Ruthenium-Catalyzed Concurrent Tandem Reactions

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Outline

I. Introduction

II. Metathesis/Metathesis
   I. Ring Rearrangement Metathesis
   II. Enyne Cascades
      I. Dienyne Metathesis
      II. Ring Rearrangement Metathesis

III. Metathesis/Non-Metathesis
    I. Metathesis/Isomerization
    II. Metathesis/Cyclopropanation
    III. Metathesis/Diels Alder

IV. Conclusion
Types of Tandem Reactions

- **Tandem reactions** are reactions in which multiple bonds are formed in one synthetic operation.

- **Sequential tandem reactions** involve coupling transformations that operate *independently* and often require changes in reaction conditions or the addition of new reagents.

  ![Diagram of sequential tandem reactions]

- **Concurrent tandem reactions** use a catalyst for multiple *cooperative* transformations without adding additional reagents or catalysts and the subsequent reactions occur as a consequence of the functionality produced in the previous step.

  ![Diagram of concurrent tandem reactions]

Examples of Sequential and Concurrent Tandem Reactions

**Sequential Tandem Reaction**  (Not Covered)

**Concurrent Tandem Reaction**


Advantages

• Atom Economy

• Efficient Access to Complex Products

• Reduces Waste

• Eliminates labor and the cost of isolating and purifying intermediates

• Access to new types of product

• Higher Yields

Disadvantages

• Potential Side Reactions

• Catalysts Compatibility

## Concurrent Tandem vs. Sequential Tandem Reactions

<table>
<thead>
<tr>
<th>Method</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent Process</td>
<td>39%</td>
</tr>
<tr>
<td>Sequential Process</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Virolleaud, M; Bressy, C; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081.
Benefits in Use of Grubbs’ Catalysts in Concurrent Tandem Reactions

- Well-defined, single-site homogenous catalysts
- Chirality Transfer in metathesis reactions
- Versatile
  - Metathesis/Isomerization/Hydrogenation/Cyclopropanations
- High Chemoselectivity (functional group tolerance) in metathesis reactions

<table>
<thead>
<tr>
<th>Titanium</th>
<th>Tungsten</th>
<th>Molybdenum</th>
<th>Ruthenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acids</td>
<td>Acids</td>
<td>Acids</td>
<td>Olefins</td>
</tr>
<tr>
<td>Alcohols</td>
<td>Alcohols</td>
<td>Alcohols</td>
<td>Acids</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>Aldehydes</td>
<td>Aldehydes</td>
<td>Olefins</td>
</tr>
<tr>
<td>Ketones</td>
<td>Ketones</td>
<td>Olefins</td>
<td>Aldehydes</td>
</tr>
<tr>
<td>Esters, Amides</td>
<td>Olefins</td>
<td>Ketones</td>
<td>Ketones</td>
</tr>
</tbody>
</table>

Increasing Reactivity

Chauvin Mechanism

Leads to a statistical ratio of products in cross metathesis without a driving force.

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   II. Metathesis/Cyclopropanation
   III. Metathesis/Diels Alder

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Ring Rearrangement Metathesis (RRM) - The tandem coupling of ring opening metathesis (ROM) and ring closing metathesis (RCM).

Strained cyclic olefins undergo RRM with relief of ring strain as the thermodynamic driving of the reaction.

Unstrained cyclic olefins undergo RRM with the entropy gain in the formation of the volatile olefin, usually ethylene, as the thermodynamic driving force.
Ring Rearrangement Metathesis of Cyclic Olefins

First published example

\[ \text{Substrate} \rightarrow \text{Product} \quad \text{Yield} \]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{G1} ): [structure]</td>
<td>( \text{G1} ): [structure]</td>
<td>82%</td>
</tr>
<tr>
<td>( \text{R} ): [structure]</td>
<td>( \text{R} ): [structure]</td>
<td>57%</td>
</tr>
<tr>
<td>( \text{R} ): [structure]</td>
<td>( \text{R} ): [structure]</td>
<td>70%</td>
</tr>
</tbody>
</table>

Two Possible Mechanisms

Mechanism 1:

Mechanism 2:

Synthesis of α,β-unsaturated Lactones

Electron poor olefins usually difficult substrates for metathesis

Enantiopure Heterocycle Syntheses

\[ \text{Reflux } \text{CH}_2\text{Cl}_2 \quad \text{H}_2\text{C}≡\text{CH}_2 \]

\[ n=1,2 \]

\[ \text{G1} = \begin{array}{c}
\text{Cl}\text{,} \\
\text{PCy}_3 \\
\text{Cl}\text{,} \\
\text{PCy}_3 \text{Ph}
\end{array} \]


Applications to azasugars

RRM/CM Tandem Sequence and Application to the Total Synthesis of (-)-Lasubine II

ROM-RCM-CM Tandem Sequence

Applied to (-)-Lasubine II

Regioselectively Restructuring Norbornene Derivatives

The products differ in regioselectivity of RCM step.

G1 = Cl, PCy3

Synthesis of the Advanced Intermediate toward Alkaloid 251F

RRM Cascade Approach
80% overall yield in 3 steps

Alternative Approach
(Ozonolysis/Aldol Strategy)
27% overall yield

The more active catalyst enables the addition of a CM step.
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Dienyne Metathesis Mechanism

Dienyne Metathesis of fused bicycles

\[
\begin{align*}
\text{OTES} & \quad \text{Me} & \quad \text{OTES} \quad \text{Me} \\
\text{Et} & \quad \text{Me} & \quad \text{OTES} \\
\end{align*}
\]

\[3 \text{ mol} \% \text{ [Ru]} \quad 65^\circ \text{C} \quad 15 \text{ h} \]
86%

1:1

Mono-substitution Directing Effect

\[
\begin{align*}
\text{OTES} & \quad \text{Me} & \quad \text{OTES} \\
\text{Et} & \quad \text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[3 \text{ mol} \% \text{ [Ru]} \quad 65^\circ \text{C} \quad 15 \text{ h} \]
83%

95%

\[
\begin{align*}
\text{Me}^I & \quad \text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[3 \text{ mol} \% \text{ [Ru]} \quad 100^\circ \text{C} \quad 1.5 \text{ h} \]
78%

88%

89%

78%

Polycyclizations via Enyne/RCM Cascade

Polycyclizations via Enyne/RCM Cascade

Dienyne Metathesis with Electron Poor Olefins

Not observing the 7-membered lactone implies that the terminal alkylidene exclusively reacts with acetylenes over acrylates

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>95%</td>
</tr>
<tr>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>86%</td>
</tr>
<tr>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>68%</td>
</tr>
<tr>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>100%</td>
</tr>
<tr>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>74%</td>
</tr>
</tbody>
</table>

Choi, T; Grubbs, R. *Chem. Comm.* **2001**, *2648*. 
Formal Synthesis of (+)-Guanacastepene A

Synthesis of Aza-Cycles via Dienyne Metathesis

Tricyclic β-Lactams

\[
\text{O}_{\text{TBS}} \quad \text{G2} \quad \begin{array}{c}
10 \text{ mol} \% \\
\text{reflux CH}_2\text{Cl}_2 \\
\text{H}_2\text{C}=\text{CH}_2
\end{array}
\xrightarrow{64\%}
\text{O}_{\text{TBS}}
\]

Ynamides to 2-Amidodienes

\[
\text{R} \quad \text{R}' \quad \text{H} \quad \text{Ot-Bu} \quad \text{base-induced isomerization} \quad \text{KOT-Bu, rt, THF, 5h}
\xrightarrow{\text{allenamide}}
\text{R} \quad \text{R}' \quad \text{N} \quad \text{H} \quad \text{Ot-Bu}
\]

\[
\text{Me} \quad \text{ynamide}
\]

\[
\text{Me} \quad \text{n = 1, 2, 3}
\]

\[
\text{75 °C 12 h}
\]

40% - 70% Mix of Isomers

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Enyne Ring Rearrangement Metathesis

Ring Rearrangement of Alkynyl Substituted Cycloolefins: Synthesis of Pyrrolines

Ring Rearrangement Metathesis with Substituted Cyclohexenes

Intramolecular enyne reaction for the cis substrate is inhibited by steric interactions between the [Ru] and the TBDMS group.
Ring Rearrangement Metathesis with Substituted Cyclohexenes

Intramolecular enyne reaction for the cis substrate is inhibited by steric interactions between the [Ru] and the TBDMS group.
Different Grubbs’ Catalyst, Different Tandem Reaction
Synthesis of γ-Lactones and Indolizidinones

Different Grubbs’ Catalyst, Different Tandem Reaction
Synthesis of γ-Lactones and Indolizidinones


Product rationale based on catalysts activity
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Ring Closing Metathesis/Olefin Isomerization Cascade

\[ \text{G2} \rightarrow \begin{cases} \text{RCM} & (X = \text{O, NTs}) \\ n = 1,2... \\ m = 1,2... \end{cases} \rightarrow [\text{Ru}-\text{H}] \rightarrow \text{Olefin Isomerization} \rightarrow \text{46-74\%} \]

\[
\begin{array}{cccc}
\text{Ph} & \text{O} & \text{Ph} & \text{O} \\
54\% & 61\% & 46\% & 74\%
\end{array}
\]

Regiochemistry of the Enol Ether

\[
\begin{align*}
\text{Ph} & \text{O} - \text{Ph} \\
\text{Δ H}^\circ & = -7.21 \text{ kcal/mol} \\
\text{More Stable} & \rightarrow \text{Observed Product} \\
\text{Δ H}^\circ & = -3.48 \text{ kcal/mol}
\end{align*}
\]

Assorted Examples of RCM/Isomerization Cascade


ROM/CM/Isomerization of Allylic Alcohol

![Mechanism diagram](image)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Substrate 1" /></td>
<td><img src="image" alt="Product 1" /></td>
<td>72%</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 2" /></td>
<td><img src="image" alt="Product 2" /></td>
<td>72%</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 3" /></td>
<td><img src="image" alt="Product 3" /></td>
<td>41%</td>
</tr>
</tbody>
</table>

Cyclopropanation/RCM of Dienynes

Diver, S.; Peppers, B.


**Probable Mechanism**

- **Path a**: Carbene metathesis
- **Path b**: Noncarbene Lewis Acid catalysis

**Interplay Mechanism**

Enyne Metathesis-Cyclopropanation Cascade

Cyclopropanation ruthenium catalyst may be different from the metathesis catalyst.

$^{31}$P NMR showed new peaks after the tandem reaction

Addition of more diene after the tandem reaction does not undergo metathesis

Enyne Metathesis-Cyclopropanation Cascade Scope

\[ \text{G1} = \text{Cl, } \text{PCy}_3 \text{Ru} = \text{Cl, } \text{PCy}_3 \text{Ph} \]

RCM-Isomerization-Cyclopropanation Cascade

Synthesis of Fused Tricycles via RRM/CM/Diels Alder Cycloaddition

10 mol % \( G2 \)

\[ \text{CH}_2\text{Cl}_2 \text{ 80 °C} \]

\( \text{H}_2\text{C}=\text{CH}_2 \)

30%

55%

45%

20%

Synthesis of Fused Tricycles via RRM/CM/Diels Alder Cycloaddition

Proposed Mechanism

Imhof, S.; Blechert, S. Synlett. 2003, 609.
Three Component Metathesis/Diels-Alder Cascade

\[
\text{X} = \text{NTs, CR}_2
\]

\[
\begin{align*}
\text{X} & \quad \text{R} \quad \text{Ring Size} \quad \text{Yield (\%)} \\
\text{NTs} & \quad \text{Bu} \quad 5 \quad 83 \\
\text{NTs} & \quad \text{Bn} \quad 5 \quad 75 \\
\text{NTs} & \quad \text{Bu} \quad 6 \quad 71 \\
\text{NTs} & \quad \text{Bn} \quad 6 \quad 78 \\
\text{CE}_2 & \quad \text{Bu} \quad 6 \quad 74
\end{align*}
\]

Conclusion

- Ruthenium-catalyzed concurrent tandem reactions enable efficient access to various enantiomerically pure polycycles in a single step

- The versatility of Grubbs’ catalysts enable the cooperation of very mechanistically different reactions in effective cascades

- Although ruthenium-catalyzed concurrent tandem catalysis is still in its infancy it has shown significant
Acknowledgements

Jeff Johnson

Johnson Group
Rationale for the Observed Product

Ring Rearrangement Mechanism

Ruthenium Catalysis: A History

- 1950’s – Discovery of Olefin Metathesis
- 1970’s - Schrock begins to develop metathesis catalysts using tungsten and molybdenum
- 197? – N. Calderon at Goodyear Tire and Rubber coined the term olefin metathesis
- 1990 – Schrock unveils a very active well-defined catalyst
- 1992 – Grubbs unveils first generation ruthenium catalyst
- 2005 – Grubbs, Schrock and Chauvin awarded the Nobel Prize for their work in metathesis
Fused Cyclic Polyethers

Synthesis of Spirocyclic Pyrans from Oxabicyclooctene Derivatives


Synthesis of the Oxabicyclooctene derivatives
Synthesis of Spirocyclic Pyrans- The Importance of Substituent Effects

Unsubstituted examples

More strained systems

Reduced substrates

Synthesis of Tricyclic Enones from Norbornene Derivatives

G1 provides cyclohexa[c]indine skeleton in excellent yield and with high selectivity.

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G1 and G2 gave a poor selectivity for the cyclopenta[c]indine skeleton vs. the undesired tricycle

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Synthesis of Tricyclic Enones from Norbornene Derivatives

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G1 and G2 gave a poor selectivity for the cyclopenta[c]indine skeleton vs. the undesired tricycle.

G2 provided a very good yield of the allylic alcohol cyclopenta[c]indine.

Synthesis of Aza-cycles

Five and six membered aza-cycles possible
For trans-configured derivatives, yields dramatically improved by switching protecting groups from Ns to benzyloxy carbonyl group

Proposed Mechanism

Scope of the RRM/CM for Alkynyl Substituted Cycloolefins

\[
\text{IRu} = \text{Cl}, \text{P} \text{Cy}_3
\]

5 mol% \text{[Ru]}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Olefin</th>
<th>Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO₂C <img src="substring.png" alt="image" /> MeO₂C <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /></td>
<td>H₂C=CH₂</td>
<td><img src="substring.png" alt="image" /> MeO₂C <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> (80%)</td>
</tr>
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<td><img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /></td>
<td><img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /></td>
<td><img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> (75%) E/Z = 3:1</td>
</tr>
<tr>
<td><img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /></td>
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<td><img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /></td>
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<td><img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> <img src="substring.png" alt="image" /> (50%) E/Z = 3:1</td>
</tr>
</tbody>
</table>


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m = 1 (67%)

m = 1 (5%)

m = 2 (60%)

m = 6 (47%)


**Ring Rearrangement Metathesis Mechanism**

---

**Ring Rearrangement Metathesis (RRM)** - The tandem coupling of ring opening metathesis (ROM) and ring closing metathesis (RCM).

**Strained cyclic olefins** undergo RRM with relief of ring strain as the thermodynamic driving of the reaction.

**Unstrained cyclic olefins** bearing two olefin substituents can undergo RRM involving a double RCM. The driving force for this reaction is the entropy gain in the formation of the volatile olefin, usually ethylene.