Cheletropic Reactions

Background

“We define as cheletropic reactions those processes in which two σ bonds which terminate at a single atom are made, or broken, in concert.”


Cheletropic reactions are a separate class of pericyclic reactions that are subject to orbital symmetry analysis. They must obey the Woodward-Hoffman rules the same way that cycloadditions and sigmatropic rearrangements do.

Linear approach vs. Non-linear approach

Cheletropic reaction analysis is typically done in the addition direction. Consider fragment “x” to be a single atom that contributes two electrons to the pericyclic transition state. The approach of “x” can be either linear or non-linear. The rotation of the π system will be either disrotatory or conrotatory based on the approach of fragment “x”

Linear

The HOMO of x points directly at the π system.

Non-linear

The HOMO of x approaches the π system at a skew angle.

Disrotatory

Conrotatory

LUMO

HOMO

Selection rules for cheletropic reactions

<table>
<thead>
<tr>
<th>π electrons</th>
<th>Allowed Ground State Reactions</th>
<th>Allowed Excited State Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4n</td>
<td>disrotatory</td>
<td>conrotatory</td>
</tr>
<tr>
<td>4n+2</td>
<td>conrotatory</td>
<td>disrotatory</td>
</tr>
</tbody>
</table>

Stereochemical outcome

\[
\text{H}_3\text{C-S}=\text{O} \xrightarrow{150 \degree \text{C}} \text{H}_3\text{C}=\text{CH}_3
\]

disrotatory elimination

\[
\text{H}_3\text{C-S}=\text{O} \xrightarrow{150 \degree \text{C}} \text{H}_3\text{C}=\text{CH}_3
\]

disrotatory elimination

Most frequently encountered examples

\[
\text{SO}_2 \rightarrow \text{H}_3\text{C}=\text{CH}_3
\]

Reactivity general guideline

Cycloversion

Only

\[
\Theta \text{C}=\Theta \text{O}
\]

Singlet carbene addition to olefins

Singlet carbenes have an unoccupied p orbital and two non-bonding electrons in the σ orbital. Only singlet carbenes can participate in cheletropic reactions.

“The most importatnt cheletropic reaction is the addition of singlet carbenes to make cyclopropanes.”

Anslyn and Dougherty

Linear approach

Non-linear approach

4-electron

Hückel forbidden

2-electron

Möbius forbidden

4-electron

Möbius allowed

2-electron

Hückel allowed

Only select carbene examples will be discussed here. See K. Chen’s GM on carbenes

Cheletropic Reactions

Sequential cycloaddition-cycloreversion and a strange caged structure

Intramolecular [4+1] Cycloaddition

The intramolecular Ramberg-Bäcklund reaction: a convenient method for the synthesis of strained bridgehead olefins

An unprecedented tandem 1,3-dipolar cycloaddition-cheletropic elimination: a facile approach to novel push-pull olefins

Germanium Analogues of Carbenes

Tellurium Extrusion: Synthesis of Benzocyclobutene

1.) EtMgBr
2.) t-BuOK, THF, -78 °C

Synthesis of new chiral σ2λ2-phosphenium cations

Germanium Analogue of Carbenes

The Chemistry of Organic Germanium, Tin and Lead Compounds, John Wiley and Sons, Chichester, 2002 (Chapter 1)

Tellurium Extrusion: Synthesis of Benzocyclobutene

"moderate yield"
Cheletropic Reactions

Tandem Cope-cheletropic reaction: a new molecular rearrangement

[Chemical structures and reactions]

retro-Cheletropic ene Reactions with 2-carbena-1,3-dioxolane as the chelefuge

Nitric oxide cheletropic traps (NOCTs)

Phenanthyrene and bis-benzene
Applications in Total Synthesis

-The examples presented here will consist of the three main cheletropic reactions seen in total synthesis. Cheletropic reactions involving Fischer carbenes will not be discussed here beyond examples of the Simmons-Smith cyclopropanation. For an in depth presentation and discussion of Fischer carbenes see K. Chen's group meeting on Fischer carbenes.

Early studies on the formation of cyclobutarene

Δ

The first report of this type of reactivity dates back to 1913. This topic remained unexplored until it was returned to in 1935.
Staudinger, H. German Patent 506,839; [Chem. Abstr. 1913, 25, 522]

Cheletropic extrusion of SO₂: The search for a diene equivalent
Inspiration from W. Oppolzer


K.C.N.'s idea: intramolecular trapping of o-quinodimethanes

The methylstylene side product was observed in only a small (unspecified) amount.

Synthesis of estra-1,3,5,(10)-trien-17-one

Winkler's retrosynthetic analysis:

"It is interesting to note that neither Lewis acid is capable of catalyzing both Diels-Alder reactions."
Cheletropic Reactions

Ruben Martinez

Total Synthesis of Colombiasin A

First generation:

\[
\begin{align*}
\text{TBSO} & \quad \overset{\text{AgO, 6M HNO}_3}{\longrightarrow} \quad \overset{\text{1,4-dioxane, rt, 3h}}{\longrightarrow} \quad \text{OMe, OMe, OMe} \\
\text{TBSO} & \quad \overset{\text{AgO, 6M HNO}_3}{\longrightarrow} \quad \overset{\text{1,4-dioxane, rt, 3h}}{\longrightarrow} \quad \text{OMe, OMe, OMe}
\end{align*}
\]

"numerous unidentified by-products"

Second generation:

\[
\begin{align*}
\text{TBSO} & \quad \overset{\text{AgO, 6M HNO}_3}{\longrightarrow} \quad \overset{\text{1,4-dioxane, rt, 3h}}{\longrightarrow} \quad \text{OMe, OMe, OMe} \\
\text{TBSO} & \quad \overset{\text{AgO, 6M HNO}_3}{\longrightarrow} \quad \overset{\text{1,4-dioxane, rt, 3h}}{\longrightarrow} \quad \text{OMe, OMe, OMe}
\end{align*}
\]

many by-products lacking the diene system

The solution:

\[
\begin{align*}
\text{TBSO} & \quad \overset{\text{SO}_2, \text{rt, 20 min}}{\longrightarrow} \quad \overset{\text{91\%}}{\longrightarrow} \quad \text{OMe, OMe, OMe} \\
\text{TBSO} & \quad \overset{\text{AgO, 6M HNO}_3}{\longrightarrow} \quad \overset{\text{1,4-dioxane, rt, 3h}}{\longrightarrow} \quad \text{OMe, OMe, OMe}
\end{align*}
\]

An "almost" cheletropic elimination of SO$_3$ from 11-gorgiacoreol

Total Synthesis of (+)-Rishirilide B

\[
\begin{align*}
\text{1.) } \text{SO}_2, \text{h}_\nu & \quad \text{2.) } \text{MeOH, } \rho\text{-TsOH} \\
\text{ZnO} & \quad \text{155 \degree C} \\
\end{align*}
\]

Diel-Alder and $\beta$-elimination

DDQ steps

Burgess' reagent PhH, reflux 40%

43% brsm

exclusive endo product

Cheletropic Reactions

Ruben Martinez

Ramberg–Bäcklund Reaction
The reaction was first discovered in 1940 but no further work was published until 1950.

Early studies toward the synthesis of the enediyne moiety of calicheamicin

A Novel application of the Ramberg-Bäcklund Rearrangement to a Highly Stereoselective Synthesis of (+)-Eremantholide A

Total Synthesis of (+)-Estradiol

Total Synthesis of Ampelopsin D
Total Synthesis of Ampelopsin D continued

1.) t-BuOH, aq. KOH
2.) BBr₃

40% over two steps

Total Synthesis of Hirsutellone B

Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation

)...the first example of directed and stereoselective C-C bond construction fusing two different cyclotryptamine fragments at vicinal quaternary stereocenters.
**Cheletropic Reactions**

**Ruben Martinez**

**Baran Group Meeting**

**06/01/13**

**Simmons-Smith cyclopropanation**

First discovered in 1944. Many asymmetric modifications have been throughout the years. The most notable being the Charette asymmetric modification.

\[
\text{ZnEt}_2 + \text{CH}_2\text{I}_2 \rightarrow \text{EtZnCH}_2\text{I} \rightarrow \text{EtZnI} \rightarrow \text{EtZnCH}_2\text{I} \rightarrow \text{EtZnI}
\]

For an excellent review on stereoselective cyclopropanation reactions see: *Chem. Rev.* 2003, 103, 977.

**Total synthesis of (±)longifolene**


1.) H₂ (3 atm) Pd/C (10%)  
2.) selective Wittig olefination

**Enantioselective total synthesis of oleanolic acid, erythrodiol, β-amyrin, and other pentacyclic triterpenes from a common intermediate**


**Simple synthetic route to the limonoid system**


"The most obvious approach" gave poor results.
**Cheletropic Reactions**

**Total Synthesis of (±)-Taxusin**

1. \( \text{Et}_2\text{Zn, CH}_2\text{Cl}_2 \) (6h)
2. \( \text{PDC, rt} \) 85%

**Total Synthesis of (±)-Maoecrystal V**

1. Lombardo reagent
2. \( \text{CH}_2\text{Cl}_2, \text{Zn/Ag} \) 75%

**Total Synthesis of (+)-Ambruticin**
Regioselective, asymmetric cyclopropanation

**Highly Enantioselective Simmons-Smith Fluorocyclopropanation of Allylic Alcohols**

**State of the art in cyclopropanation**