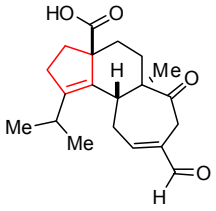
THE NAZAROV CYCLIZATION: DEVELOPMENT AND APPLICATIONS

Reported by Jenna Klubnick September 24, 2009

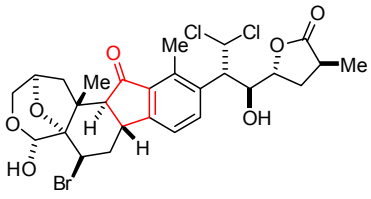
INTRODUCTION

The classic Nazarov cyclization is a Lewis or Brønsted acid catalyzed 4-π electrocyclic ring closure of a divinyl ketone to a 2-cyclopentenone. Cyclopentenones and five-membered carbocycles are common structural motifs in biologically active compounds. Consequently, a number of methods have been developed to access these moieties.[1] Recent modifications to the Nazarov cyclization have made this reaction a powerful tool for the construction of these important structural themes. For example, the Nazarov cyclization was essential to the syntheses of the three biologically active natural products shown in Scheme 1.[2a-c]

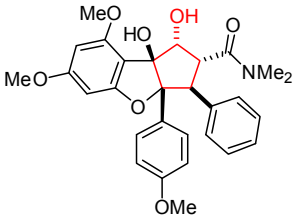
Scheme 1. Natural Products Synthesized *via* the Nazarov Cyclization



(-) -Scabronine G



Nakiterpiosin

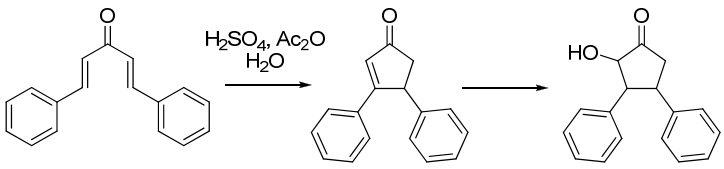


(±)-Rocaglamide

DISCOVERY AND ELUCIDATION OF MECHANISM

The history of the Nazarov cyclization dates back more than a century. In 1903, David Vorlander reported a cyclization of dibenzylideneacetone upon treatment with acetic anhydride and sulfuric acid.[3] He was unable to determine the structure the product, but it was later identified as the

Scheme 2. Cyclization Observed by D. Vorlander

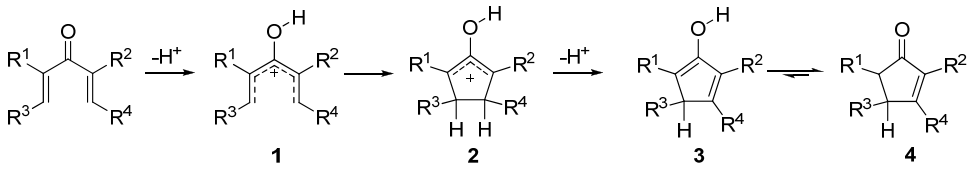


cyclic ketol by Shoppee and coworkers (Scheme 2).[4] In the context of his work on the hydration of dieneynes, C. S. Marvel also noted a cyclization but was unable to correctly identify the structure of the product.[5] Similar hydration studies were what led Igor Nazarov to the discovery of the Nazarov cyclization in 1942.[6] During his work on mercuric salt and acid-catalyzed formation of allyl vinyl ketones from divinyl acetylenes, Nazarov observed the spontaneous cyclization of the intermediate allyl vinyl ketones under the acidic conditions to yield 2-cyclopentenones. Nazarov published extensively on the mechanism of the cyclization, after which other chemists began to refer to the reaction by his name.

In 1953, Igor Nazarov he established that vinyl allyl ketones isomerize under the reaction conditions to become divinyl ketones which then undergo the cyclization to 2-cyclopentenones.[7] A 1952 report by Braude and Coles suggested that the purpose of the acid is to protonate on of the sites of unsaturation, leading to a carbocation intermediate.[8] However, it was not until the 1967 study by Woodward that the pericyclic nature of the Nazarov cyclization was revealed.[9] Armed with new orbital symmetry rules and the suspicion that the cyclization might be a 4-π electrocyclic ring closure of a pentadienyl cation, he deduced the reaction mechanism through careful examination of the stereochemical outcomes.

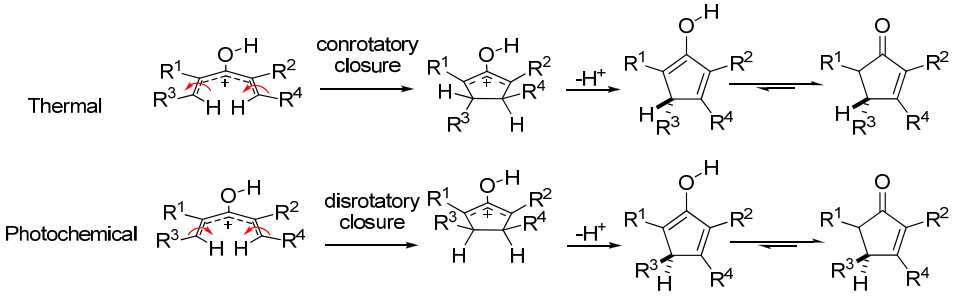
The accepted mechanism of the Nazarov cyclization is as follows (Scheme 3):[10] Coordination of the divinyl ketone to a Lewis or Brønsted acid yields pentadienyl cation (**1**). 4-π Electrocyclic ring closure of the pentadienyl cation yields oxallyl cation (**2**), which subsequently undergoes E_1 elimination to yield enone (**3**). This enone tautomerizes to give cyclopentenone (**4**).

Scheme 3. Mechanism of the Nazarov cyclization



Woodward found the Nazarov to be in agreement with his rules for the conservation of orbital symmetry pertaining to cyclization4-π electrocyclic ring closures – under thermal conditions the ring closure was conrotatory and under photochemical conditions the closure was disrotatory. Further confirmation was provided by Shoppe and coworkers in their study of the closure of αα′-dimethyldibenzylideneacetone. Through deuterium labeling and an NMR analysis of the stereochemical outcome they confirmed that the cyclization occurred in a conrotatory fashion under thermal conditions (Scheme 4).[11]

Scheme 4. Stereochemical outcome of the Nazarov Cyclization



REACTIVITY

Characteristics

A wide variety of substrates are susceptible to the Nazarov cyclization. Biscyclic, monocyclic, and acyclic precursors with varying substitution patterns are all amenable to cyclization. In addition to traditional divinyl ketones, allene vinyl ketones, aryl vinyl ketones, and allyl vinyl ketones can undergo Nazarov cyclizations. Heteroatom and heterocyclic substituents are also well tolerated.[10,12]

Reaction rate is thought to be largely controlled by the stabilization of the two carbocation intermediates (Scheme 3).[13] It is thought that the electrocyclization is the slow step, so substituents that stabilize the pentadienyl intermediate **1** are predicted to slow the reaction rate. Substitutents that stabilize the oxallyl cation intermediate **2** are believed to speed the reaction rate due to the lowering of the transition state energy as the reaction progresses from the pentadienyl cation intermediate to the oxallyl cation.

Traditionally, the reaction conditions of the Nazarov cyclization have been somewhat harsh. Usually one or more equivalent of a strong Lewis acid ($AlCl_3$, $BF_3{\cdot}OEt_2$, $TiCl_4$) or Brønsted acid (HCl, H_2SO_4, H_3PO_4) is needed to promote the reaction. The cyclization can proceed in a wide variety of solvents, such as dichloromethane, toluene, THF, and methanol. Typically, reactions are conducted at room temperature or below, but it is not uncommon to see elevated temperatures.[12]

Recent Developments

Recently, there have been a number of approaches to combat the requirement of a full equivalent of acid to promote the Nazarov cyclization. The Frontier group reported a method of subtrate conrol wherein the divinyl ketone is substituted with an electron-donating group and an electron-withdrawing group.[14] It is proposed that the electronic difference creates a “vinyl nucleophile” and a “vinyl

electrophile" which allows the reaction to proceed with 2 mol % copper triflate. The major drawback to this method is that it demands product substitution that may be undesirable.

The Frontier group also reported the catalysis of a tandem Nazarov cyclization-Michael addition of β-ketoesters with nitroalkenes.[15] The reaction proceeds with 4 mol % of an iridium catalyst. This system was also shown to catalyze a simple Nazarov cyclization in the Frontier group's total synthesis of (±)-merrilactone.[16]

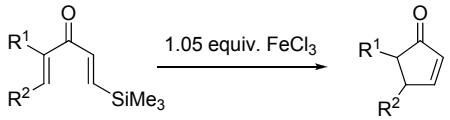
The most recent development in this area is the use of 5 mol % $Fe(ClO_4)_3{\cdot}Al_2O_3$ to promote Nazarov cyclizations of pyrrole substituted β-ketoesters. Unfortunately, the substrate scope is so far limited to these highly specific substrates.[17]

SITE SELECTIVITY

The issue of site selectivity has been another issue in the development of the Nazarov cyclization. Elimination by deprotonation of oxallyl **2** can take place at the β or β′ position, leading to two constitutional isomers. Elimination usually occurs according to Zaytsev's rule: the more highly substituted alkene, which is thermodynamically more stable, will be formed.[18] Product mixtures of constitutional isomers are usually the result of uncontrolled Nazarov cyclization.

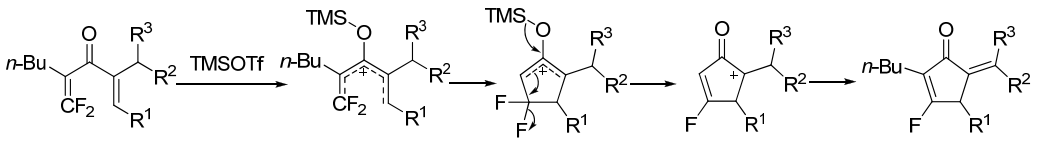
In 1982 Denmark and coworkers presented a method for elimination site selectivity.[18] They theorized that carbocation stabilization through the β-silicon effect could override Zaytsev's rule. A series of β-silyl divinyl ketones were cyclized to yield exclusively the less thermodynamically stable product (Scheme 5). The trimethyl silyl group is eliminated as an electrofuge, so the silicon-directed Nazarov cyclization is traceless.

Scheme 5. Silicon-Directed Nazarov Cyclization



The tin-directed Nazarov cyclization was introduced in 1986 by C. R. Johnson.[19] The mechanism is proposed to work analogously to the silicon-directed Nazarov cyclization. Unfortunately, the toxicity of stannanes makes this method of control unattractive. The fluorine-directed Nazarov

Scheme 6. Fluorine-Directed Nazarov Cyclization

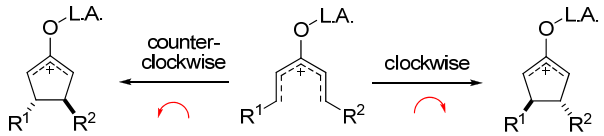


cyclization was introduced in 1995 by Ichikawa and coworkers, and is thought to work by the mechanism presented in Scheme 6.[20] The major drawback to this method of control is the retention of fluorine in the product. Thus, the silicon-directed Nazarov cyclization remains the state-of-the-art method of controlling the placement of the double bond in the product.

STEREOSELECTIVITY

Torquoselectivity is control of the direction of ring closure in a conrotatory or disrotatory mechanism (Scheme 7). The direction of rotation determines the stereochemistry at the newly formed

Scheme 7. Torquoselectivity

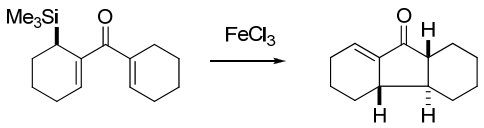


stereogenic center and thus is of great importance. There have been a number of developments in the control of torquoselectivity in recent years. The three main ways of controlling torquoselectivity are chiral auxiliary control, substrate control, and chiral Lewis Acids, the former two of which will be discussed here.

Substrate Control

A 1990 report from the Denmark group indicated that the presence of a stereodefined trimethyl silyl substituent in the β-position could exhibit remarkable torquoselectivity (Scheme 8).[21] The proposed stereocontrolling element is a stereoelectronic interaction between the silicon-carbon bond and the tau orbitals of the vinyl group that promote cyclization in one direction. This interaction is proposed

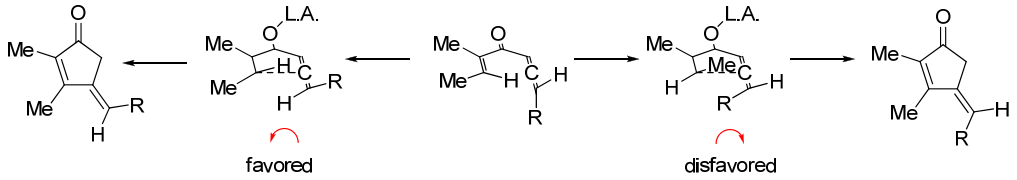
Scheme 8. Torquoselective Silicon-Directed Nazarov Cyclization



to increase the orbital coefficient on the same face as the silyl group, encouraging the other vinyl group (acting as the electrophile) to attack from that face. Again, the trimethyl silyl group leaves as an electrofuge, so the stereocontrolling element is traceless.

In 1999, Tius and coworkers showed that stereodefined vinyl allenyl ketones control torquselectivity through steric interactions of the two terminal substituents.[22] A vinyl allenyl ketone undergoes the Nazarov cyclization to yield a 2-cyclopentenone with an exocyclic double bond (Scheme 9). The size of the substituent on the allene is directly related to the degree of torquselectivity – the rotation will take place in the direction that minimizes the steric interacton between the β and γ substituents.

Scheme 9. Allene Substrate Controlled Torquoselectivity.

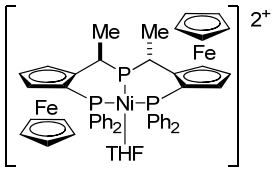


Chiral Lewis Acids

A 2003 report by Aggarwal describes the use of copper bisoxazoline complexs to control torquoselectivity.[23] The direction of rotation is induced by a steric interaction between one of the substituents on the divinyl ketone and the bisoxazoline ligand. As such, the degree of stereocontrol is largely dependent on the size of the subtituent. It is proposed that two-point binding of the substrate to the copper is required, so the only substrates reported are β-keto esters. Unfortunately, this method requires one equivalent of the copper complex, and the enantiomeric excesses are variable at 1-86%.

In 2008 the Togni group reported the substoichiometric enantioselective catalysis of Nazarov cyclizations by the use of Ni(II) Pigiphos complexes (Scheme 10).[24] However, the reaction time is very

Scheme 10. Ni(II) Pigiphos



slow, requiring days if 10% catalyst is used, and the substrate scope appears to be limited to β-keto esters. Although the yields are variable (0-96%) and the enantiomeric excesses are hardly better (45-

86%), this is the first report of substoichiometric enatioselective Lewis acid ctalysis for the Nazarov cyclization.

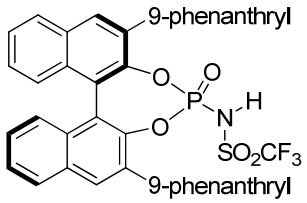
Face Selectivity

In addition to torquoselectivity, the protonation during tautomerization has been studied recently. The creation of this stereogenic center is usually substrate controlled, but there have been two reports reporting the use of chiral acids to control the creation of this stereogenic center as well.

The Trauner group reported in 2004 a scandium pybox system that was able to promote Nazarov cyclizations with 10 mol %.[25] There is no control of torquoselectivity claimed; the only stereocontrolling element is the face selectivity of the protonation. The enantiomeric excesses were generally good, ranging from 76 to 97%. The yields were a variable (65-94%), but generally good. Again, two point binding is required, so the reported substrate scope was limited to cyclic 2-alkoxy dienones.

A report from the Rueping group in 2007 describes the use of a chiral phorphoramide Brønsted acid as a means to control enantioselectivity (Scheme 11).[26] This report claims both control of torquoselectivity and face-selectivity, but the control of torquoselectivity appears to be low in

Scheme 11. Chiral Brønsted Acid



comparison to the face-selective protonation. Evidence for this trend is provided by low diastereomeric ratios (about 3:1) but high enantiomeric excesses (87-98%) of each of the diastereomers. The authors propose a contact ion pair to control both aspects of stereocontrol, but more evidence is needed to support this claim.

CONCLUSION AND FUTURE DIRECTIONS

The Nazarov cyclization is a useful tool for the generation of cyclopentenones, especially with the advances in stereoselectivity in the recent years. However, there is still a lot of work that remains to be done. Except for in limited cases presented earlier, most Nazarov cyclizations still require a full equivalent of Lewis or Brønsted acid. Also, there is still no general and widely applicable method for

control of torquoselectivity and face selective protonation. Finally, no methods exist for control of stereochemistry in the photochemically activated Nazarov cyclization. Work in the field of the Nazarov cyclization is ongoing and developments in the next few years can be expected.

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