Recent Developments of the Nazarov Reaction

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Outline

- Directed Nazarov reactions
- Asymmetric Nazarov reactions
- Other recent variants of the Nazarov reaction
Introduction

- Named after the eminent Russian chemist I. N. Nazarov (1906–1957)

\[ \text{Acid (protic or Lewis) induced cationic } 4\pi \text{ conrotatory electrocyclic ring closure reaction of divinyl ketone to form cyclopentenones} \]

- Carbocation intermediate

- Proceeds via \( \alpha,\alpha' \)-divinyl ketone

- Intramolecular electrocyclization reaction

Definition of the classical acid-catalyzed Nazarov reaction:

\[ \text{Acid (protic or Lewis) induced cationic } 4\pi \text{ conrotatory electrocyclic ring closure reaction of divinyl ketone to form cyclopentenones} \]


Mechanism of Classical Nazarov Reaction

Reactant cation \[ \rightarrow \] Transition state \[ \rightarrow \] Product cation

Comments:

1. Stabilization of the positive charge on the terminal carbons increases the energy of activation and lowers the heat of cyclization.

2. Stabilization of the positive charge on the carbons \( \beta \) to the hydroxyl group decreases the energy of activation and increases the heat of cyclization.

3. Steric effects should also be considered.

Stereochemistry

AcOH/H₃PO₄

50°C
(Conrotatory)

Mechanism and stereochemistry are coupled

benzene

254 nm
(Disrotatory)
Duality of the Electrocyclization Pathway: Torquoselectivity

This term was coined by K. N. Houk.

Limitations of the Classical Nazarov Reaction

1. Lack of control over torquoselectivity

2. Lack of positional control of the double bond

3. Strong acidic media leading to some undesirable rearrangements

Directed Nazarov Reactions

- Silicon-directed Nazarov reactions
- Tin-directed Nazarov reactions
- Fluorine-directed Nazarov reactions
Silicon-Directed Nazarov Reactions

Advantages:

1. Controlled introduction of a double bond
2. Ready isomerization of the double bond to the most substituted position or its transformation to other functionalities if needed

Tin-Directed Nazarov Cyclization

Fluorine-Directed Nazarov Reaction


Note: HFIP = Hexafluoroisopropanol
Another Variant of Fluorine-Directed Nazarov Reaction

Conclusions on Directed-Nazarov Reactions

- Regiocontrol is possible through directed-Nazarov reactions

- Silicon and tin can function as a $\beta$-cation stabilizer and also as electrofuge to control the introduction of the double bond of the cyclopentenone product in a position depending on the placement of silicon or tin

- Fluorine can function as a $\beta$-cation destabilizer and as a nucleofuge to control the introduction of a double bond away from fluorine in the cyclopentenone product

Asymmetric Nazarov Reactions

- Substrate control
- Reagent control
Electronic Control of Torquoselectivity

Asymmetric Nazarov: *Axial to Tetrahedral Chirality Transfer*

For synthesis of chiral cyclopentenone here we need an asymmetric environment!
Carbohydrate-Derived Auxiliaries


Stereospecific reaction
Summary of the Results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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Possible Reason: *Mechanistic Insight*

Direction of conrotation is governed by the anomeric carbon atom and that might involve the interaction of pyran oxygen atom

Limitations of the Carbohydrate-Derived Auxiliary Approach

- Nucleophilicity of the lithiated allenes was unsatisfactory
- Erosion of the %ee took place upon scale up of the reaction
- Preparation of carbohydrate-derived auxiliary was tedious on large scale
Camphor-Derived Auxiliary

Auxiliary on Stereogenic Allenes: *Matched and Mismatched Cases!!!*

### Outcome:

1. If auxiliary directs the conrotation, two allene enantiomers would give products with same stereogenic center $\beta$ to the carbonyl group.

2. If allene directs the conrotation, different allene enantiomers would give enantiomerically different products.
An Example Where Auxiliary Controls the Conrotation

An Example Where Allene Controls the Conrotation

Application of Chiral Auxiliary Approach: Synthesis of Roseophilin

Some Other Auxiliaries

Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* 2003, 1380-1381.


Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* 2003, 1380-1381.
**Reagent Controlled Nazarov: Catalytic Asymmetric Nazarov Cyclization**

\[
\begin{align*}
R^1 & \quad \text{O} \quad \text{O} \\
\text{Ph} & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{Ph}
\end{align*}
\]

\[\text{Ligand} *, \text{CuBr}_2, \text{AgSbF}_6, \text{CH}_2\text{Cl}_2, \text{r.t.}\]

\[\text{R}^1 \quad \text{O} \quad \text{O} \quad \text{R}^3\]

* Ligand = 3 when \(R^3 = \text{OEt}\) = 4 when \(R^3 = \text{NEt}_2\)

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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>(R^1)</th>
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<th>Yield (%)</th>
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<td>Me</td>
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<tr>
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<td>1f</td>
<td>Ph</td>
<td>Ph</td>
<td>NEt(_2)</td>
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<td>85</td>
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Origin of the Stereoselection: Stereochemical Model

Catalytic Asymmetric Nazarov Cyclization: Another Example

Probably Sc is binding to both oxygens forming a distorted complex structure and predisposing the orbital lobes to favor clockwise conrotation

Conclusions on Asymmetric Nazarov Reaction

- Both substrate and reagent controlled asymmetric induction is possible

- Chiral auxiliaries induce asymmetry by favoring one mode of conrotation

- Chiral catalysts distort the divinyl ketone to favor one conrotation over the other
Other Recent Variants of the Nazarov Reaction

- Polarized Nazarov reactions
- Pd(II)-catalyzed Nazarov reactions
- Intercepted Nazarov reactions
- Retro-Nazarov reactions
Polarized Nazarov Reaction


Entry | Ketone          | R                  | Time  | Yield (%) |
------|-----------------|--------------------|-------|-----------|
1     | 3a              | 2,4,6-trimethoxyphenyl | 5 min | > 99      |
2     | 3b              | 4-methoxyphenyl    | 3.5 h | 99        |
3     | 3c              | 3-methoxyphenyl    | 48 h  | 96        |
4     | 3d              | phenyl             | 108 h | 99        |
5     | 3e              | cyclohexyl         | 240 h | < 50      |

D = Electron donating group
E = Electron withdrawing group
Role of Vinyl Nucleophile and Vinyl Electrophile

TMP = 2,4,6-trimethoxyphenyl

\[ \text{TMP} = \text{O}^\text{CO}_2\text{Me}\]

\[ \text{TMP} = \text{O}^\text{CO}_2\text{Me}\]

\[ \text{O}^\text{CO}_2\text{Me}\]

\[ \text{O}^\text{CO}_2\text{Me}\]

\[ \text{O}^\text{LA}\]

\[ \text{O}^\text{LA}\]

\[ \text{O}^\text{LA}\]

\[ \text{O}^\text{LA}\]

\[ \text{R}^1\]

\[ \text{R}^2\]

\[ \text{R}^3\]

\[ \text{R}^4\]

\[ \text{R}\]

\[ \text{A} = \text{Cu(OTf)}_2 \text{ (2 mol%) Cl(CH}_2\text{)}_2\text{Cl (0.06 M)}\]

Palladium(II) Catalyzed Nazarov Reaction

Intercepted Nazarov Reactions: *Intramolecular*

**Mechanistic Rationale:**

Intercepted Nazarov reactions help to conserve the stereocenters formed from the electrocyclic ring closure.

Domino-Nazarov Reaction

Intermolecular Trapping of Nazarov Intermediate: Reductive Nazarov Cyclization

[4+3] Capture of Oxyallyl Intermediate: Another Intermolecular Case

Retro-Nazarov Reaction

Probable Mechanism !!!

Retro-Nazarov: misnomer?

Conclusions

- Classical acid catalyzed Nazarov cyclization reaction is a $4\pi$ conrotatory electrocyclic ring closure reaction of divinyl ketones.

- Directed Nazarov reactions attempt to overcome the problems related to regiocontrol of the double bond in the product.

- Asymmetric Nazarov reactions provide a means to selectively favor one mode of conrotation in the electrocyclic ring closure.

- Polarization of the precursor divinyl ketone gives the Nazarov product with regiocontrol under milder conditions.

- Trapping of the oxyallylic intermediate of the reaction can be done both intra and intermolecularly and that helps to conserve the stereocenters created by the electrocyclic ring closure.
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<td>Dr. Robert Maleczka</td>
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<td>Edith</td>
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