Nazarov Cyclization Reaction: Challenges and Opportunities

Tülay A Ateşin*

Department of Chemistry, The University of Texas-Pan American, 1201 W University Drive, Edinburg, TX 78539, USA

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 

![Scheme 1: The mechanism of the Nazarov cyclization.](image)

with five-membered carbocycles. New catalysts have been developed to cyclize substrates 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.

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

1) Use of super-stoichiometric strong acids used to suppress undesired competing processes, such as Wagner/Meerwein rearrangements.
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 torque selectivity: 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.
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.

References