

Ring-Closing Metathesis (RCM)

关环复分解反应

A Bilingual Detailed Explanation / 双语详解

Compiled for Organic Chemistry Study

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1 Introduction / 引言

English

Ring-Closing Metathesis (RCM) is an intramolecular olefin metathesis reaction in which a diene (a molecule with two carbon–carbon double bonds) is converted into a cyclic alkene, releasing a small olefin (typically ethylene, $\text{CH}_2=\text{CH}_2$) as a byproduct. RCM is one of the most powerful and widely used methods for constructing carbon–carbon double bonds within ring systems. It has revolutionized the synthesis of medium- and large-ring compounds, which are notoriously difficult to prepare by other methods.

The term *metathesis* comes from the Greek *metatithemi*, meaning “to transpose.” In olefin metathesis, the substituents on two double bonds are formally exchanged (“transposed”) through cleavage and re-formation of $\text{C}=\text{C}$ bonds, mediated by a transition-metal carbene catalyst.

中文

关环复分解反应 (Ring-Closing Metathesis, RCM) 是一种分子内的烯烃复分解反应：一个含有两个碳碳双键（二烯）的分子在金属卡宾催化剂的作用下，形成一个新的环状烯烃，同时释放出一个小分子烯烃（通常为乙烯 $\text{CH}_2=\text{CH}_2$ ）。

RCM 是构建环状碳碳双键最有力的方法之一，尤其在合成中环和大环化合物方面具有革命性意义——这些化合物用其他方法通常很难制备。

“复分解” (metathesis) 一词源自希腊语 *metatithemi*，意为“交换”。在烯烃复分解反应中，两个双键上的取代基通过 $\text{C}=\text{C}$ 键的断裂和重新组合进行“交换”，这一过程由过渡金属卡宾催化剂介导。

2 Historical Background / 历史背景

English

Olefin metathesis was first observed in the 1950s and 1960s in industrial polymer chemistry (e.g., the Phillips petroleum process). However, the mechanism remained a mystery until **Yves Chauvin** proposed the metal-carbene mechanism in 1971.

The development of well-defined, functional-group-tolerant catalysts by **Robert H. Grubbs** and **Richard R. Schrock** in the 1990s made RCM practical for organic synthesis. The three chemists were awarded the **2005 Nobel Prize in Chemistry** “for the development of the metathesis method in organic synthesis.”

Key milestones:

- **1971** —Chauvin mechanism proposed.
- **1990** —Schrock’s Mo-based alkylidene catalysts.
- **1992** —Grubbs’ 1st-generation Ru catalyst (Grubbs I).
- **1999** —Grubbs’ 2nd-generation catalyst (Grubbs II) with NHC ligand.
- **2000s** —Hoveyda–Grubbs catalysts and further developments.

中文

烯烃复分解反应最早在 1950–1960 年代的工业高分子化学中被观察到（例如 Phillips 石油公司的工艺）。但其机理直到 **Yves Chauvin**（伊夫·肖万）于 1971 年提出金属卡宾机理后才被阐明。

Robert H. Grubbs（罗伯特·格拉布斯）和 **Richard R. Schrock**（理查德·施罗克）在 1990 年代开发了具有良好官能团耐受性的催化剂，使得 RCM 在有机合成中变得切实可行。三位化学家于 **2005 年**因“在有机合成中发展了复分解方法”而获得**诺贝尔化学奖**。重要里程碑：

- **1971** —Chauvin 机理被提出。
- **1990** —Schrock 的钼基烷叉催化剂。
- **1992** —Grubbs 第一代钨催化剂（Grubbs I）。
- **1999** —Grubbs 第二代催化剂（Grubbs II），含 NHC 配体。
- **2000s** —Hoveyda–Grubbs 催化剂及后续发展。

3 The General Reaction / 一般反应式

English

The general RCM transformation can be written as:



The driving force is the **release of gaseous ethylene**, which escapes the reaction mixture (Le Chatelier's principle), shifting the equilibrium toward product formation.

Typical conditions: 1–10 mol% catalyst, **dilute** conditions (to favor intramolecular cyclization over intermolecular oligomerization), refluxing CH_2Cl_2 or toluene, under inert atmosphere (N_2 or Ar).

中文

RCM 的一般反应可以表示为：



反应的驱动力是**气态乙烯的释放**：乙烯逸出反应体系（勒夏特列原理），使平衡向生成环状产物的方向移动。

典型条件：1–10 mol% 催化剂，**稀释条件**（有利于分子内关环，而非分子间寡聚），在 CH_2Cl_2 或甲苯中回流，惰性气氛（ N_2 或 Ar）。

4 Mechanism: The Chauvin Cycle / 机理: Chauvin 循环

Chauvin Mechanism / Chauvin 机理

The accepted mechanism for all olefin metathesis reactions (including RCM) is the **Chauvin mechanism**, which proceeds through a series of $[2+2]$ cycloadditions and retro- $[2+2]$ cycloreversions involving a **metallacyclobutane** intermediate.

4.1 Step-by-Step Mechanism / 逐步机理

English — Step-by-Step

Step 1: Coordination. The metal carbene catalyst $[M]=CHR$ coordinates to one of the two olefinic groups of the diene substrate.

Step 2: $[2+2]$ Cycloaddition. The metal carbene and the coordinated olefin undergo a $[2+2]$ cycloaddition to form a four-membered **metallacyclobutane** ring. Although $[2+2]$ cycloadditions are thermally forbidden for purely organic substrates (Woodward–Hoffmann rules), the d-orbitals of the metal make this process symmetry-allowed.

Step 3: Retro- $[2+2]$ Cycloreversion. The metallacyclobutane ring opens in the productive direction to release a small olefin (ethylene) and generate a **new metal carbene species** that is now tethered to the substrate.

Step 4: Intramolecular $[2+2]$ Cycloaddition. The new carbene, now part of the same molecule as the second double bond, undergoes a second $[2+2]$ cycloaddition with the remaining olefin, forming a second metallacyclobutane — this time as part of the ring.

Step 5: Retro- $[2+2]$ Cycloreversion (ring closure). The second metallacyclobutane undergoes cycloreversion to release the **cyclic alkene product** and regenerate the metal carbene catalyst, completing the catalytic cycle.

中文 — 逐步解析

第 enumi 步: 配位。 金属卡宾催化剂 $[M]=CHR$ 与二烯底物上的一个烯基配位。

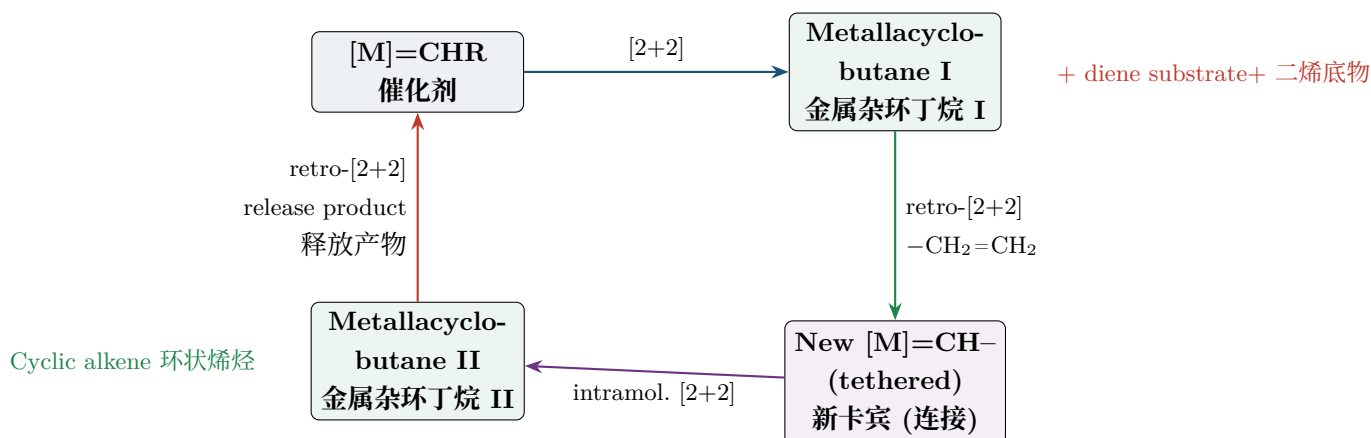
第 enumi 步: $[2+2]$ 环加成。 金属卡宾与配位的烯烃进行 $[2+2]$ 环加成, 形成四元环 **金属杂环丁烷** (metallacyclobutane)。虽然 $[2+2]$ 环加成对纯有机底物在热条件下是对称性禁阻的 (Woodward–Hoffmann 规则), 但金属的 d 轨道使这一过程在对称性上是允许的。

第 enumi 步: 逆 $[2+2]$ 环裂解。 金属杂环丁烷以生产性方向开环, 释放一个小分子烯烃 (乙烯), 并生成新的 **金属卡宾物种**——该卡宾现已连接在底物链上。

第 enumi 步: 分子内 $[2+2]$ 环加成。 新生成的卡宾与分子内剩余的另一个双键发生第二次 $[2+2]$ 环加成, 形成第二个金属杂环丁烷——此时它已包含在环结构中。

第 enumi 步：逆 [2 + 2] 环裂解（关环）。第二个金属杂环丁烷发生环裂解，释放环状烯烃产物并再生催化剂，完成催化循环。

4.2 Catalytic Cycle Diagram / 催化循环图



5 Common Catalysts / 常用催化剂

English

The most commonly used RCM catalysts are ruthenium-based, prized for their air stability, functional group tolerance, and ease of handling compared to Schrock's early-transition-metal catalysts.

NHC = N-heterocyclic carbene (typically SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene).

中文

最常用的 RCM 催化剂是钌 (Ru) 基催化剂，因其空气稳定性好、官能团耐受性强、操作方便而受到青睐。

NHC = N-杂环卡宾。第二代催化剂用 NHC 替代了一个 PCy_3 配体，显著提高了催化活性。

6 Ring Size and Selectivity / 环的大小与选择性

English

RCM is most effective for forming **five- and six-membered rings**, which are thermodynamically and kinetically favored (low ring strain, favorable entropy).

- **5- and 6-membered rings:** Very facile; often proceed at room temperature with low catalyst loading (1–2 mol%).
- **7- and 8-membered rings:** Moderate difficulty; may require higher temperatures,

longer times, or higher catalyst loading.

- **Medium rings (9–12):** Challenging due to transannular strain and unfavorable entropy; require high dilution and sometimes specialized catalysts.
- **Large rings (≥ 13):** Macrocyclic RCM is possible and widely used in natural product synthesis, but requires very high dilution (typically ≤ 1 mM substrate concentration).

The competition between intramolecular RCM and intermolecular acyclic diene metathesis polymerization (ADMET) is controlled by **dilution**: lower concentration favors RCM.

中文

RCM 最擅长形成五元环和六元环（热力学和动力学都有利：环张力低，熵变有利）。

- **5 元和 6 元环**：非常容易；通常室温、低催化剂用量（1–2 mol%）即可进行。
- **7 元和 8 元环**：难度适中；可能需要更高温度、更长时间或更多催化剂。
- **中环 (9–12 元)**：由于跨环张力和不利熵变，较为困难；需高稀释和特殊催化剂。
- **大环 (≥ 13 元)**：大环 RCM 在天然产物合成中广泛应用，但需非常高的稀释度（底物浓度通常 ≤ 1 mM）。

分子内 RCM 与分子间非环二烯复分解聚合（ADMET）之间的竞争由**稀释度**控制：低浓度有利于 RCM。

7 Key Factors Affecting RCM / 影响 RCM 的关键因素

English

1. **Thorpe–Ingold effect (gem-disubstitution effect).** Having substituents on the carbon chain connecting the two olefins brings the reactive ends closer together, accelerating cyclization. This conformational effect is often exploited deliberately.
2. **Olefin substitution pattern.** Terminal olefins (monosubstituted) react fastest. Disubstituted olefins are slower but still feasible. Trisubstituted olefins are challenging and require highly active catalysts (e.g., Grubbs II or Hoveyda–Grubbs II).
3. **Functional group compatibility.** Ruthenium catalysts tolerate alcohols, esters, amides, ethers, and even some amines and thiols. However, free amines, thiols, and phosphines can coordinate to the metal and poison the catalyst. *Protection* of these groups (e.g., Boc for amines) is common.
4. **Concentration.** High dilution (~ 1 – 10 mM) favors RCM over oligomerization. Slow addition of substrate (*syringe pump*) is also used.
5. **Temperature.** Refluxing CH_2Cl_2 ($\sim 40^\circ\text{C}$) or toluene ($\sim 110^\circ\text{C}$) is typical. Higher temperatures increase catalyst activity but may also accelerate decomposition.
6. **Ethylene removal.** Removing ethylene (by inert gas sparging or reduced pressure) drives the equilibrium forward.

中文

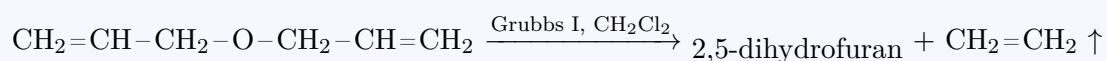
1. **Thorpe–Ingold 效应 (偕二取代效应)**。在连接两个烯烃的碳链上引入取代基, 可使反应端基靠近, 加速关环。此构象效应常被有意利用。
2. **烯烃取代模式**。端烯 (单取代) 反应最快; 二取代烯烃较慢但可行; 三取代烯烃困难, 需高活性催化剂。
3. **官能团兼容性**。钨催化剂可耐受醇、酯、酰胺、醚等。但游离胺、硫醇和膦可与金属配位, 毒化催化剂。常需保护这些基团 (如胺用 Boc 保护)。
4. **浓度**。高稀释 (~1–10 mM) 有利于 RCM 而非寡聚。注射泵缓慢加料也常使用。
5. **温度**。常在 CH_2Cl_2 (~40 °C) 或甲苯 (~110 °C) 中回流。高温提高催化活性, 但可能加速催化剂分解。
6. **乙烯移除**。通过惰性气体鼓泡或减压除去乙烯, 推动平衡正向移动。

8 Representative Examples / 代表性反应实例

8.1 Example 1: Five-Membered Ring Formation / 五元环形成

English

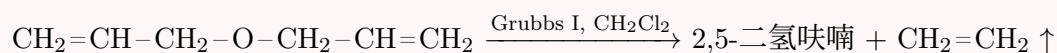
One of the simplest demonstrations of RCM is the cyclization of diallyl ether to form 2,5-dihydrofuran:



This reaction proceeds quantitatively at room temperature within minutes, illustrating the ease of 5-membered ring closure.

中文

RCM 最简单的示例之一是二烯丙基醚关环生成 2,5-二氢呋喃:



此反应在室温下数分钟内定量完成, 说明五元环关环的容易程度。

8.2 Example 2: Macrolactonization via RCM / 大环内酯的 RCM 合成

English

Many biologically active natural products contain macrocyclic lactones (macrolides). RCM has been used in landmark total syntheses such as:

- **Epothilone A & B** —16-membered macrolide anticancer agents.
- **Sch 38516 (fluvirucinin A₁)** —14-membered ring closure by RCM.

- **Stemonamide** —a complex alkaloid synthesized using RCM as a key step.

In these syntheses, the RCM step typically requires high dilution ($< 1 \text{ mM}$) and Grubbs II or Hoveyda–Grubbs II catalyst.

中文

许多生物活性天然产物含有大环内酯结构。RCM 已在以下里程碑式全合成中应用：

- **Epothilone A/B** —16 元大环内酯类抗癌药物。
- **Sch 38516 (fluvirucin A₁)** —14 元环关环。
- **Stemonamide** —一种复杂生物碱，以 RCM 为关键步骤。

这些合成中，RCM 步骤通常需要高稀释度 ($< 1 \text{ mM}$) 和 Grubbs II 或 Hoveyda–Grubbs II 催化剂。

9 Comparison with Related Metathesis Reactions / 与相关复分解反应的比较

Reaction Type 反应类型	Substrates 底物	Products 产物	Notes 备注
RCM 关环复分解	Diene (intramol.)	Cyclic alkene + $\text{CH}_2=\text{CH}_2$	Ring formation; dilute conditions
CM 交叉复分解	Two olefins (inter-mol.)	New olefin	E/Z selectivity can be challenging
ROM 开环复分解	Cyclic olefin	Diene or oligomer	Driven by ring strain release
ROMP 开环复分解聚合	Strained cyclic olefin	Polymer	Norbornene, cyclooctene, etc.
ADMET 非环二烯复分解	α,ω -diene (inter-mol.)	Linear polymer + $\text{CH}_2=\text{CH}_2$	Competes with RCM

10 Applications / 应用

English

1. **Total Synthesis of Natural Products.** RCM is a go-to strategy for constructing macrocyclic frameworks found in bioactive molecules (macrolides, cyclopeptides, terpenes).
2. **Pharmaceutical Chemistry.** Several FDA-approved drugs and clinical candidates feature ring systems formed by RCM, including **simeprevir** (Hepatitis C protease inhibitor) and **BILN 2061**.

- 3. Materials Science.** ROMP (the polymer counterpart) produces specialty polymers, but RCM itself is used in monomer synthesis.
- 4. Green Chemistry.** Metathesis can replace multi-step sequences, improving atom economy. Ethylene is the only byproduct.
- 5. Bioconjugation & Chemical Biology.** RCM has been used to “staple” α -helical peptides, reinforcing their secondary structure for therapeutic applications.

中文

- 1. 天然产物全合成。** RCM 是构建生物活性分子中大环骨架的首选策略（大环内酯、环肽、萜类化合物）。
- 2. 药物化学。** 多种 FDA 批准药物和临床候选药物含有由 RCM 形成的环系统，包括 **simeprevir**（丙肝蛋白酶抑制剂）和 **BILN 2061**。
- 3. 材料科学。** ROMP（聚合物对应版本）用于生产特种高分子，而 RCM 本身用于单体合成。
- 4. 绿色化学。** 复分解可替代多步合成，提高原子经济性。乙烯是唯一副产物。
- 5. 生物偶联与化学生物学。** RCM 已被用于” 钉合” (stapling) α -螺旋肽，增强其二级结构以用于治疗。

11 Limitations and Challenges / 局限性与挑战

English

- **E/Z selectivity.** Standard RCM gives mixtures of E and Z isomers. Z-selective catalysts (e.g., by Grubbs and Hoveyda) have been developed but are still substrate-dependent.
- **Catalyst decomposition.** Ru catalysts can decompose at high temperatures or in the presence of certain functional groups. Ruthenium residues can be difficult to remove.
- **Substrate limitations.** Electron-poor olefins (e.g., α,β -unsaturated carbonyls) and very hindered olefins are sluggish.
- **Medium ring difficulty.** Rings of 8–12 members remain challenging targets.
- **Ruthenium removal.** Trace Ru in pharmaceutical products is a regulatory concern. Scavengers (e.g., activated carbon, DMSO, lead tetraacetate) or silica chromatography are used.

中文

- **E/Z 选择性。**标准 RCM 通常得到 E/Z 异构体混合物。Z-选择性催化剂已被开发,但仍取决于底物。
- **催化剂分解。**高温或某些官能团会导致 Ru 催化剂分解。钌残留的去除可能困难。
- **底物局限性。**贫电子烯烃(如 α,β -不饱和羰基)和空间位阻大的烯烃反应缓慢。
- **中环难题。**8-12 元环仍然是合成中的挑战。
- **钌残留。**药物产品中的微量 Ru 是监管关注点。需用活性炭、DMSO 或硅胶色谱除去。

12 Summary / 总结

English — Key Takeaways

1. RCM converts a diene into a cyclic alkene + ethylene, catalyzed by metal carbenes.
2. The mechanism follows the Chauvin cycle: alternating $[2+2]$ and retro- $[2+2]$ steps via metallacyclobutane intermediates.
3. Grubbs-type Ru catalysts are the workhorses due to their stability and functional group tolerance.
4. Ring size, dilution, olefin substitution, and the Thorpe-Ingold effect are critical for success.
5. RCM is indispensable in modern organic synthesis, from natural products to pharmaceuticals.

中文 — 核心要点

1. RCM 将二烯转化为环状烯烃 + 乙烯,由金属卡宾催化。
2. 机理遵循 Chauvin 循环:通过金属杂环丁烷中间体交替进行 $[2+2]$ 和逆 $[2+2]$ 步骤。
3. Grubbs 型 Ru 催化剂因其稳定性和官能团耐受性而成为主力。
4. 环大小、稀释度、烯烃取代模式和 Thorpe-Ingold 效应是成功的关键因素。
5. RCM 在现代有机合成中不可或缺,从天然产物到药物合成。