CJC Chinese Journal of Chemistry
中国化学 - An International Journal

Check for updates

Accepted Article

Title: Awakening Sleeping Beauty: Vinyl Esters for Macrolactonization

Authors: Qi Song, Luyao Kong, Lili Zhu, Ran Hong,* and Sha-Hua Huang*

This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2020**, *38,* 10.1002/cjoc.202000571.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.202000571.

WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6
mc.manuscriptcentral.com/cjoc
www.cjc.wiley-vch.de

Emerging Topic

acetylene, amide bond, macrolactonization, vinyl ester, ynamide

CJC Chinese Journal of Chemistry 中国化学 - An International Journal

Awakening Sleeping Beauty: Vinyl Esters for Macrolactonization

Qi Song,[a] Luyao Kong,[b] Lili Zhu,[b] Ran Hong,*[,b] and Sha-Hua Huang*[a,b]

[a] School of Environmental and Chemical Engineering, Shanghai Institute of Technology, 100 Haiquan Road, Shanghai 201418, PR China
[b] CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry (CAS), 345 Lingling Road, Shanghai 200032; University of Chinese Academy of Sciences, 19A Yuquan Road, Beijing 100049, PR China

Cite this paper: *Chin. J. Chem.* **2019**, *37*, XXX—XXX. **DOI: 10.1002/cjoc.201900XXX**

Macrolactones play a critical role in pharmaceuticals and agrochemicals. Numerous efforts have been devoted to developing synthetic methods for them. We highlighted a recent progress for building macrocycles (≥ 12-membered) via bench-stable vinyl ester (VE) intermediates, which have been underdeveloped for half century. These methods are mild and racemization-free and warrant wide recognition in macrocyclization as the key step in complex molecule synthesis.

Background

Macrolactones are essential in pharmaceuticals and agrochemicals bearing unique bioactivities. Tremendous efforts have been devoted to method development for the construction of an array of macrolactones. [1] In the field of natural product synthesis, macrolactonization has constituted an inspiring playground for synthesis practitioners over the past half century. Many efficient methods, such as Mukaiyama, Corey-Nicolaou, and Yamaguchi macrolactonization, and various modifications have achieved recognition in textbooks (Figure 1). The general principle is to prepare the activated form of an acid through a pyridinium salt, thioester or mixed anhydride. To expedite the following ring-forming step, a large excess of reagents, such as silver salts or additional bases (i.e., *N*,*N*-dimethyl aminopyridine), and harsh conditions (reflux in organic solvents) were generally adopted to convert the acid derivatives into esters. However, these methods were always plagued by side reactions, including the epimerization of adjacent stereocenters or the isomerization of alkenes. It is even more challenging when a protection strategy must be employed before selective macrolactonization due to the presence of competitive functional groups in the substrate.

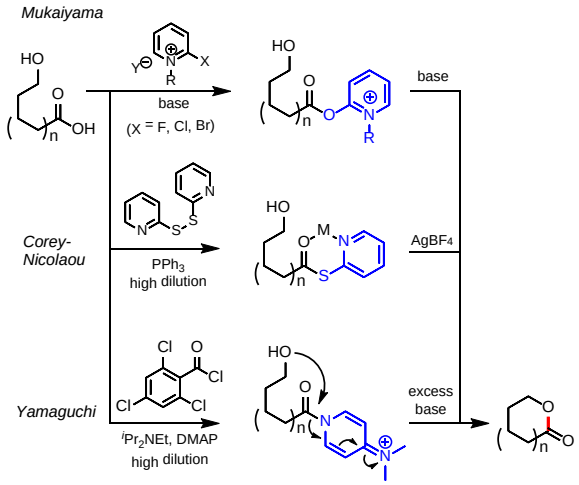
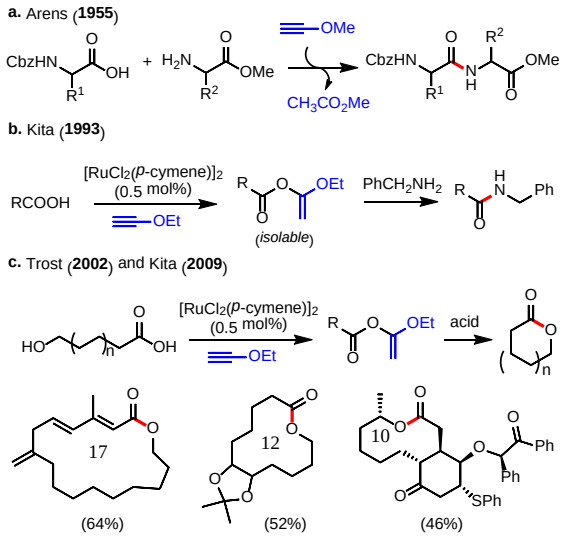


Figure 1 Selected approaches for macrolactonization.

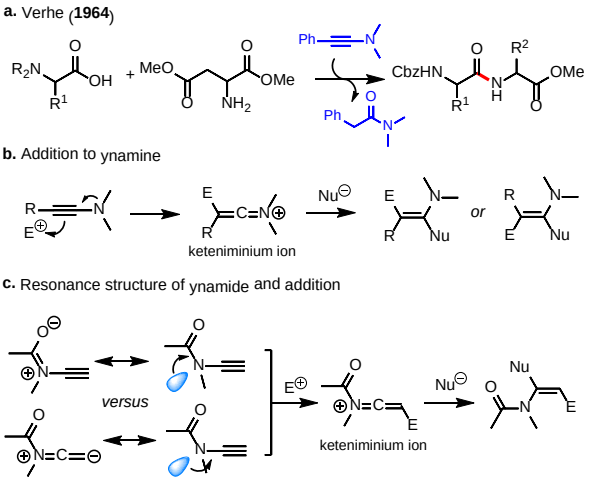
Retrospective and Recent Advances

In 1955, Arens first introduced methoxyacetylene (MW: 50) to activate a carboxylic acid and further reacted it with an amine to form an amide bond. This method was demonstrated in dipeptide synthesis with excellent yield (Scheme 1a). [2] However, the proposed alkoxyvinyl esters (AVEs) were not convincingly adapted to organic synthesis until Kita and coworkers [3] reported a mild and practical ruthenium complex-catalyzed protocol for readily preparing various AVEs (Scheme 1b) which was adapted by Trost and Chisholm to prepare various large lactone rings in an intramolecular manner (Scheme 1c).[4] AVEs are generally isolable and useful for esterification under mild conditions. The mild acid-catalyzed conditions proved to be compatible with the epimerizable stereogenic centers and reduced the tendency of the double bond to isomerize when classical Yamaguchi esterification was applied. The effectiveness of the Trost-Kita method has been validated in the total syntheses of several complex bioactive macrolactones.[5]



Scheme 1 AVE-based macrolactonization: (a) Initial discovery for the amide bond formation; (b) Ru-catalyzed addition of ethoxyacetylene; (c) development of macrolactonization and selected examples of macrolactones.

The low boiling point of ethoxyacetylene (b.p. 50 °C) and the use of a transition metal catalyst might lead to limitations for some substrates with low reactivity toward the addition of an alkyne. Therefore, a more reactive and facile operation for forming an activated acid derivative is still in high demand. In parallel with the exploration of alkoxyacetylenes in peptide synthesis, ynamines were also introduced to the community as a highly reactive species in organic synthesis. The history of their discovery can be traced back to 1892 when several research groups tried to synthesize ynamines. No success was achieved until Zaugg and coworkers reported the first preparation of an ynamine.[6] Although the report was questioned over the next five years, Viehe devised a representative method for synthesizing ynamines and revealed some fascinating properties, including a dehydration process toward the formation of amide bonds in the following landmark paper (Scheme 2a).[7] Viehe's seminal discovery has traversed a half century and inaugurated a golden era of ynamine chemistry that has lasted to the present day.

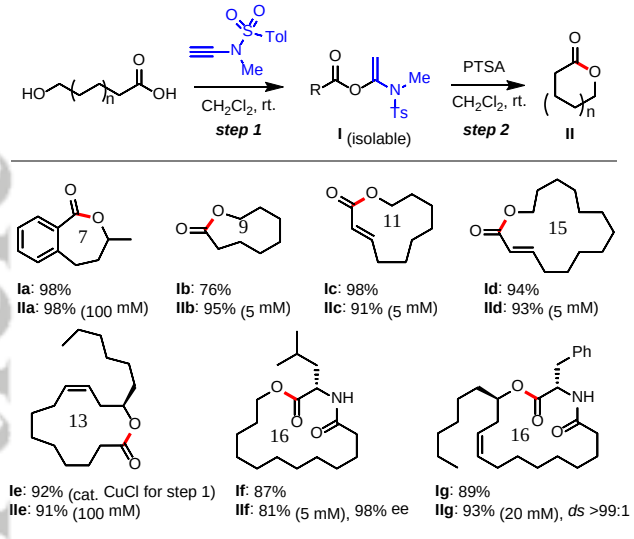


Scheme 2 Ynamines versus ynamides: : (a) Initial discovery for the amide bond formation; (b) addition to ynamine; (c) resonance structure of ynamide.

Like alkoxyacetylenes and enamines, the β-carbon atom of ynamines is also nucleophilic and capable of reacting with various electrophiles, as indicated by the resonance structures shown in Scheme 2b. However, ynamines are very sensitive to hydrolysis and thus difficult to be handled in general, which, more detrimentally, hampers the development of ynamine chemistry. Gais and coworkers proposed a "push-pull" approach via an introduction of acyl group on the terminal alkyne and the resulting ynamine was revealed to be valuable for the formation of macrolactone ring.[8] By introducing an electron-withdrawing group (such as a carbonyl or sulfonyl) to the nitrogen atom, the ability to donate the nitrogen lone pair to the alkynyl motif is greatly attenuated through resonance delocalization into carbonyl oxygen (Scheme 2c). After the electrophilic addition, the corresponding keteniminium ion would be readily trapped by incoming nucleophiles. Therefore, these electron-deficient ynamides not only have stability superior to traditional ynamines but also offer a good balance between reactivity and stability.

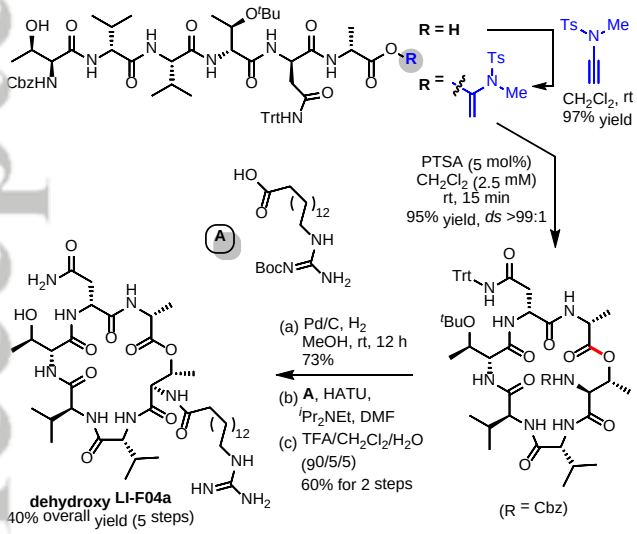
The application of ynamides in the process of lactonization has been underdeveloped until a recent exciting report contributed by Zhao and coworkers (Scheme 3). [9] In contrast to the reactivities of the intermolecular variants, the reactivities of the acid and alcohol should be differentiated by the addition of an ynamide. A bench-stable ynamide reagent, namely, *N*-methyl ynetoluenesulfonamide (MYTsA, MW: 209), was derived by coupling tosylamide with dichloroethylene on a decagram scale. Thankfully, the seco acid preferentially reacted with the ynamide to form α-acyloxyenamide at ambient temperature due to the acidity of the carboxylic acid. The corresponding vinyl ester was stable for isolation and characterization. Following acid treatment (i.e., para-toluenesulfonic acid) in the same media, lactonization with the alcohol at the other end of the linear chain proceeded smoothly to give various medium and large rings in excellent yield. This two-step procedure could be performed in one pot without extracting the intermediate. Notably, the concentration for lactoni-

zation was generally 5~100 mM, which is essentially beneficial for synthetic usage, and the general concept of using an extremely diluted solution (~1 mM in most cases) was indispensable for macrolactonization.



Scheme 3 Substrate scope (selected examples; ds: diastereoselectivity).

Notably, a complex cyclic peptide bearing a lactone motif was constructed in a highly efficient manner via this innovative method. Despite seven secondary amides, the free acid at the C-terminus of a hexapeptide was first reacted with an ynamide (MYTsA) to produce an isolable *N*,*O*-ketene (vinyl ester) in 97% yield (Scheme 4). The following acid-catalyzed lactonization was



Scheme 4 Synthesis of dihydroxy LI-F04a via ynamide-based macrolactonization.

extremely successful, giving the requisite cyclodepsipeptide in excellent yield (95%) without appreciable epimerization (ds >99/1) of the C-terminal amino acid. Additionally, the Zhao group employed other conventional condensation methods to reproduce the desired macrocycle, and all conditions resulted in low yields along with severe epimerization and diolide contaminants. The LI-F family of macrolides produced by *Bacillus* (*Paenibacillus*) species exhibits significant antifungal activity. This mild and racemization-free protocol was also applied to peptide synthesis and a broad substrate scope was demonstrated (see the Supporting Materials for detailed citations). Ynamide-mediated macrocyclization to produce these complex substances paves an avenue for future structure-activity relationship studies of antimicrobial cyclopeptides.

Potential and Challenges

The renaissance of two half-century-old acyl donors to address current challenging problems reminds us that the reactivities of specific functional groups are still waiting to be explored. Today, novel reactions always rely on uncovering new reactivities to serve new objectives. Since the first discovery and initial demonstration of the potential of these vinyl esters-based methods in organic synthesis in the 1950s, their unique features have been discovered and used to address some of the most challenging problems. Interestingly, the original synthesis method of heteroatom-substituted acetylenes was invented for amide bond formation in peptide synthesis, demonstrating the long-term objective of organic synthesis even today. Efficient syntheses of peptides with increasingly higher molecular weights (i.e., >100 amino acid residues) and proteins are still in high demand. It must be considered that the potential by-product alkyl ester (RCH_2CO_2Et) derived from an alkoxyacetylene may induce the acylation of any alcohol or amine that is designed to only couple with reactive vinyl esters. Therefore, the low reactivity of an amide ($RCH_2CO_2NR'_2$) derived from an ynamine (ynamide) may be beneficial for inhibiting this type of side reaction.

Macrocyclization via vinyl ester intermediates is apparently advantageous because a low molecular weight ester or amide is the only remnant of the coupling reagent and is easy to deplete. In the past two decades, the VE-based methodology has occasionally been adapted and has sometimes been the last resort for complex molecule synthesis.[4] The neutral conditions for the addition of acetylene in the first step and the mild acid promotor used in the second step of the cyclization are particularly valuable for substrates bearing acid- or base-sensitive functional groups. On the other hand, macrocyclization is always designed for late stage of synthesis and is thus essential for the efficiency of the overall synthetic sequence. The Trost-Kita and Zhao methods are complementary to other macrolactonization methods and thus have great potential for future applications. However, their utility in macrolactonization must be exhaustively pursued to define the scope and functional tolerance as well as the limitations. The vast applications of macrolactones in various disciplines, such as materials science, chemical biology, and medicines, require that the enforced reactivities of functional groups be revealed to further establish new parameters for improving the current methods.

Acknowledgements

We are grateful for the financial support from the Drug Innovation Major Project (2018ZX09711001-005), the Program of Shanghai Academic Research Leader (20XD1404700), the Key Research Program of Frontier Sciences (QYZDY-SSWSLH026), and the Strategic Priority Research Program (XDB20000000) of the Chinese Academy of Sciences.

Supporting Materials

A full list of critical references related to this topic is attached in the Supporting Materials online.

References

[1] Parenty, A.; Moreau, X.; Niel, G.; Campagne, J. M. Update 1 of: Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, PR1–PR40.
[2] Arens, J. F. The Chemistry of Acetylenic Ethers XIII. Acetylenic Ethers as Reagents for the Preparation of Amides. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 769–770.
[3] Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. A Novel Efficient Synthesis of 1-Ethoxyvinyl Esters and Their Use in Acylation of Amines and Alcohols: Synthesis of Water-Soluble Oxaunomycin Derivatives. *Synlett* **1993**, 273–274.
[4] Trost, B. M.; Chisholm, J. D. An Acid-Catalyzed Macrolactonization Protocol. *Org. Lett.* **2002**, *4*, 3743–3745.
[5] Ohba, Y.; Takatsuji, M.; Nakahara, K.; Fujioka, H.; Kita, Y. A Highly Efficient Macrolactonization Method via Ethoxyvinyl Ester. *Chem.–Eur. J.* **2009**, *15*, 3526–3537.
[6] Zaugg, H. E.; Swett, L. R.; Stone, G. R. An Unusual Reaction of Propargyl Bromide. *J. Org. Chem.* **1958**, *23*, 1389–1390.
[7] Viehe, H. G.; Reinstein, N. Addition Reactions of Alkynylamines. *Angew. Chem. Int. Ed.* **1964**, *3*, 581.
[8] Gais, H. J. Lactonisierung von Makrolid-secosäuren mit "Push-Pull Acetylenen". *Tetrahedron Lett.* **1984**, *25*, 273–276.
[9] Yang, M.; Wang, X.; Zhao, J. *ACS Catal.* **2020**, *10*, 5230–5235.

Manuscript received: XXXX, 2019
Manuscript revised: XXXX, 2019
Manuscript accepted: XXXX, 2019
Accepted manuscript online: XXXX, 2019
Version of record online: XXXX, 2019

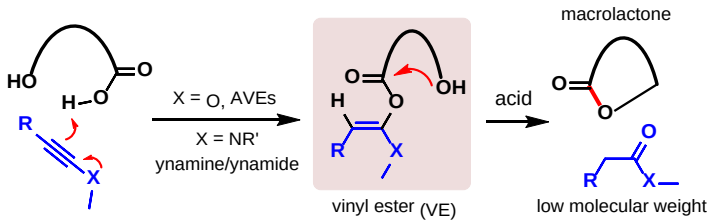
Entry for the Table of Contents

Page No.

Awakening Sleeping Beauty: Vinyl Esters for Macrolactonization

Qi Song, Luyao Kong, Lili Zhu, Ran Hong*, and Sha-Hua Huang*

Max. Table height 6 cm



The renaissance of two half-century-old acyl donors, derived from AVEs and ynamines or ynamides, reminds us that the reactivities of specific functional groups are still waiting to be explored. The macrocycliztion via the vinyl ester intermediates is mild, racemization-free, and an ease of work-up due to readily depletion of ester or amide derived from the coupling reagent. This novel approach is complementary to other macrolactonization methods and thus are of great expectation to future application.

