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Nazarov Cyclization Reaction: Challenges and Opportunities

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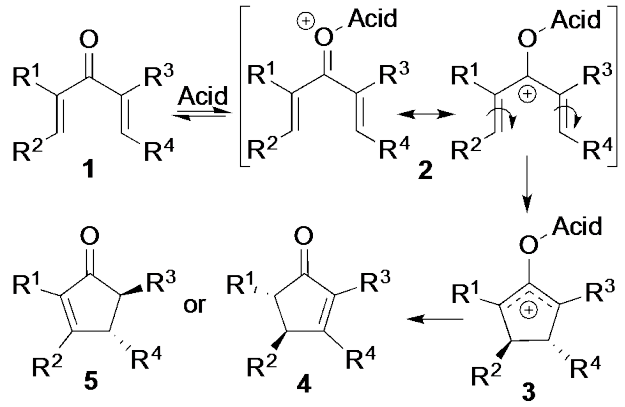
The Nazarov cyclization [1-3] is a 4π electrocyclization used for the synthesis of cyclopentenones. It is a powerful reaction for the assembly of five membered rings that are part of many biologically active natural products. Increasing interest in the total synthesis of natural products with five-membered carbocycles has resulted in exploration of the versatility, generality, and applicability of the Nazarov cyclization [4-17].

The mechanism of a typical Nazarov cyclization is shown in Scheme 1. The reaction is initiated by the reversible coordination of either a Brønsted or a Lewis acid to the dienone **1** to form a pentadienyl cation **2**. The key step of the reaction mechanism involves a cationic 4 π electrocyclization, which yields an oxyallyl cation **3**. The trans relationship between substituents R^2 and R^4 in **3** is a result of the conrotatory cyclization. This step is usually followed by a loss of proton from cation **3**, to give either cyclopentenone **4** or **5**, or a mixture of the two. The trans stereochemistry between R^1 and R^2 in **4** or between R^3 and R^4 in **5** is due to the formation of the thermodynamically more stable products.

The diastereospecificity of the reaction is a result of orbital symmetry rules, which is due to an antarafacial overlap of the two cyclization termini in the transition state, leading to stereospecific conrotatory cyclization. The orbital reorganization yields new stereocenters in the oxyallyl cation **3**, which can be preserved in the pentacyclic products (**4** and **5**). These fundamental characteristics have generated interest in the improvement of the reaction and it has recently attracted substantial attention in the field of organic synthesis for its potential to produce synthetically useful cyclopentenones.

Although the Nazarov cyclization was first reported in 1941, it has been underutilized synthetically due to several factors, such as drastic reaction conditions (concentrated protic acid and high temperature) and typical formation of regioisomeric product mixtures. The reaction has been extensively studied over the past decade to overcome these synthetic problems. The introduction of Lewis acids as cyclization initiators in aprotic media as well as the innovation of 'directed Nazarov cyclizations' employing *β*-silyl- or *β* -stannyl-substituted dienones dramatically increased the synthetic utility of this reaction. It has been successfully used as the key step in the synthesis of a variety of natural products and bioactive molecules possessing five membered carbocycles. New catalysts have been developed to cyclize substrates that were unreactive with other known catalysts. Tandem reaction sequences were developed to rapidly form complex functionalized cyclopentenones.



Scheme 1: The mechanism of the Nazarov cyclization.

Despite these improvements, some of the current limitations of the Nazarov cyclization can be summarized as follows:

1) Use of super-stoichiometric or stoichiometric amounts of promoters is often required despite many catalytic conditions described.

2) Catalytic Nazarov reaction is still unsuccessful for some unactivated dienones.

3) Asymmetric catalysis has been limited to predominantly very reactive substrates.

4) Slow catalyst turnovers and product inhibition are some of the challenges in catalytic asymmetric induction.

Currently, a general catalytic asymmetric Nazarov reaction has not been described.

Towards developing a more general and versatile reaction, the following problems must be addressed:

1) Avoid super-stoichiometric strong acids used to suppress undesired competing processes, such as Wagner/Meerwein rearrangements.

2) For an enantioselective Nazarov cyclization, control the absolute stereochemistry of the product by controlling the absolute sense of conrotation, or the torquoselectivity: the stereochemistry indicated for **3** is a consequence of clockwise conrotation of **2**, viewed from the bottom of the structure as it is shown in Scheme 1. The counter clockwise conrotation of **2** will result in the formation of the enantiomer of **3**.

3) Avoid the production of isomeric mixtures of cyclopentenones by directing the proton loss from **3** so that it does not take place arbitrarily in the termination step.

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The Nazarov cyclization is potentially a very useful synthetic method for the construction of multi-substituted cyclopentenones, with excellent stereochemical control on at least two adjacent ring carbon atoms. Developing a general catalytic asymmetric Nazarov reaction still remains a challenge. As the limitations and the synthetic problems associated with this reaction are addressed, the versatility, generality, and applicability of the Nazarov cyclization will further increase.

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