Conquering the Challenges of the Nazarov Cyclization

Mikail E. Abbasov
March 28th, 2011
Advisor: Professor Daniel Romo

Abstract:

One of the most powerful synthetic transformations with the ability to stereospecifically create new carbon-carbon bonds by simple orbital reorganization are electrocyclic reactions. One of the most recognized electrocyclic reactions is known as Nazarov cyclization.¹ This reaction involves the conversion of divinyl ketones to cyclopentenones by activation with a Brønsted or Lewis acid.² It was originally discovered by Ivan Nikolaevich Nazarov (1906-1957) in 1942 while studying the rearrangements of vinyl ethinyl carbinols and allyl vinyl ketones (Scheme 1).

\[
\begin{align*}
\text{HgSO}_4 & \quad \text{MeOH} \\
\text{H}_2\text{SO}_4 & \quad \text{H}_2\text{O} \\
\end{align*}
\Rightarrow
\begin{align*}
\text{allyl vinyl ketone} & \quad \text{cyclopentanone}
\end{align*}
\]

Scheme 1. Transformation of allyl vinyl ketone into substituted cyclopentanone

This transformation is thought to proceed via complexation of divinyl ketone to the Lewis acid to generate a pentadienyl cation, which subsequently undergoes cyclization to give an oxyallyl cation (Scheme 2). The elimination of a proton gives a Lewis-acid bound enolate, which upon protonation of the enolate gives a cyclopentenone product. The cyclization of pentadienyl cation proceeds with conservation of orbital symmetry.³ Thus, in the ground state, the rotation of 4-electron ring closure under thermal conditions is conrotatory to give a product with an anti relationship between \( R_1 \) and \( R_2 \). Since disrotatory closure under thermal conditions is electronically forbidden, as a result the bond formation proceeds stereospecifically.

\[
\begin{align*}
\text{LA} & \quad \text{R}_1 \quad \text{R}_2 \\
\text{R}_3 & \quad \text{LA} \\
\end{align*}
\Rightarrow
\begin{align*}
\text{cyclopentenone} & \quad \text{cyclopentenone}
\end{align*}
\]

Scheme 2. Mechanism of the classical Nazarov cyclization activated by Lewis acid

However, the Nazarov cyclization has serious reactivity and selectivity problems that have compromised its use as a synthetic tool. Specifically, (1) control over unidirectional conrotation; (2) unwanted cationic rearrangements; (3) regioselective induction of carbon-carbon double bond; (4) stereoselective protonation of the enolate; and (5) lack of asymmetric catalytic cyclization strategies. This seminar will discuss these and other solutions to the problems, summarize the current level of mechanistic
understanding, and present applications of the Nazarov cyclization to natural product synthesis.

The control over unidirectional conrotation (or torquoselectivity) has been documented in the silicon-directed Nazarov cyclization.\textsuperscript{4,5} The stereochemical results can be explained by a steric argument where orbital overlap can be achieved more easily on the less-hindered face of the cyclohexenyl unit containing silyl group. Therefore, the approach from the face opposite the allylic substituent on the ring is preferred (Scheme 3). Furthermore, the silicon atom provides additional stabilizing effect to a carbocation via hyperconjugation also known as the $\beta$-silicon effect.

\textbf{Scheme 3.} Torquoselectivity in the silicon-directed Nazarov cyclization

The regioselective induction of carbon-carbon double bond has been documented in the fluorine-directed Nazarov cyclization.\textsuperscript{6} As oppose to a silicon atom, fluorine possesses a $\beta$-cation destabilizing effect due to its high electronegativity and electron-withdrawing nature. This allows for the resultant oxyallyl cation to delocalize away from the fluorine to restore the stabilization. Subsequently, the placement of the carbon-carbon double bond in energetically less stable positions is possible (Scheme 4). These facts suggest that not only silicon but also fluorine might be a controller of the Nazarov electrocyclic reaction.

\textbf{Scheme 4.} Regioselectivity in the fluorine-directed Nazarov cyclization

Enantioselective enolate protonation during Nazarov cyclization has been challenging, possibly due to the reversibility during\textit{keto-enol} tautomerization. In the first published study of asymmetric Nazarov cyclization using chiral Lewis acid complexes, Aggarwal and Belfield report modest yield and good enantiomeric excess (Scheme 5).\textsuperscript{7} Highest levels of enantioselectivity were achieved with bulky $\alpha$-substituents. The facial selectivity of the enolate protonation was proposed to be controlled by a chiral scaffold of the metal-ligand complex and a bidentate chelation nature of the substrate.
Intending to improve upon the asymmetric methods in the Nazarov cyclization using metal-carbonyl coordination, Pridgen and his co-workers used a commercially available (S)-oxazolidinone as the chiral auxiliary for their systems bearing a specific alkenyl geometry prior to cyclization (Scheme 6).\(^8\) Pridgen suggested that the selectivity is thought to arise from the transoid geometry of the imide, which is thought to position the exocyclic β-carbon in an optimal configuration for the electrocyclic cyclization. Additionally, following the cyclization, the substrate-controlled protonation of enolate can be differentiated under thermodynamic and kinetic control.

Since the carbonyl group bound to the chiral promoter is spatially distant from the bond-forming event at the β-carbon, generating an asymmetric intermediate during Nazarov cyclization has been challenging. In 2010, Tang and his co-workers have developed a highly regio-, diastereo-, and enantioselective asymmetric Nazarov reaction that is catalyzed by the combination of chiral tris(oxazoline) and Cu(II) (Scheme 7).\(^9\) Tang suggested that the pendant group or a sidearm of the chiral tris(oxazoline) ligand influence the conformation of the catalytic species through steric hindrance, leading to a discrimination between the transition states and different enantioselectivities. The mild reaction conditions, high enantioselectivity, reasonable yields, and their utility in the construction of quaternary stereogenic carbon centers make this methodology potentially highly useful in organic synthesis.
References: