CASCADE REACTIONS

Introduction

What is a Cascade reaction?

- A consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates.
- Several bonds are formed in sequence without isolation of intermediates, changing of reaction conditions, or adding reagents.
- Multistep, salt-generating chemical synthesis can be replaced with efficient catalyzed reactions.
- Tandem methodology provides excellent tactics to combine different concurrent or sequential processes.
- Chirality embedded in the carbocyclic starting material is completely transferred into the product.

Why doing CASCADE reactions in total synthesis?
Total Synthesis of Progesterone by Johnson et al.


RCM-CM in Ring Fragment of Ciguatoxin

ROM-RCM in Synthesis of Cyanthiwigin U

Mechanism:

Tandem RCM-EM

Zipper reaction for steroid-like skeleton

Palladium Polyene Cyclization


Gold-Catalyzed One-Pot Cascade Construction of Highly Functionalized Pyrrolo[1,2-a]quinolin-1(2H)-ones

Propargylic Ene Reaction/Diels-Alder Cycloaddition

\[
\begin{align*}
\text{Propargylic ene reaction} & \\
\begin{array}{c}
\text{Z} \\
\text{G}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{R}^1
\end{array} & + \\
\begin{array}{c}
\text{H}
\end{array} & \\
\begin{array}{c}
\text{Z} \\
\text{G}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{R}^2
\end{array} & \rightarrow \\
\begin{array}{c}
\text{R}^3
\end{array} & \rightarrow [4 + 2] \\
\text{cycloaddition}
\end{align*}
\]


Construction of the Tricyclic Furanochroman Skeleton of Phomactin A via the Prins/Conia-Ene Cascade Cyclization

One-Pot Three-Component Tandem Metathesis/Diels-Alder Reaction

\[
\begin{align*}
X = \text{NTs, CE}_2 & \quad R = \text{CH}_2\text{TMS}, \\
E=\text{COOEt} & \quad \text{Ph, Bn}
\end{align*}
\]

\[
\begin{align*}
\text{G-II (10 mol\%)} & \quad \text{DCM, reflux}
\end{align*}
\]


Asymmetric Cascade Reactions of Acrylate-Linked Nitro olefins

Development of Cascade Reactions for the Concise Construction of Diverse Heterocyclic Architectures

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CONSPECTUS

Heterocyclic structural architectures occur in many bioactive natural products and synthetic drugs, and these structural units serve as important intermediates in organic synthesis. This Account documents our recent progress in the development of cascade reactions to construct complex carbocycles and heterocycles. We describe the rational design of cascade reactions and in-depth investigations of their mechanism as well as their applications in the synthesis of drugs, natural products, and related molecular analogs.
Summary

- Useful strategy in the synthesis of various intricate molecules & Natural Products.
- Reaction is often fast due to its intramolecular nature, it is also clean.
- Displays high atom economy and does not involve workup and isolation of many intermediates.
- Builds a large degree of complexity in one transformation.
- Eliminates the cost of purifying the intermediates.
- Reduces labour and time to effect given transformation.

Multi-component Reactions

What is Multi-component Reaction?

Multicomponent Reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product, incorporating essentially all of the atoms in the adducts. Generally, there are different classification schemes of MCRs possible, e.g. according to the reaction mechanisms or the components involved.

**Classification of Multi-component reactions**

**Domino or Cascade Reactions:** All the reactants are initially present and the reaction proceeds without modification of reaction conditions. The intermediates cannot be isolated.

**Sequential reactions:** The reagents are added in a well-defined order under constant conditions. The intermediates may be isolable.

**Consecutive reactions:** In these reactions, the conditions are changed stepwise and the intermediates are isolable.

**Multicomponent Reactions**

- **Why Multi-component?**
  - Less waste
  - Convergent
  - Atom Economy
  - Diversity Oriented
  - Environmentally Benign
  - Wide range of possibilities
  - Simultaneous bond-forming reactions
  - Minimize isolation of intermediates
  - Avoids complicated purification operations
The Brief History of MCRs

Strecker Reaction, 1850
By Strecker

Hantzsch Reaction, 1882
By Hantzsch

Biginelli Reaction, 1891
By Biginelli

Mannich Reaction, 1912
By Mannich

Passerini Reaction, 1921
By Passerini

Ugi Reaction, 1959
By Ugi

Organometallic MCRs

Miscellaneous MCRs
Strecker Reaction (discovered in 1850)

Components: Amine, Carbonyl, Cyanide

1. DIASTEREOSELECTIVE APPROACH

\[ \text{H}_2\text{N-Ph} + \text{ArCO} \xrightarrow{\text{NaCN}} \text{ArNC}{-\text{Ph}} \xrightarrow{} \text{AMINO ACIDS} \]
(d.r. 1:1)

\[ \text{R}^1\text{R}^2\text{NH}_2 + \text{R}^2\text{H} \xrightarrow{\text{KCN}, \text{NaHSO}_3, \text{MeOH}} \text{R}^1\text{R}^2\text{NH-CN} \]
(d.r. 9:1)

\[ \text{t-BuO-} \xrightarrow{\text{TMSCN / i-PrOH}} \text{t-BuO-} \]
(23%, d.r. > 95:5)
2. ENANTIOSELECTIVE APPROACH

Mannich Reaction (discovered in 1912)

Components: Amine, non-enolizable aldehyde, enolizable carbonyl

1. DIASTEREOSELECTIVE APPROACH

S. Kobayashi, JACS, 2000, 122, 762

M. Shibasaki, JACS, 2001, 123, 6801
2. ENANTIOSELECTIVE MANNICH

\[
\text{Ph} + (\text{CH}_2\text{O})_n + \text{NH}_2\text{C} = \text{O} \\
\text{LiA/}\text{H}_4 \quad \text{(10\%)} \\
\text{La(O/}\text{TF})_3 \quad \text{(10\%)} \\
\text{PhMe} \quad \text{(10\%)} \\
\quad \text{PhO} \quad \text{N} \quad \text{H} \\
\quad \text{Ph} \quad \text{(16\%, 64\%ee)} \\
\]

The first Enantioselective Mannich MCR


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**Biginelli Reaction** (discovered in 1891)

Components: Urea, Aldehyde, 3-Ketoester

\[
\text{H}_2\text{N} \quad \text{C} = \text{O} \quad \text{C} = \text{O} \quad \text{C} = \text{O} \\
\text{NH}_2 \quad \text{PhO} \quad \text{PhO} \\
\text{BnO} \quad \text{BnO} \quad \text{BnO} \\
\text{BnO} \quad \text{BnO} \\
\text{(65\%, d.r. 85:15)} \\
\]

Chemist Pietro Biginelli

**Hantzsch Reaction** (discovered in 1882)

**Components**: Enamine, Aldehyde, 1,3-Dicarbonyl

![Hantzsch Reaction Diagram]

(10%, d.r. 60:40)

1,4-Dihydropyridine


**Passerini Reaction** (discovered by 1921)

**Components**: Aldehyde, Acid, Isocyanide

1. **DIASTEREOSELECTIVE APPROACH**

![Passerini Reaction Diagram]

(> 85%, d.r. > 96:4)


Mario Passerini, the inventor of the most significant isocyanide based MCRs.

**L. Bani, G. Guanti, R. Riva, Chem. Commun.** **2000**, *985*
Ugi Four Component Reaction

Components: Aldehyde, Amine, Isocyanide, Carboxylic acid

\[
\begin{align*}
\text{Boc} & : \text{R}^1 \bigg\| \text{N} \bigg\| \text{R}^2 \\
\text{O} & : \text{R}^3 \bigg\| \text{H} \\
\text{R}^4 \text{NH}_2 & + \\
\text{R}^5 \text{NC} &
\end{align*}
\]

(d.r. < 51: 49)


Organometallic 1,2-Addition Process

\[ R-\text{C}==\text{CH} + R^1-\text{CHO} + H^+ R^2 N R^3 \xrightarrow{\text{CuBr (5%)/PhMe}} R^1^-N^-R^3^- \]

Cycloaddition-Based MCRs


Asymmetric Sakurai MCRs

![Chemical structure](image)

(90%, d.r. < 99:1)


Pauson-Khand Based MCRs

![Chemical structure](image)