in hexane and allowing the solution to stir at room temperature for just 30 min (Scheme 2 a). This reaction furnished the desired alkenyl triflate derivative **2a** with basically quantitative mass return (98% isolated yield). Interestingly, this is an example of a totally

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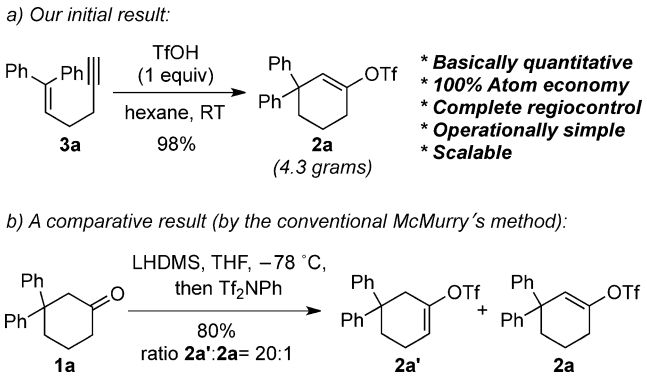
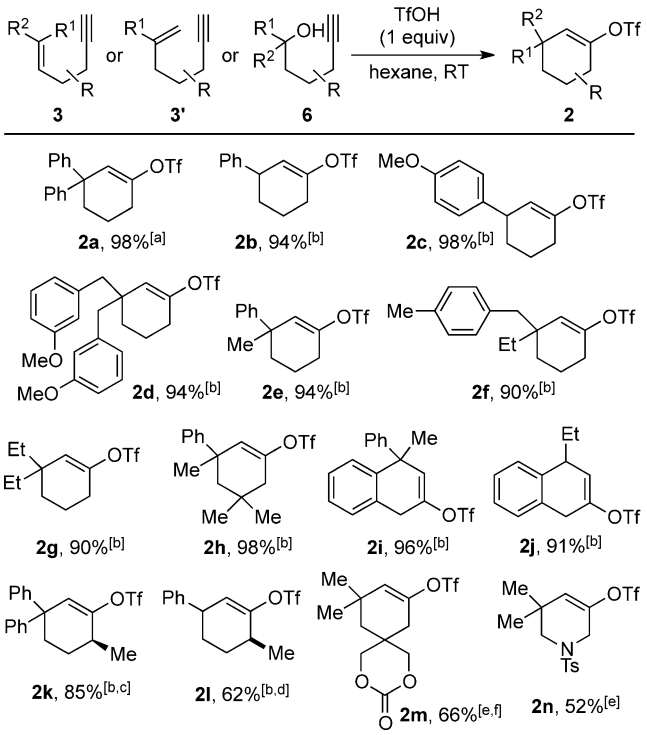


Scheme 2. Initial results and comparison with the conventional methodology.

efficient process because all reactants are converted into a unique final product, no by-products are formed, and the process does not require any catalyst or promoter (100% atom economy). The starting material is easily available, the final product does not require purification and the process can be performed on a gram scale without problems (4.3 grams of **2a** in one batch). It should be noted that compound **2a** was obtained as a single regioisomer and isomerization of the carbon-carbon double bond was not observed. Interestingly, this regiochemical control could not be achieved by following the conventional method (Scheme 2b). In fact, when we attempted the synthesis of triflate **2a** from 3,3-diphenylcyclohexanone **1a**, we observed the formation of a mixture of the two expected regioisomers **2a** and **2a′**, with the alkenyl triflate derivative **2a** being the very minor regioisomer (**2a**:**2a′** ratio = 1:20). This experiment not only served to demonstrate the utility of our reaction, but also highlighted its complementarity over the traditional methods for the synthesis of alkenyl triflates.

The scope of the cationic cyclization reaction was surveyed by synthesizing a series of cyclic alkenyl triflates **2** (Scheme 3). These reactions were usually performed with 1,5-enynes **3** or 1,6-enynes **3′** as starting materials. It should be noted that these enyne derivatives are normally synthesized from the corresponding alcohol **6** (Scheme 3) through a simple dehydration reaction. In this regard, we have observed that alkenyl triflates **2** can be directly accessed from alcohols **6** without isolating the corresponding enyne intermediates. When these alkynol derivatives **6** are used, formation of cations **4** (Scheme 1) suggests the release of a molecule of water. As shown in Scheme 3, the reaction allowed the synthesis of cyclohexenyl triflates **2** substituted at several positions. The reaction worked well for starting materials containing a terminal alkyne. In these cases, exclusive formation of the endocyclic alkene derivatives **2** was observed. However, when internal alkynes were reacted under the standard reaction conditions, formation of mixtures of different products, including *endo*- and exocyclic alkene derivatives, was observed. Moreover, we were not able to extend this method to the synthesis of other cycloalkenyl derivatives with different ring sizes. The reaction is also limited to substrates where the required acidic conditions do



Scheme 3. Synthesis of alkenyl triflate derivatives **2**. [a] Yield refers to the reaction performed from the corresponding enyne derivative **3**. [b] Yield referred to the reaction performed from the corresponding alcohol **6**. [c] Hexafluorobenzene as solvent and reflux for 1.5 h were the optimal conditions. The enantiomeric excess (90%) was preserved. [d] Product obtained as a 2:1 mixture of diastereoisomers from the corresponding alkynol (d.r. = 1:1). [e] Yield refers to the reaction performed from the corresponding enyne derivative **3′**. [f] Isolated as a 3:1 mixture of regioisomers.

not pose a major problem and/or substrates where formation of the corresponding cation intermediate **5** is relatively easy.

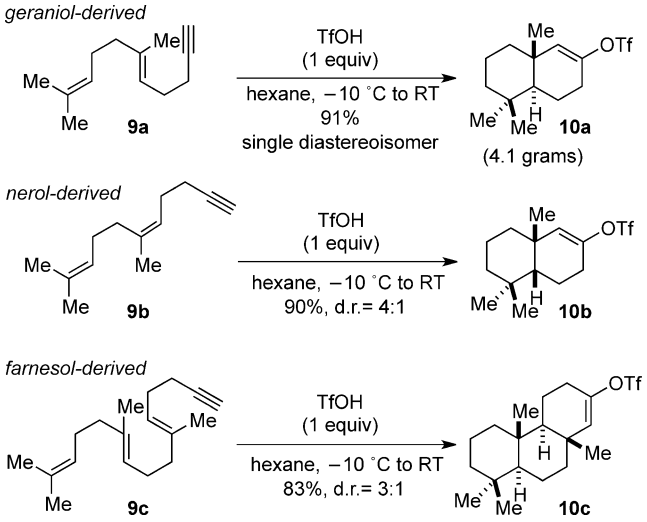
Some of the products obtained by this reaction are particularly interesting (Scheme 3). For example, the compound **2k** would be very difficult to isolate in enantiopure form by conventional methods from the corresponding ketone derivative **1** (Scheme 1). Thus, apart from the regiochemical problems (described above) associated with the enolization of this type of disubstituted ketones (Scheme 2b), it should be noted that, in this particular case, the starting ketone would contain an stereocenter in the α-position to a carbonyl group (**1B** in Scheme 1a), and then a base-promoted racemization would be expected. However, in our case, compound **2k** was accessed in high yield from the corresponding enantiopure alkynol derivative **6**.[6]

Considering the interest of dihydronaphthalene derivatives in medicinal chemistry,[7] our efficient synthesis of compounds **2i** and **2j** is also remarkable (Scheme 3). The presence of the triflate group in these molecules allows further functionalization through well-established carbon–carbon cross-coupling reactions, and then the straightforward synthesis of libraries of these interesting molecules.

Finally, this new reaction provides an alternative method to access heterocyclic compounds, such as the dihydropyridine **2n** (Scheme 3). Along with being important structural

motifs in total synthesis,[2b] these molecules are very interesting in medicinal chemistry, serving as precursors of promising therapeutic agents in the field of Alzheimer's and Parkinson's diseases.[8]

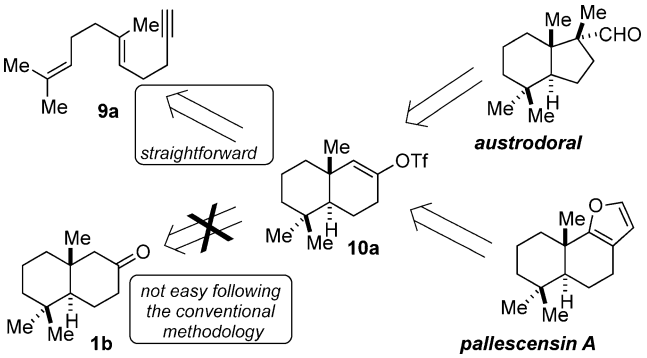
From a conceptual point of view, these results demonstrate not only the viability and efficiency of the proposed method, but also its complementarity over the conventional methods to access these types of products. At this point, we also felt that from the synthetic point of view this reaction had a high potential. In particular, we became interested in the extension of this simple reaction for the biomimetic polycyclization of acyclic terpene-derived polyenyne derivatives (Scheme 4). Interestingly, the polycyclic triflate-containing



Scheme 4. Biomimetic cyclizations of polyenyne derivatives **9** to generate terpenoids **10**.

products of these reactions could be further elaborated to easily synthesize some natural products. Thus, geraniol- and nerol-derived dienynes **9a,b**, and farnesol-derived trienyne **9c** were reacted under the reaction conditions described above. To our delight, the corresponding bi- and tricyclic meroterpenes **10a–c** were obtained in high yield.[9] To our knowledge, these are the first examples of cationic biomimetic cyclization reactions applied to the synthesis of alkenyl triflates. Moreover, these reactions could be performed on a gram scale by easily preparing 4.1 grams of **10a** as a single diastereoisomer in one batch without problems.

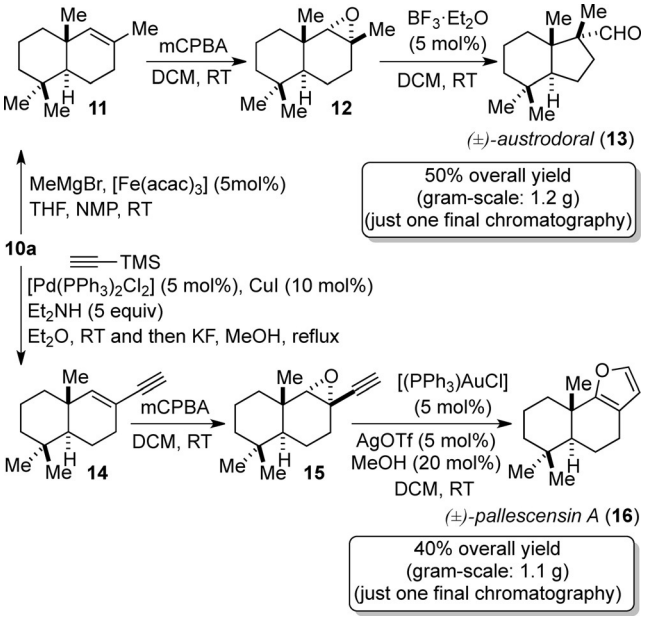
At this point, it should be noted that the method described here to access cyclic alkenyl triflates offers the opportunity to explore new strategies in the context of the total synthesis of natural products. As an illustration, we have applied this reaction as the key step in the synthesis of the terpenes austrodoral[10] and pallescensin A.[11] Note that the disconnection here considered through the intermediate **10a** (Scheme 5) would probably be discarded if molecule **10a** had to be constructed from ketone **1b** through conventional methods because of the regiochemical problems associated with the enolization of ketone **1b**. Thus, as previously shown in Scheme 2b, a mixture of two regioisomeric triflate



Scheme 5. Potential applications of the reaction in total synthesis.

derivatives (or mainly the opposite regioisomer) would be obtained from ketone **1b** following the conventional method. However, as shown in Scheme 4, following our method, compound **10a** is easily available at multigram scale and very high yield from geraniol-derived dienyne **9a**.

Thus, the retrosynthetic analysis above suggested we could easily synthesize both terpenes from the common intermediate **10a** (Scheme 6). For the synthesis of austro-



Scheme 6. Applications of the reaction in the synthesis of the terpenes austrodoral and pallescensin A.

doral, an initial cross-coupling reaction of this triflate derivative **10a** with methylmagnesium bromide under the iron-catalyzed conditions described by Fürstner and coworkers delivered the alkene **11**.[12] The crude product of this reaction was reacted with *meta*-chloroperbenzoic acid (mCPBA) to provide the expected epoxide **12** as a single diastereoisomer. Without purification, the crude product of this reaction was treated with a catalytic amount (5 mol%) of boron trifluoride diethyl ether complex ($BF_3{\cdot}Et_2O$). Under

these conditions, a Lewis acid-induced rearrangement of the epoxide occurred to cleanly deliver (±)-austrodoral (**13**) as a single diastereoisomer (3 steps from triflate **10a**, 50% global yield). Interestingly, the entire synthetic sequence could be performed on a gram scale (1.2 g of austrodoral in one batch) and without any purification of the intermediates (just a final column chromatography).

The synthesis of pallescensin A started with a Sonogashira-type cross-coupling reaction of **10a** with trimethylsilylacetylene to afford the enyne derivative **14**. Epoxidation of the carbon–carbon double bond with *meta*-chloroperbenzoic acid (mCPBA) led to the formation of epoxide **15** as a single diastereoisomer. Finally, the furan scaffold was easily obtained in one step following a slightly modified procedure of the gold-catalyzed cyclization reaction reported by Pale and co-workers.[13] Following this simple sequence, (±)-pallescensin A (**16**) was synthesized in just 3 steps from triflate **10a** (4 steps from dienyne derivative **9a**) in 40% global yield. Again, the entire sequence could be performed on a gram-scale (1.1 g of pallescensin A in one batch) and without any purification of the intermediates (just a final column chromatography).

Note that the shortness and efficiency of these syntheses was mainly due to the possibility of applying the new biomimetic polycyclization reaction presented here.

In summary, we have developed a new cationic cyclization reaction of enyne derivatives (or alkynols) to generate cyclic alkenyl triflates. This high-yielding reaction is technically very simple, cost effective, scalable, and it proceeds without the need of any metallic reagent or catalyst. In fact, when the reaction is performed from enyne derivatives the reaction is 100% atom economical. This reaction complements and challenges conventional methodologies, not only because of its simplicity, but also because the regiochemical and racemization problems associated with the existing strategies are not an issue with the method described here. We have further extended the concept to the development of biomimetic cationic cyclization reactions of polyenyne derivatives to yield interesting triflate-containing polycyclic compounds. Moreover, this new reaction opens the door to explore innovative approaches in the context of total synthesis of natural products. As a demonstration, we have applied the reaction in the synthesis of two simple terpenes: austrodoral and pallescensin A. The new approach allowed the syntheses of these natural products in very simple, short, and efficient ways. Other non-conventional routes to challenging natural products are actively being investigated in our laboratories using this process.

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