Cascade Reactions in Chain-Growth Polymerization

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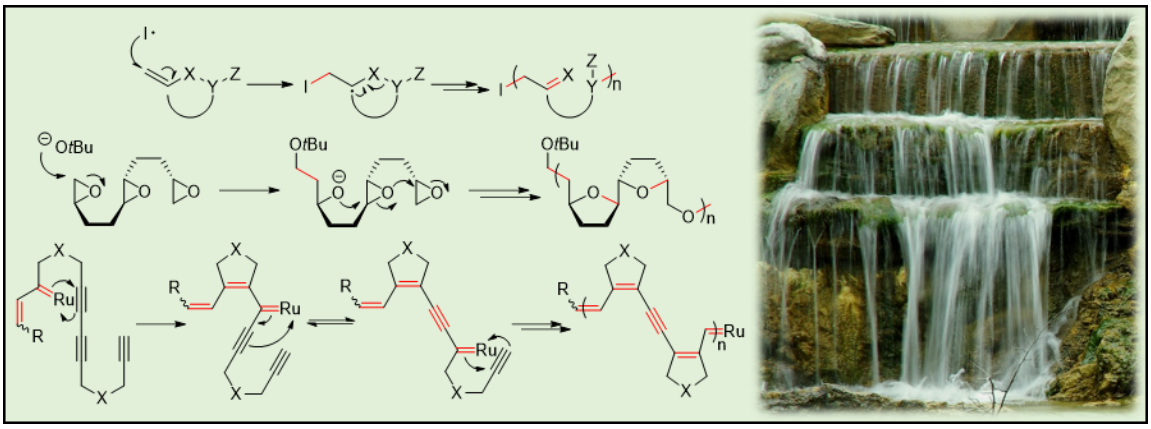


Abstract. While the design and implementation of cascade reactions in organic chemistry and enzymatic biosynthesis flourished in the past decades, cascade reactions in polymerization remain an emerging concept with exciting opportunities. Cascade polymerization techniques can be used to generate polymers in which unique structures and functionalities are incorporated in the backbone of polymers, making them powerful tools to address the ever-increasing demand for new materials with improved functionality and sustainability. This Perspective highlights existing strategies for chain-growth cascade polymerizations following radical, ionic, nucleophilic, and transition metal catalysis mechanisms, with a focus on the design principle and reaction mechanism. Collectively, recent work illustrates the considerable potential and predicts future developments of chain-growth cascade polymerization, an active research field at the intersection of polymer science and organic chemistry.

1. Introduction

A hallmark of biopolymers, such as DNA, RNA, proteins, and polysaccharides, is their multidimensional structural complexity at the primary, secondary, and tertiary structure levels, which in turn is essential for their highly diverse functions.[1,2] In contrast, despite the profound developments of the modern living/controlled polymerization techniques in the past three decades,[3-6] the structures and properties of synthetic polymers to date are still not as sophisticated as biopolymers.[7] The limited structural scope of existing synthetic polymers has increasingly prompted polymer chemists to turn to sister disciplines (*e.g.*, organic chemistry, inorganic chemistry, supramolecular chemistry, and chemical biology) to uncover tools that would allow precise construction of macromolecular sequences[8-10] and structures[11,12] with an increasing level of sophistication for better functions.

Both in nature and in organic synthesis, cascade reaction has been a promising strategy for generating molecular scaffold complexity in terms of atom economy and energy input.[13] Nature is a master designer of enzymatic cascade reactions, commonly incorporating exergonic steps to drive otherwise energetically disfavored reactions to completion.[14,15] Following the same principle but employing chemical catalysis and transformations, organic chemists plan and implement cascade reactions to shorten synthetic routes and improve overall yields in the chemical synthesis of complex molecules.[16] The efficiency and atom economy of cascade reactions have been exemplified in a series of landmark total syntheses.[17]

Emulating the efficient cascade reactions achieved by nature and in organic chemistry, polymer chemists have implemented both the principle and the practices of cascade reactions in polymer synthesis to achieve two primary goals: incorporating complex functionalities into polymers and providing the driving force for otherwise energetically disfavored polymerization reactions.

Combining cascade reactions with contemporary polymer synthesis methods, such as living/controlled polymerization, template-assisted polymerization, compartmentalized polymerization, and solid-phase synthesis, could have the potential to generate polymers with new structures and functions that cannot be accessed via traditional approaches.

In this Perspective, we highlight seminal works and recent progress in the cascade reactions in chain-growth polymerization with a focus on the design principles and mechanistic analyses of the cascade processes. Hereafter, to describe these reactions, we define chain-growth cascade polymerization as a polymerization process in which two or more consecutive intramolecular bond-forming or bond-cleaving transformations take place at the polymer main chain upon the addition of each monomer. The following discussion on this definition should be noted. (1) Inspired by the concept of cascade reactions in organic chemistry described in the landmark reviews by Tietze,[18,19] Nicolaou,[20] and Walsh and Moore,[21] the definition of chain-growth cascade polymerization is made in consistent with a recent review by Peterson and Choi.[22,23] (2) The consecutive transformations in the chain-growth cascade polymerization must take place under the same reaction conditions. The latter transformations must rely on the structures generated by the previous transformation. (3) Side-chain cascade transformations that do not contribute to the construction of main-chain structures are excluded from this Perspective. (4) While sometimes also referred to as "cascade polymerization", one-pot polymerization in which two or more chain-forming reactions occur on the same initiator, but essentially in isolation from one another is also excluded.

To better understand the advances in this field, the chain-growth cascade polymerizations are grouped into three sections based on their mechanisms: radical, ionic and nucleophilic, and transition metal-catalyzed cascade polymerization. The opportunities and future directions of the

chain-growth cascade polymerization will also be discussed. Additionally, readers of this Perspective are encouraged to read the excellent recent reviews on related topics such as step-growth cascade polymerization,[24-26] which typically involves multicomponent reactions among several monomers, and cascade processes beyond polymerization including depolymerization and mechanochemistry.[27-30]

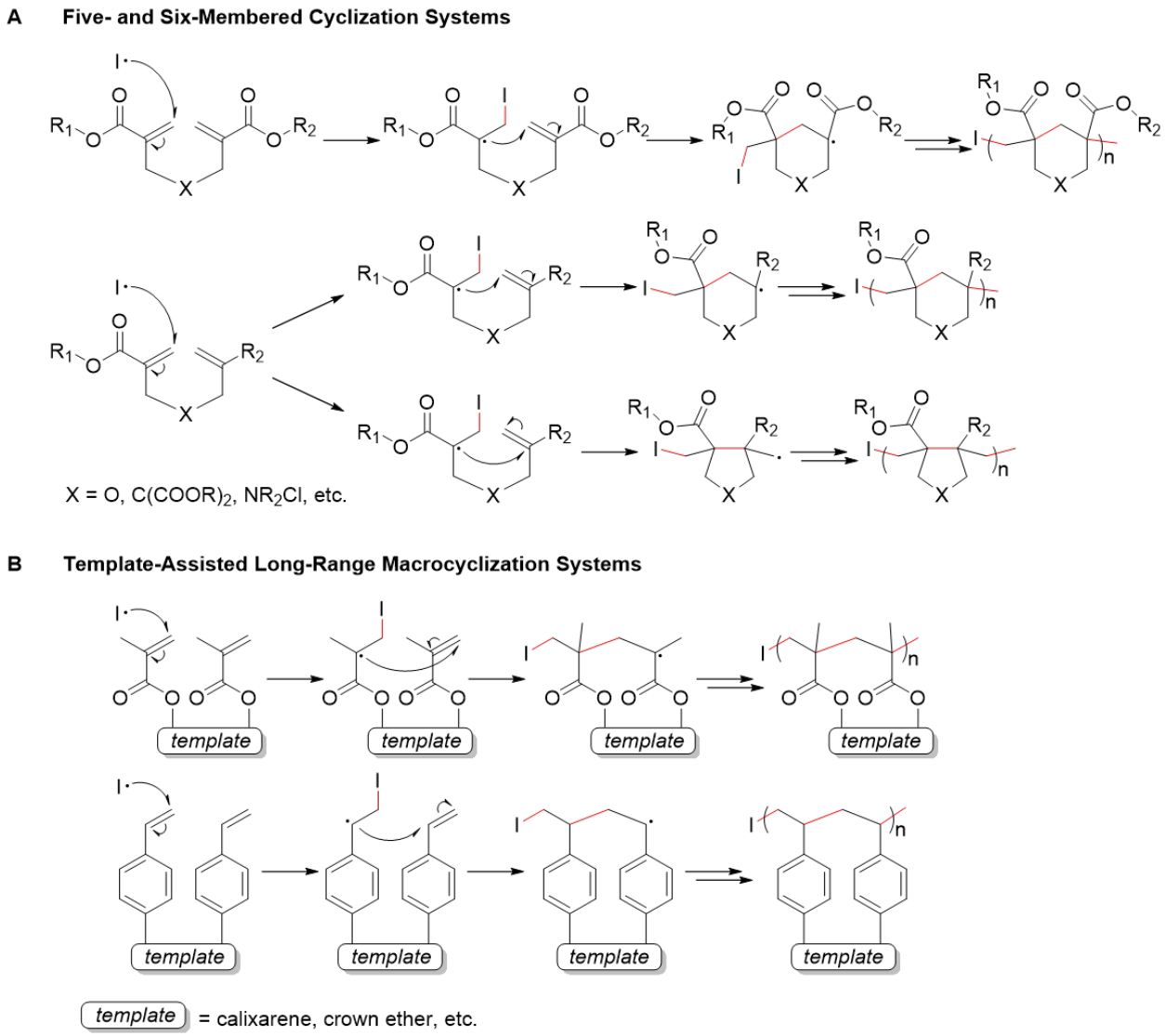
2. Radical cascade polymerization

In this section, representative examples of two classes of radical cascade polymerization are discussed based on their chain propagation mechanism: radical ring-closing cascade polymerization (rRCCP) and radical ring-opening cascade polymerization (rROCP).

2.1. Radical ring-closing cascade polymerization (rRCCP)

The main idea of rRCCP is the use of thermodynamically and/or kinetically favored five-membered (*5-exo-trig*) and six-membered (*6-endo-trig*) ring formation or template-assisted macrocyclization to provide the driving force for cascade processes. Vinyl, vinyl ether, and (meth)acrylate C=C double bonds are common functional groups in the structures of the monomers for rRCCP. In five- and six-membered cyclization systems, the composition, length, and conformation of the spacer between two C=C double bonds are important factors for the ring-closing cascade (**Scheme 1A**). For example, the Thorpe–Ingold effect, a well-known phenomenon in organic chemistry dictating that the placement of bulky substituents on a linear reactant makes it favor intramolecular reactions over intermolecular ones, was found to play an important role in cyclization efficiency.[31] Functional groups that can induce a large Thorpe–Ingold effect such as quaternary ammonium ($X=NR_2Cl$) [32,33] and malonate ($X=C(COOR_2)$)[34] are often necessary for an

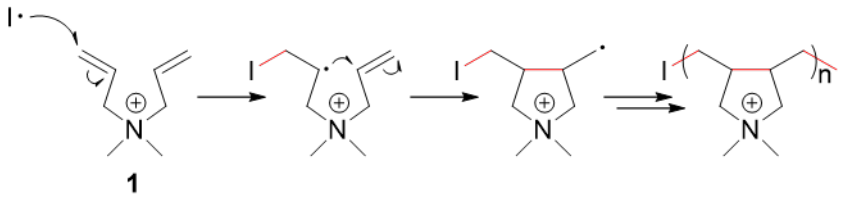
effective ring-closing process. In template-assisted long-range macrocyclization systems, intramolecular macrocyclization is achieved through judicious template design (**Scheme 1B**). Typical examples of these templates include 1,2-disubstituted cyclohexane,[35] *gem*-disubstituted silyl ester,[36] calixarene,[37] and crown ether,[38,39] etc., where the rigidity of the templates or their abilities to establish ligand-metal coordination are essential for the intramolecular ring-closing. In both rRCCP systems, a non-optimal spacer or template between the two C=C double bonds in a monomer can lead to undesired 1,2-polymerization, in which only one C=C double bond participates in chain propagation, leaving unreacted dangling olefins as potential crosslinking sites detrimental to polymerization control. It is also noteworthy that rRCCP can greatly benefit from the recent developments of controlled radical polymerization techniques, including atom transfer radical polymerization (ATRP),[36,40,41] reversible addition-fragmentation chain-transfer polymerization (RAFT),[35,42,43] and nitroxide-mediated polymerization (NMP).[44] These developments allow for precise control over polymerization rate, dispersity, architecture, and sequence.



Scheme 1. Schematic illustration of two rRCCP systems, where initiator is denoted as I·. (**A**) Five- and six-membered cyclization systems. (**B**) Template-assisted long-range macrocyclization systems.

The earliest examples of five- and six-membered rRCCP dates back to the 1950s.[32,45] Bulter et al. noticed that *N, N*-dimethyl-*N, N*-diallylamonium monomer (**1**) derived polymers were not cross-linked since they were completely water-soluble (**Scheme 2**). They went on to discover what they referred to as cyclopolymerization, an intramolecular cyclization and intermolecular chain

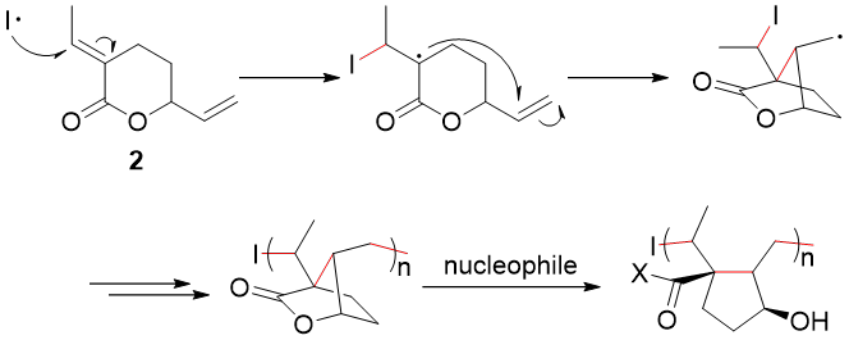
propagation pathway alternative to the 1,2-polymerization mechanism, and successfully explained the lack of pendant C=C double bonds in the polymer. Smith and Butler performed a series of model compound studies in the late 1970s to prove the kinetic ring closure (*5-exo-tet* or *5-exo-trig*) was preferred over the thermodynamic ring closure (*6-endo-tet* or *6-endo-trig*).[46] Since the discovery of cyclopolymerization, several notable studies on the rRCCP of **1** were carried out. Houk et al. conducted theoretical studies to compare **1** with its less substituted analogues *N, N*-diallylamine and *N*-methyl-*N, N*-diallylamine in terms of cyclization efficiency and rates.[47,48] Agarwal et al. showed that RAFT polymerization could be successfully applied to **1**. Controlled rRCCP was achieved as evidenced by exclusively five-membered ring formation by NMR analysis, M_n close to theoretical values (from 2.1 to 30.0 kg/mol), narrow dispersity ($Đ$ ~ 1.1), and intact chain-end groups amendable to chain extension.[43]



Scheme 2. rRCCP of *N, N*-dimethyl-*N, N*-diallylamonium monomer (**1**).

In 2014, Nozaki et al. reported that a lactone monomer 3-ethylidene-6-vinyltetrahydro-2*H*-pyran-2-one (**2**) derived from 1,3-butadiene and carbon dioxide could successfully undergo rRCCP, affording polymers with high M_n (up to 85 kg/mol) and CO_2 incorporation ratio (up to 33 mol%, **Scheme 3**).[49] Although the presence of multiple possible reaction pathways resulted in complex polymer structures, under optimized reaction conditions a bicyclic lactone repeating unit was formed predominantly. The cascade reaction during chain propagation consisted of an initial radical addition to the acrylate moiety, followed by the *5-exo-trig* cyclization and the formation of

a primary carbon-centered radical to which the next monomer was added. The resulting bicyclic lactone repeating unit could further undergo post-polymerization modifications such as hydrolysis and aminolysis.[50] Overall, these works highlighted the advantage of rRCCP to build elaborate structures and provided access to novel carbon dioxide derived sustainable polymeric material.



Scheme 3. rRCCP and postpolymerization modification of lactone monomer **2**.

In nature, template-assisted polymerization is the molecular essence of nucleic acids and proteins, two important classes of biopolymers. Similarly, template-assisted polymerization also holds great promises in enabling sequence control in synthetic polymers. In 2005, the Sherrington group reported an elaborate strategy to control the chirality of poly-(meth)acrylate main chains.[51] In this report, a chiral zinc complex, (-)-sparteine zinc(II), was simultaneously coordinated with the carboxyl groups of two adjacent (meth)acrylate monomers (**Scheme 4A**). The random copolymerization of (-)-sparteine zinc(II)-(meth)acrylate complexes (**3**) and styrene in dichloroethane (DCE) successfully yielded a polymer with good solubility that showed no vinyl signals in ^{1}H NMR and FTIR spectra. Further workup removed the (-)-sparteine zinc(II) moiety and afforded a poly-styrene-(meth)acrylic acid copolymer (PS-(M)AA) with well-defined

dextrorotatory optical rotation. This good stereoselectivity is in contrast to the PS-(M)AA copolymers synthesized from achiral zinc complex, of which no optical rotation was observed. However, the requirement of electron-rich co-monomer (*e.g.*, 2-vinylnaphthalene) and stoichiometric metal complexes limited the scope of the monomers suitable for this technique. In another notable example, Sawamoto and co-workers developed a rRCCP approach that enabled two consecutive cyclization steps in the cascade to achieve repetitive ABA sequence, where two styrene (S) and one 4-vinylpyridine (P) units were linked together by a palladium–2,6-pyridinedicarboxamide template (**Scheme 4B**).[52] Taken together, these methods provided novel approaches to "traceless" control over polymer chirality or sequence without the need for covalent modification.

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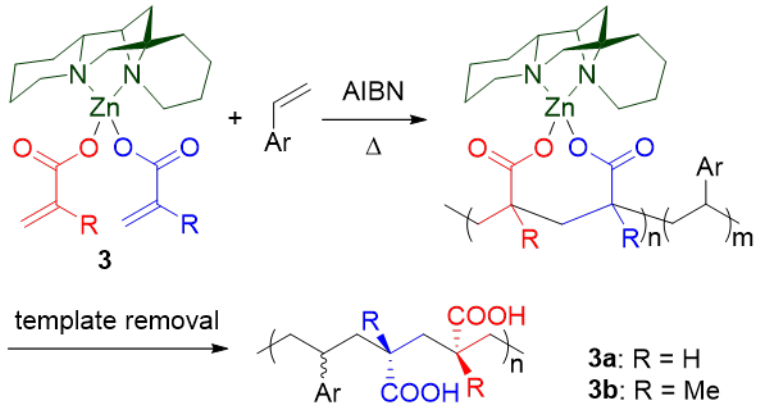

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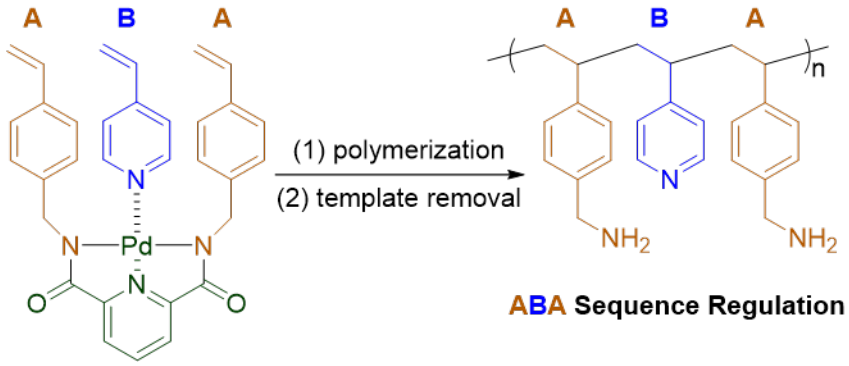
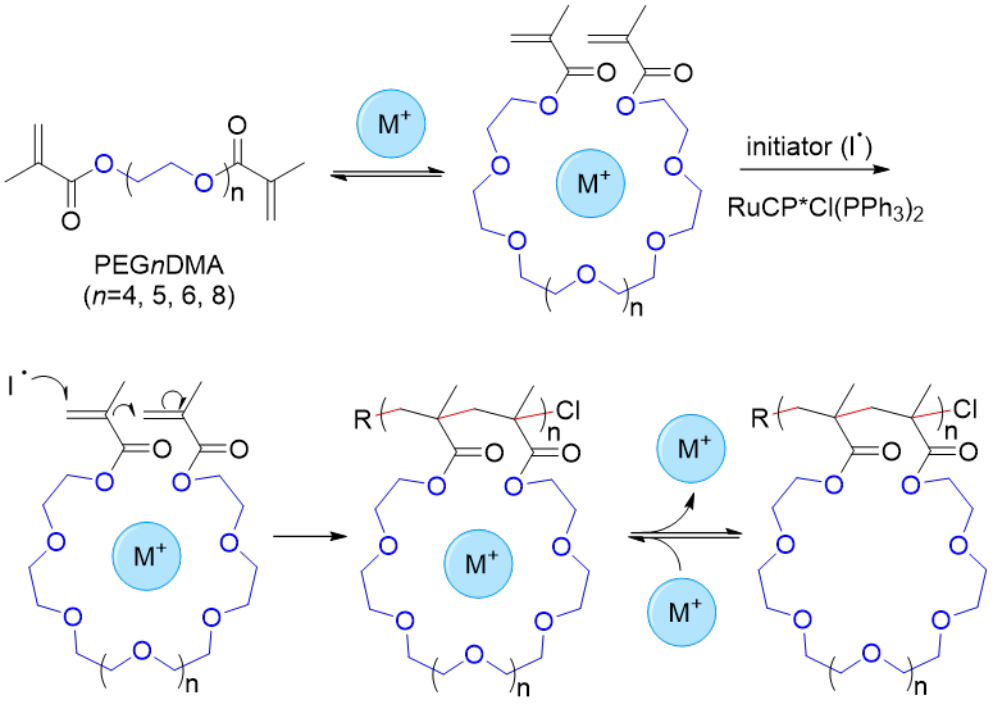


Scheme 4. (**A**) rRCCP of (-)-sparteine zinc(II)-(meth)acrylate complexes **3**. (**B**) A template-assisted rRCCP enabled by a palladium–2,6-pyridinedicarboxamide complex.

An impressive example of the cation template-assisted rRCCP was presented by Sawamoto and co-workers (**Scheme 5**).[38] In this work, two methacrylate moieties were tethered by an oligo ethylene glycol (OEG) linker and were polymerized when alkali metal cations were added for coordination. The interaction between the chelating OEG group and the metal cation was both strong and specific to ensure highly efficient cyclization. Linear polymers with low dispersity ($Đ$ ~ 1.2) were readily prepared in high conversion (>97%) without gelation or residual dangling olefin left. In contrast, direct polymerization without a metal cation only resulted in products with high dispersity ($Đ$ ~ 2.0) or gelation. The resulting main-chain cyclopolymers exhibited higher affinity and selectivity in cation binding than the corresponding monomers. This work demonstrated a simple and efficient template-assisted rRCCP strategy, as well as provided pseudo-crown ether containing polymers with tailor-made cation recognition capabilities.

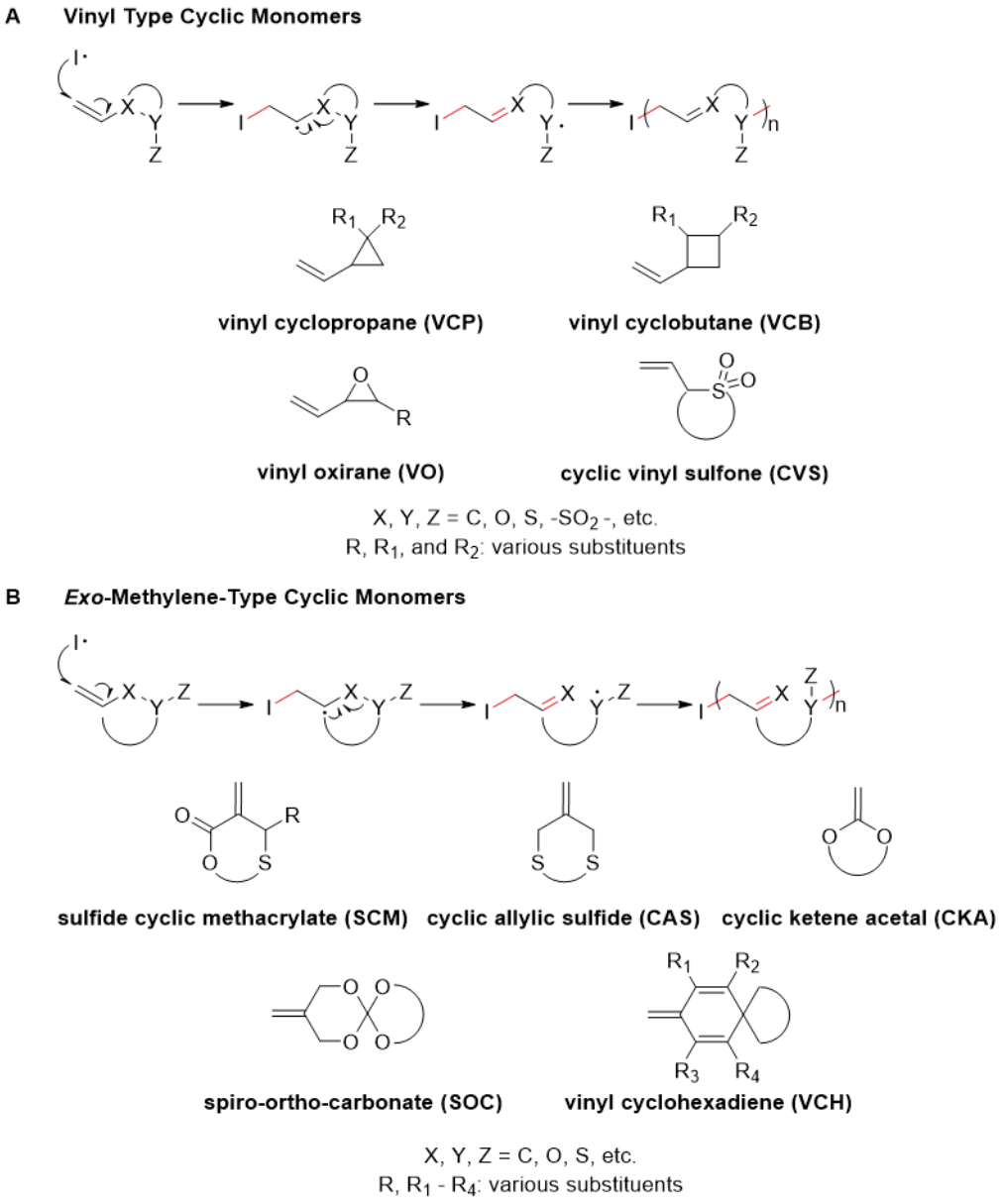


Scheme 5. Chelating OEG and cation template-assisted rRCCP.

2.2. Radical ring-opening cascade polymerization (rROCP)

Radical polymerization is best known for constructing all-carbon polymer backbones. While an all-carbon backbone demonstrates high chemical and mechanical stability, it becomes a liability when the degradability of polymer is a property of interest. With the ever-growing need for degradable polymers in biomedical applications and our society's increasing awareness of sustainability and carbon neutrality, polymers with bio-based, or degradable main-chain functionalities have recently attracted significant attention.[53,54] Therefore, rROCP approaches capable of facilely incorporating degradable main-chain functionalities into polymer backbones hold great potential. In general, monomers capable of rROCP often contain a cyclic structure bearing a vinyl group or an *exo*-methylene group, as shown in **Scheme 6**. During polymerization,

radical addition to the terminal double bond is followed by a ring-opening process to release the ring strain and yield thermodynamically favored open-chain intermediates capable of propagation.[55] Therefore, an effective cascade pathway that enables highly efficient ring-opening rearrangements is crucial for a successful rROCP process. Since the first report in the 1960s,[56] numerous *exo*-methylene-type monomers rROCP monomers have been reported. Examples of the vinyl-type monomers include vinyl cyclopropane (VCP),[57] vinyl cyclobutane (VCB),[58] vinyl oxirane (VO),[59] and cyclic vinyl sulfone (CVS)[60,61] (**Scheme 6A**). Examples of *exo*-methylene-type monomers include sulfide cyclic methacrylate (SCM),[62] cyclic allylic sulfide (CAS),[63,64] cyclic ketene acetal (CKA),[65] spiro-ortho-carbonate (SOC),[66] and vinyl cyclohexadiene (VCH)[67,68] (**Scheme 6B**). The long-term popularity of these polymers comes not only from the unique cascade chemistry, but also from their intriguing material properties. Extensive works have been devoted to implement these cascade polymerization techniques to fabricate functional materials for applications such as low shrinkage materials,[69] degradable polymers,[70] and drug delivery,[71] etc. Given that many of the rROCP monomers have been discussed in the recent reviews by Guillaneuf et al.[72] and Endo et al.,[73] hereafter, we will focus on the design principle and mechanistic insights into representative rROCP systems: CKA, VCP, SCM, and a unique example of rROCP of low strain macrocyclic monomer.

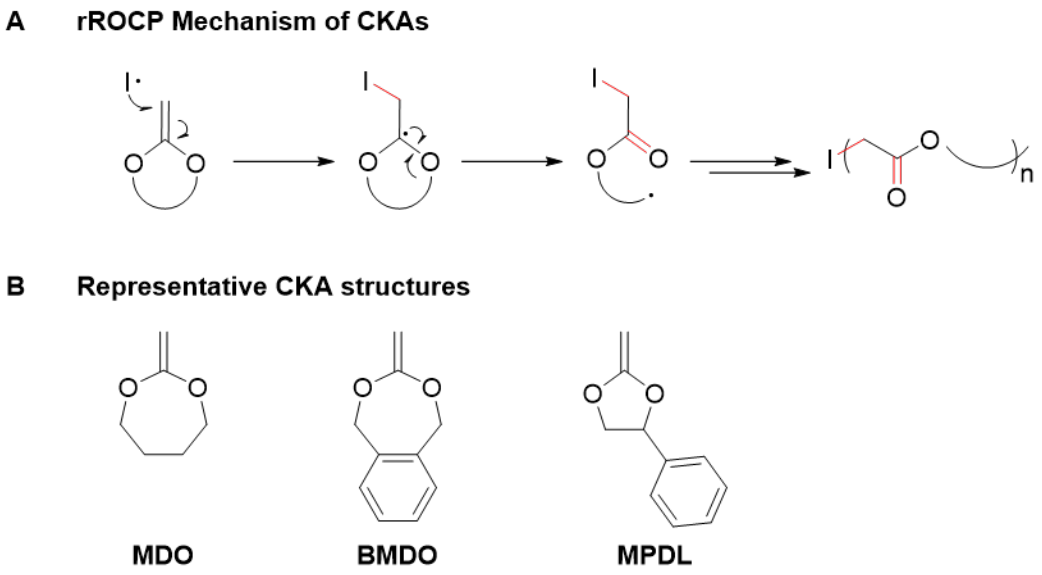


Scheme 6. Structures of the two types of cyclic monomers capable of rROCP. (**A**) Vinyl-type cyclic monomers. (**B**) *Exo*-methylene-type cyclic monomers.

Among rROCP monomers, cyclic ketene acetals (CKAs) were comprehensively studied over several decades. The popularity of CKAs can be primarily attributed to its ability to facilely

generate aliphatic polyesters by rROCP, which are well known for their excellent biodegradability. As depicted in **Scheme 7A**, the mechanism of the CKA rROCP includes the radical addition of the exomethylene group and the subsequent ring-opening process to form an ester group in the main chain. A main side reaction in the polymerization of CKAs is the 1, 2-addition pathway that generates an all-carbon main chain structure, resulting in the heterogenous backbone composition and non-degradable segments. Although great efforts have been made in studying how ring size, steric hindrance, solvent, and temperature influence the reactivity of CKAs, a general monomer design principle still remains elusive. To date, only 2-methylene-1,3-dioxepane (MDO), 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), and 2-methylenephenyl-1,3-dioxolane (MPDL) (**Scheme 7B**) are known to undergo quantitative ring-opening polymerization under a broad range of conditions.[72]

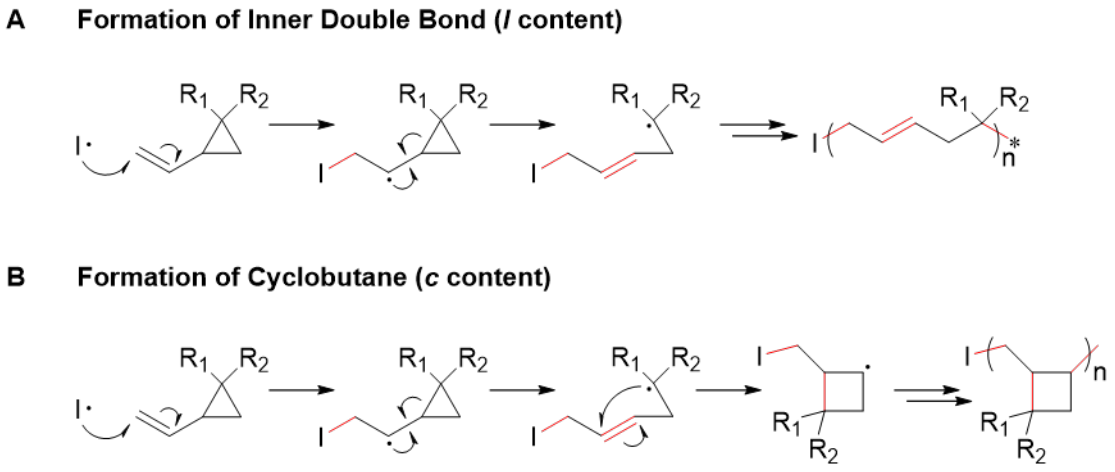
As the main interest of CKA rROCP lies within the incorporation of degradable functionality into the polymer backbone, copolymerization of CKA monomers with traditional acyclic monomers (*e.g.*, styrene and acrylates) provides a promising solution, as it combines the degradability from CKAs with the low cost and predictable reactivity of styrene and acrylates. Moreover, copolymerization allows the regulation of polymer degradability by simply varying monomer ratios. However, the low reactivity of CKAs compared to styrene and acrylates makes it a great challenge to achieve high ratio of the degradable units.[74,75]



Scheme 7. (**A**) rROCP mechanism of CKAs. (**B**) Representative CKA structures.

The rROCP of vinylcyclopropanes (VCPs), a vinyl-type cyclic monomer, has been subjected to extensive studies.[57] The original interests in this monomer class stem from their ability to undergo the unique 1,5-ring-opening pathway to form an internal double bond (denoted as *l*) in the polymer main chain (**Scheme 8A**). However, a competing intramolecular cyclization to form cyclobutane (denoted as *c*) often occurred at non-negligible frequencies (**Scheme 8B**). The first rROCP of VCP that led to predominant 1,5-ring-opening products was the ATRP polymerization of 1,1-bis(ethoxycarbonyl)-2-vinylcyclopropane (ECVCP) reported by Rimmer et al. (*l* content > 98%).[76] However, under these conditions, polymers were generated with only modest conversion and low M_n, perhaps caused by catalyst deactivation due to coordination with ECVCP. In 2019, this challenge was overcome by Miyake et al. using organocatalyzed ATRP (O-ATRP), where highly reducing organic photoredox catalysts (PCs) enabled a fast chain end activation/deactivation cycle and eliminated the unfavorable monomer coordination.[77,78] High molecular weight polyVCPs with well-defined linear structures were readily prepared. The

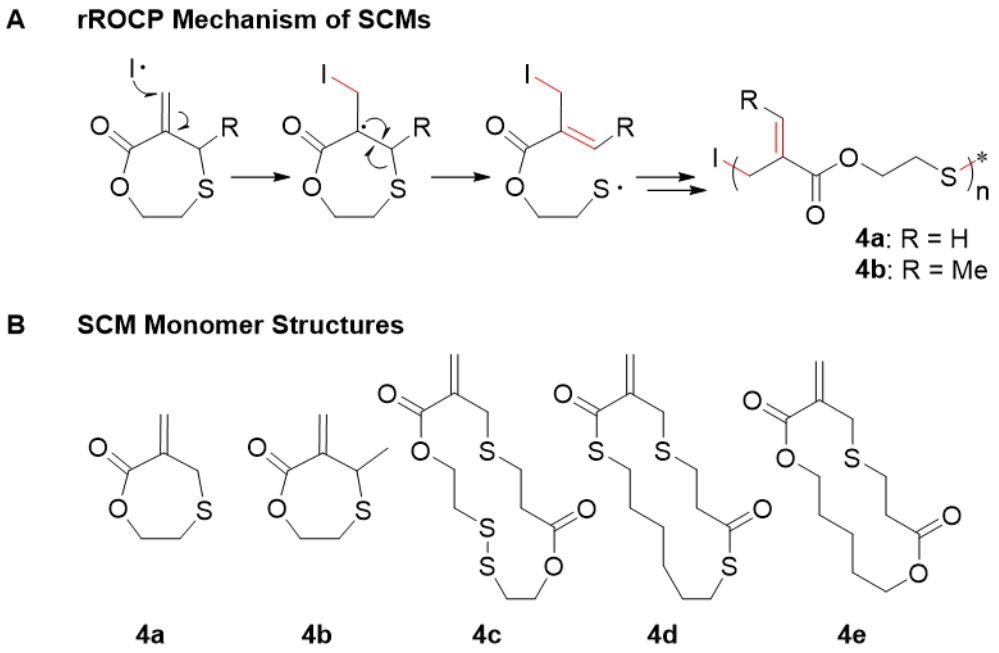
excellent polymerization control was further demonstrated by the elaborately designed control experiments, kinetic characterizations, chain-end group analysis, and block-copolymerization. The temporal control of polymerization was successfully achieved using pulsed irradiation. Interestingly, polyVCPs with high *c* content could also be prepared when reactions were conducted at low initial monomer concentration and high temperature. A highlight of this study is that the *l*/*c* contents of well-defined high molecular weight polyVCPs can be readily controlled by tuning the reaction conditions. However, the detailed mechanism that could explain the exquisite control over the *l*/*c* ratio was not included in this study. Further studies are warranted to bridge this knowledge gap.



Scheme 8. rROCP of VCPs. (**A**) Formation of the inner double bond (*l* content). (**B**) Formation of cyclobutane (*c* content).

In 1994, Rizzardo et al. reported sulfide cyclic methacrylates (SCMs) as an *exo*-methylene-type monomer for rROCP.[62] The mechanism of this cascade polymerization consists of an initial radical addition to the terminal vinyl group, followed by the β-elimination of the thiyl radical for chain propagation (**Scheme 9A**). It is noteworthy that the severe crosslinking observed in the homopolymerization of monomer **4a** could be effectively suppressed by incorporating a methyl

group at the β position (**4b**), as the tri-substituted alkene formed after the β-elimination of the thiyl radical is less susceptible to further radical attack compared to the terminal alkene formed in the reaction of **4a**. Hawker et al. further introduced ester, thioester, and disulfide groups into SCM monomers to build up main-chain degradable polymers (**Scheme 9B**, **4c-e**).[79] This seminal work highlighted the utility of rROCP in overcoming the nondegradability challenge associated with polyacrylates. However, a prominent shortcoming is the high dispersity ($Đ > 1.8$) in the homo- and copolymerization of SCMs, which is attributed to the incompatibility of the thiyl radical and RAFT process.

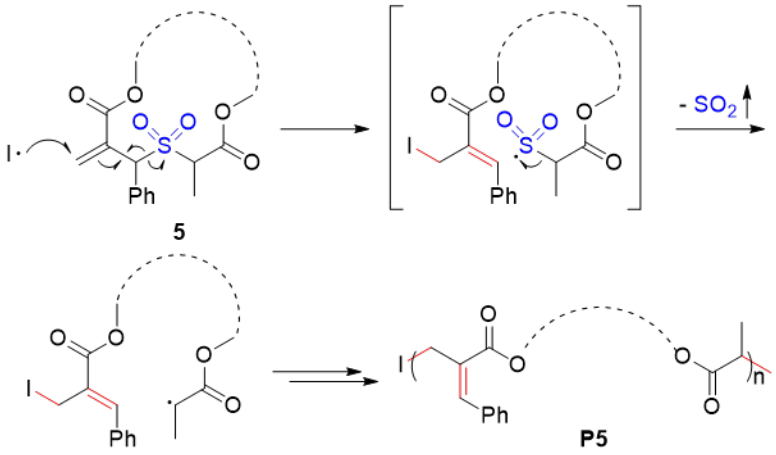


Scheme 9. (**A**) rROCP of SCMs and (**B**) examples of SCM monomers.

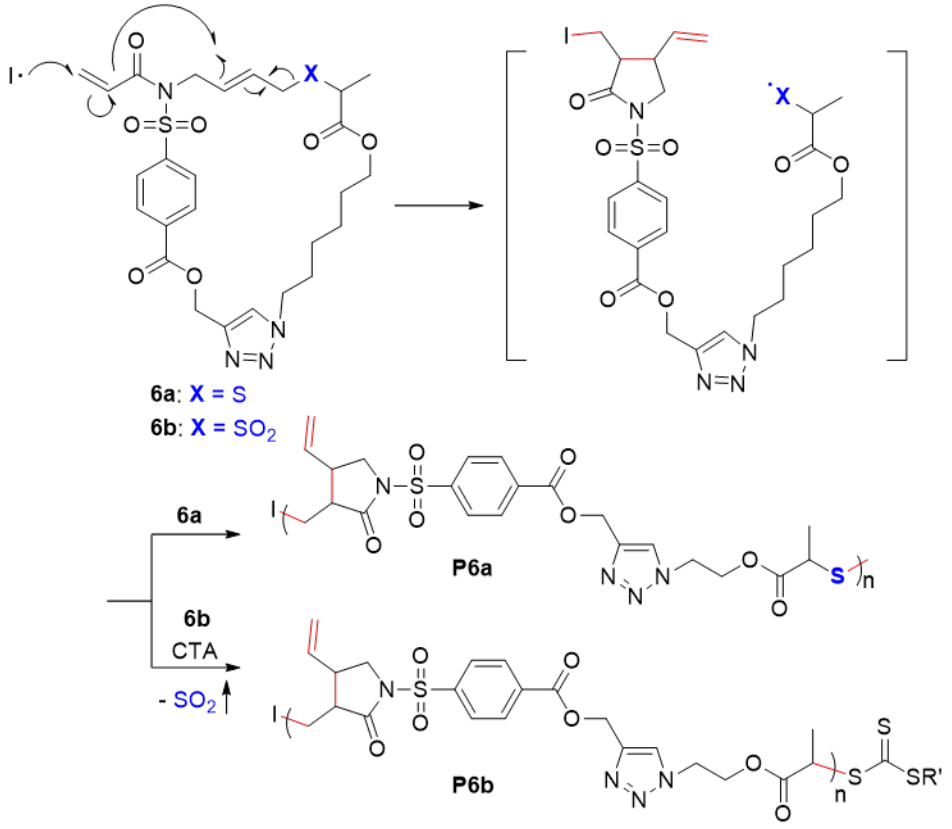
In 2018, Niu et al. reported a novel approach to achieve controlled rROCP of low-strain macrocyclic monomers (**Scheme 10**).[80] Distinct from most of the existing radical ROP reactions driven by the release of the monomer ring strain, Niu's approach is centered around the design of a "ring-opening trigger" to provide the driving force for the ROP. This ring-opening trigger

consists of an allylic sulfone structure that can be cleaved via β-elimination to form a sulfonyl radical intermediate, which subsequently undergoes rapid α-scission to extrude SO_2 and form a secondary alkyl radical stabilized by the adjacent carbonyl group (**Scheme 10A**). This "stable" radical is analogous to the propagating radical of polyacrylates and capable of chain-growth polymerization.[81-83] It was shown that rROCP of macrocyclic monomers such as **5** could be controlled by the chain-transfer agents (CTA) following a RAFT mechanism, yielding well-controlled polymers **P5**. The polymerization exhibited a linear growth of the molecular weight as the conversion increased and low dispersity. In 2019, the Niu group further developed a radical cascade ring-closing/ring-opening polymerization (rRCROCP) strategy to expand the scope of radical cascade polymerization and access polymers with complex main-chain structures.[84] A 1,6-diene-fused allylic sulfide and sulfone motifs were incorporated in the macrocyclic monomers to enable the radical ring-closing/ring-opening cascade, in which the radical addition to the terminal vinyl group prompts an *5-exo-trig* cyclization of the 1,6-diene, followed by β-elimination of the alkylsulfone radical. For **6a**, subsequent propagation yielded **P6a** with the thioether moiety, but the propagating radical could not be reversibly deactivated. For **6b**, α-scission of SO_2 from the sulfonyl radical provided a propagating alkyl radical adjacent to the carbonyl group, which generated **P6b** with the control over polymerization achieved by RAFT (**Scheme 10B**). These results highlighted the unique advantage of the ring-opening trigger design: the secondary radical formed after the radical cascade process allowed the radical cascade polymerization to achieve control via reversible deactivation, laying the foundation for connecting with contemporary controlled radical polymerization techniques, such as ATRP, NMP, and stimuli-responsive polymerization.

A **Radical Ring-Opening Cascade Polymerization Enabled by the Allylic Sulfone Trigger**



B **Radical Ring-Closing/Ring-Opening Cascade Polymerization**



Scheme 10. rROCP of low-strain macrocyclic monomers. (**A**) rROCP enabled by the allylic sulfone trigger. (**B**) rRCROCP of macrocyclic monomers consisting of 1,6-diene-fused allylic sulfide and sulfone.

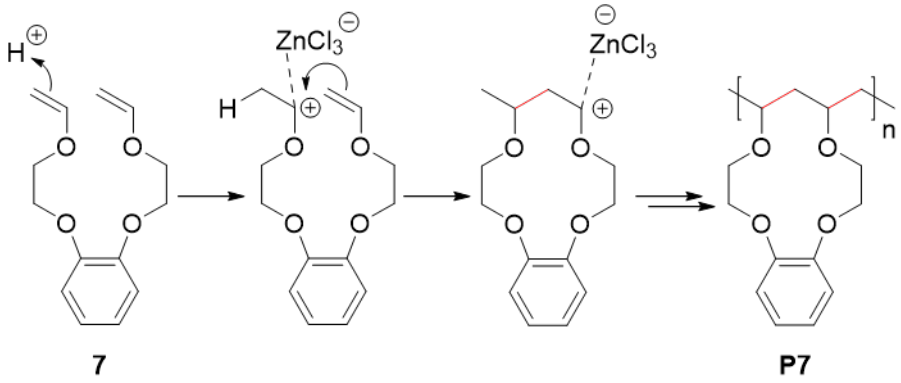
3. Ionic and nucleophilic cascade polymerization

Polymerizations proceeding with ionic or nucleophilic cascades are among some of the earliest examples of chain-growth cascade polymerization explored, and still represent important directions in this field of study. In this section, representative works on ionic ring-closing cascade polymerization (iRCCP), nucleophilic ring-opening cascade polymerization (nROCP), and ionic ring-opening/ring-closing cascade polymerization (iRORCCP) will be discussed.

3.1. Ionic ring-closing cascade polymerization (iRCCP).

The iRCCP reactions mechanistically resemble the radical ring-closing cascade polymerization (rRCCP) discussed in Section 2.1, in which five-membered and six-membered cyclization or template-assisted macrocyclization represent the main driving force for iRCCP. Vinyl ethers and aldehydes are two of the common functionalities to enable the iRCCP process. For example, 1,2-bis(2-vinyloxyethoxy)benzene (**7**, **Scheme 11**) is a well-studied divinyl ether monomer for iRCCP, in which a Lewis/Brønsted acid initiator reacts with one vinyl ether to form a cation stabilized by the Lewis acid catalyst, followed by intramolecular cyclization facilitated by the rigid catechol template to yield a ring-closed propagating cation.[85] The iRCCP of **7** and other divinyl ether monomers has also been used to generate polymers with the appended crown ether motif that has potential application on cation capture.[86] However, these monomers have two common issues: inefficient intramolecular cyclopolymerization and frequent 1,2-polymerization

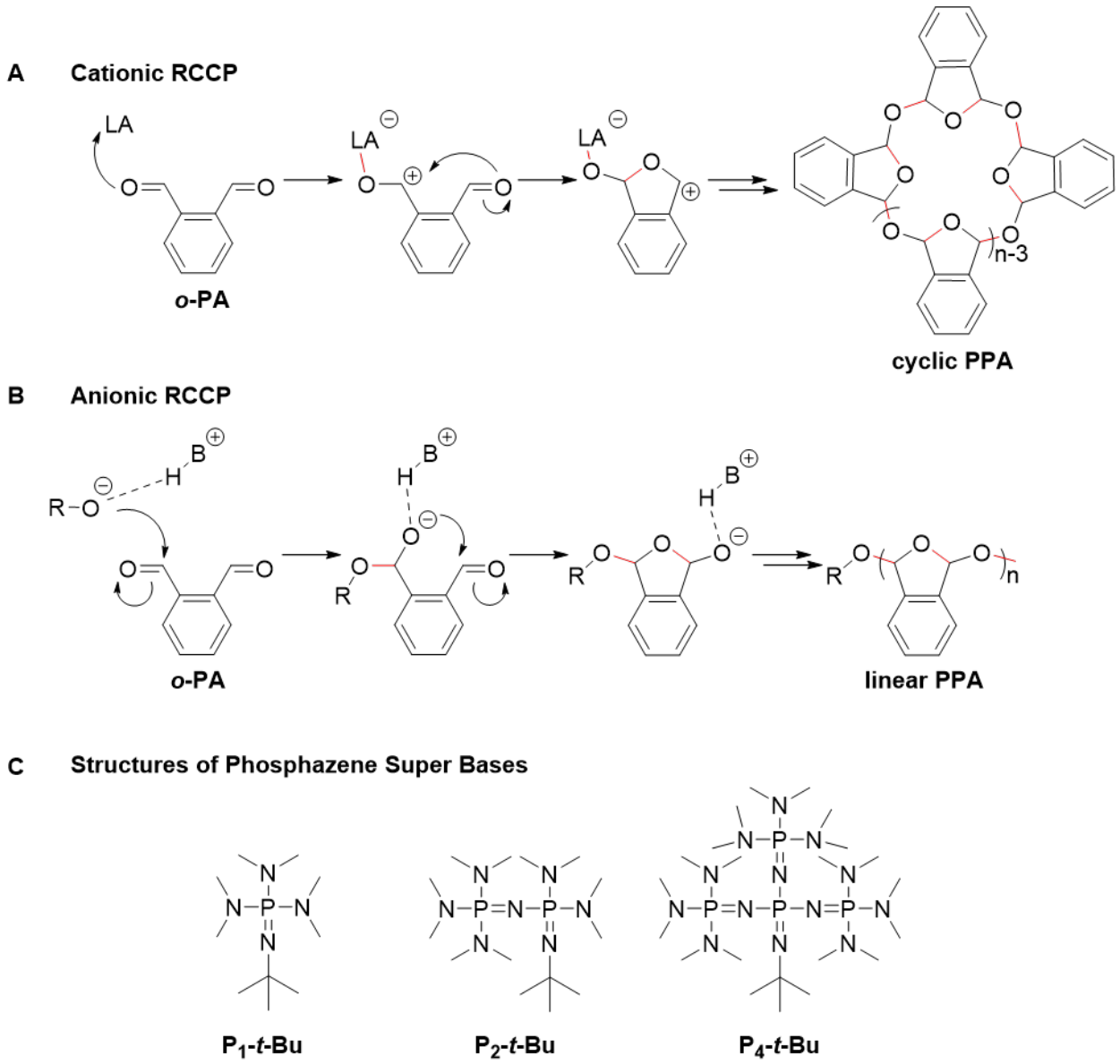
side reaction leave unreacted pendant vinyl groups as potential crosslinking sites. These crosslinking sites are detrimental to the control over polymerization and the material performance of the as-formed polymers.



Scheme 11. Cationic RCCP of **7** initiated by the HCl/$ZnCl_2$ system.

Poly(phthalaldehyde) (PPA), a well-known multi-stimuli responsive polymer has gained broad research interests in recent years.[87] The low ceiling temperature (-43 °C) and unique acid and thermal instability make PPA an ideal polymer for different applications, *e.g.*, photoresists, self-immolative plastics, and stimuli-responsive materials. The first *o*-phthalaldehyde (*o*-PA) polymerization was reported by Aso et al. using $BF_3{\cdot}Et_2O$ as the catalyst at -78 °C (**Scheme 12A**).[88] Later, cationic polymerization catalyzed by Lewis acids such as $SnCl_4$, $TiCl_4$, and $(C_6H_5)_3C^+BF_4^-$ and anionic polymerization catalyzed by strong bases such as *n*-BuLi, sodium naphthalene, and *t*-BuOK/18-crown-6 were all proved effective for *o*-PA polymerization (**Scheme 12B**).[89] Interestingly, although both the cationic and anionic polymerization of *o*-PA proceed via the cascade pathway of an intramolecular *5-exo-trig* cyclization of the two aldehydes on the same phenyl group followed by chain propagation, cationic polymerization usually leads to cyclic PPA with uncontrolled M_n and high $Đ$, whereas anionic polymerization could yield linear PPA with

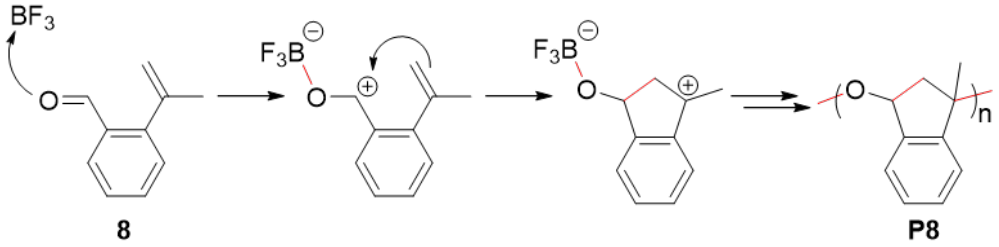
lower *Đ*. In 2010, the first controlled anionic polymerization of *o*-PA was realized by Hedrick et al. using a phosphazene super base P_2-*t*-Bu as the catalyst together with an alcohol as the initiator (**Scheme 12C**).[90] Due to the low ceiling temperature of PPA, chain end capping by trichloroacetyl isocyanate was essential to prevent depolymerization at room temperature. Later, Coulembier et al further expanded the phosphazene category to P_1-*t*-Bu and P_4-*t*-Bu.[91] The near quantitative monomer conversion, predictable M_n up to 200 kg/mol, low dispersity (*Đ*~1.2), and chain end fidelity fully showcase the robustness of this method.



Scheme 12. (**A**) Cationic and (**B**) anionic RCCP of *o*-PA. (**C**) Structures of phosphazene super bases.

In 2013, Moore et al. reported the cationic iRCCP of *o*-(α-methyl)vinylbenzaldehyde (**8**, **Scheme 13**) with quantitative conversion and high molecular weight.[92] Distinct from the polymerization of *o*-vinylbenzaldehyde where only low M_n polymer in low yield was generated, the α-methyl-substituted monomers underwent efficient cascade polymerization with complete

conversion as a result of the formation of a more stable carbocation.[93] As a consequence, polymers with M_n up to 60 kg/mol were readily prepared. This work highlights the importance of the structure optimization of monomers for achieving efficient iRCCP.

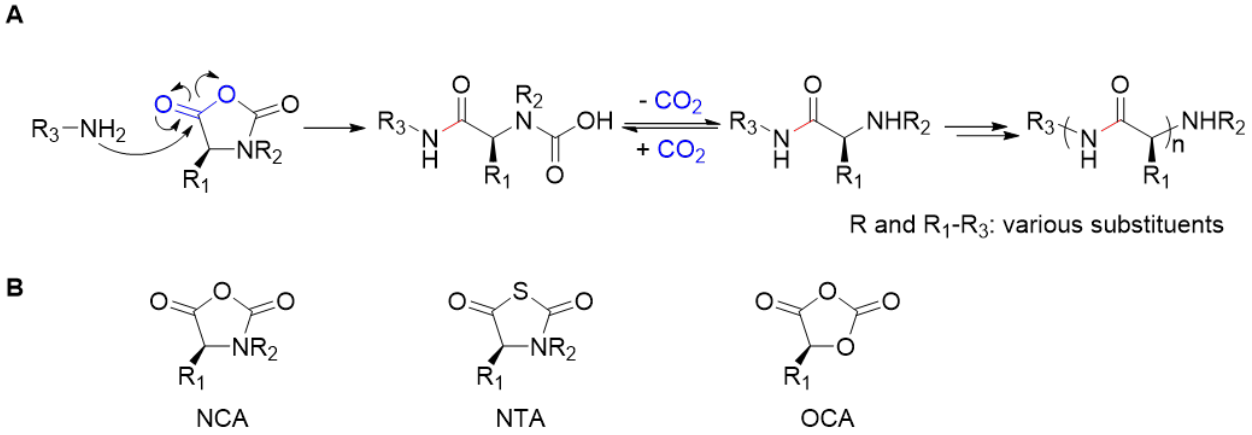


Scheme 13. Cationic RCCP of **8**.

3.2. Nucleophilic ring-opening cascade polymerization (nROCP).

A typical example of nROCP is the polymerization of α-amino acid *N*-carboxyanhydrides (NCAs) initiated by amines (**Scheme 14**).[94] In this reaction, the initiating nucleophilic amine attacks the 5-position carbonyl group, followed by the ring-opening of NCA and CO_2 extrusion due to the instability of carbamic acid group. A new amino group is generated from the rearrangement of the carbamic acid and CO_2 extrusion, allowing for further chain propagation. In addition to generating the propagating amine, CO_2 extrusion acts as the driving force to promote the ring-opening and enables the polymerization to proceed under low initial monomer concentration ($[M]_0 < 0.1$ M). This feature is distinct from conventional nucleophilic/ionic ring-opening polymerization of lactone, thiolactone, and lactam, where the release of the ring strain is the driving force and high initial monomer concentration ($[M]_0$ usually higher than 1 M, and sometimes even in bulk) is necessary to achieve high conversion. Of note, *N*-trimethylsilyl amine,[95,96] phenyl trimethylsilyl sulfide,[97] and trimethylstannyl phenyl sulfide[98] mediated NCA polymerizations also proceed with the nROCP mechanism. Some NCA analogues, such as *N*-

thiocarboxyanhydride (NTA),[99] and *O*-carboxyanhydrides (OCA)[100] can also undergo nROCP processes, where great entropy gain from gas (COS or CO_2) extrusion provides the driving force for the polymerization.

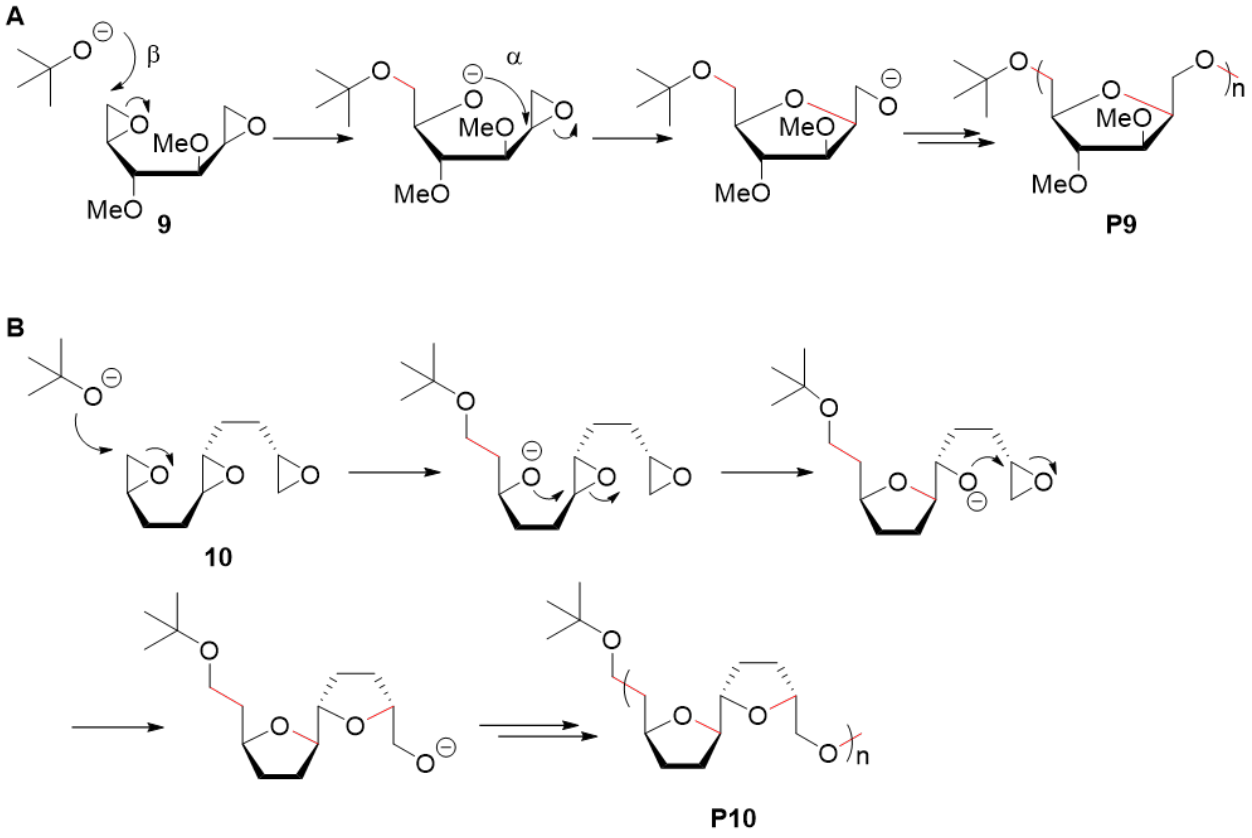


Scheme 14. (**A**) NCA nucleophilic ROCP initiated by primary amine. (**B**) Structures of NCA, NTA, and OCA.

3.3. Ionic ring-opening/ring-closing cascade polymerization (iRORCCP).

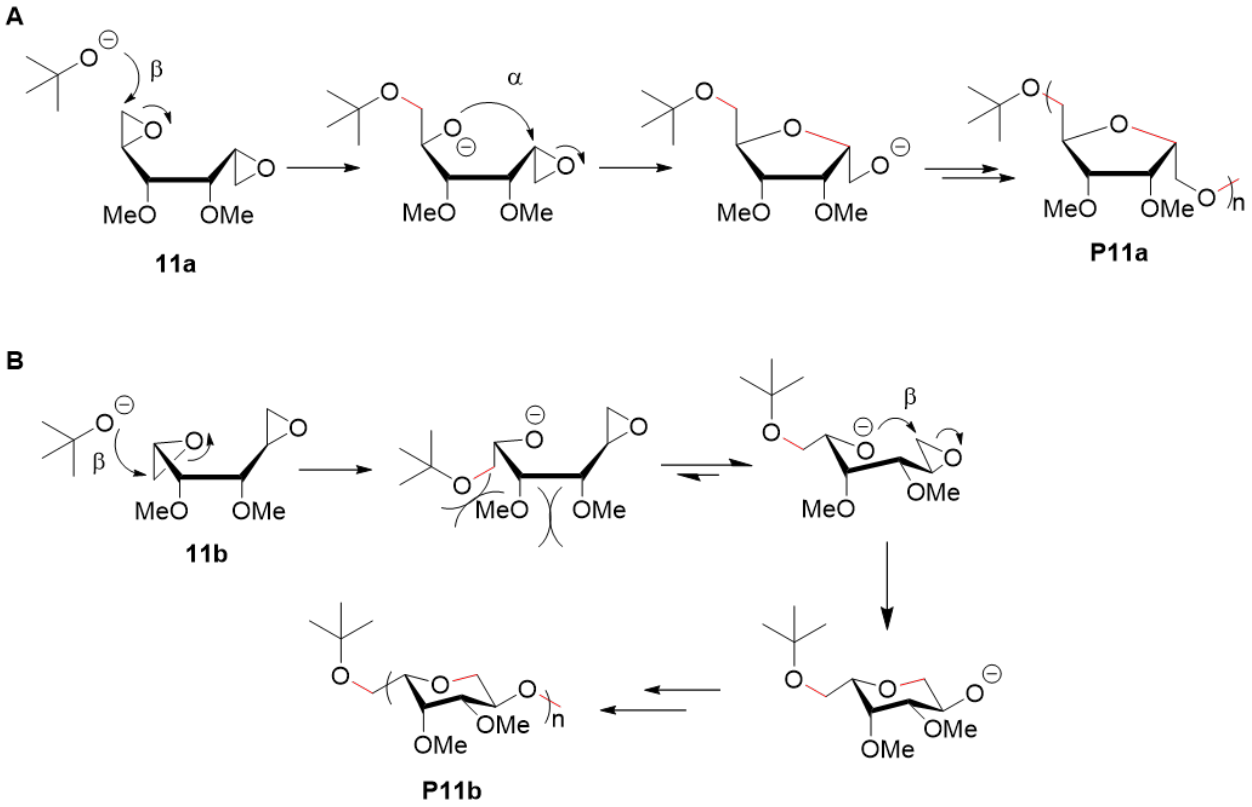
Combining consecutive ring-opening and ring-closing cascades within one monomer give rise to complex polymer main-chain structures. One example of this type of monomer design is the diepoxides reported by Satoh et al (**Scheme 15A**).[101] In this work, the diepoxides derived from 1,2:5,6-dianhydrohexitols were polymerized under anionic conditions to afford polysaccharides. To achieve highly efficient and stereoselective cyclization rather than acyclic chain growth or crosslinking, judicious choice of polymerization conditions was essential. The authors found that the anionic polymerization of diepoxide **9** using *t*-BuOK as the initiator exclusively generated polysaccharide main-chain structure **P9**. The nucleophilic ring-opening of the epoxide at the β-

position by the bulky *tert*-butoxy anion liberates a secondary alkoxide anion, which rapidly undergoes subsequent intramolecular *5-exo-tet* cyclization to ring open the second epoxide at the α-position and forms a propagating primary alkoxide anion.[102] The complexity of polymer main-chain structures generated through iRORCCP was further demonstrated in the anionic cascade polymerization of triepoxide 1,2:5,6:9,10-triepoxydecane (**10**, **Scheme 15B**).[103] This impressive ionic cascade consists of two consecutive *5-exo-tet* cyclizations following epoxide ring opening, resulting in a polymer featuring a bis-tetrahydrofuran motif in a single repeating unit. Compared to anionic polymerization, cationic polymerizations of such monomers are usually less efficient and the resulting backbone structures may contain more defects.[104]



Scheme 15. (**A**) Anionic RORCCP of diepoxide **9**. (**B**) Anionic RORCCP of triepoxide **10**.

One interesting feature of the iRORCCP of diepoxides is that different stereochemistry of monomers could lead to different backbone structures. For example, in 1999, Yokota et al. reported that 1,2:5,6-dianhydro-3,4-di-O-methylallitol **11a** and 1,2:5,6-dianhydro-3,4-di-O-methylgalactitol **11b** could both undergo anionic cascade polymerization (**Scheme 16**).[105] Although the only difference between the two monomers is their chirality of the two epoxide groups, the polymerization of **11a** afforded a polysaccharide with a furanose repeating unit (**P11a**), while the polymerization of **11b** under the same condition yielded one with a pyranose repeating unit (**P11b**). This difference is likely caused by the different cyclization pathways of the two stereoisomers: while the (2*S*,5*R*)-diepoxide favors the *5-exo-tet* cyclization (kinetically favored consecutive β- and α-scissions of two epoxides), the (2*R*,5*S*)-diepoxide favors the *6-exo-tet* cyclization (two successive β-scissions of epoxides) to reduce the steric hindrance of the neighboring *cis*-substituents of the *5-exo-tet* intermediate.



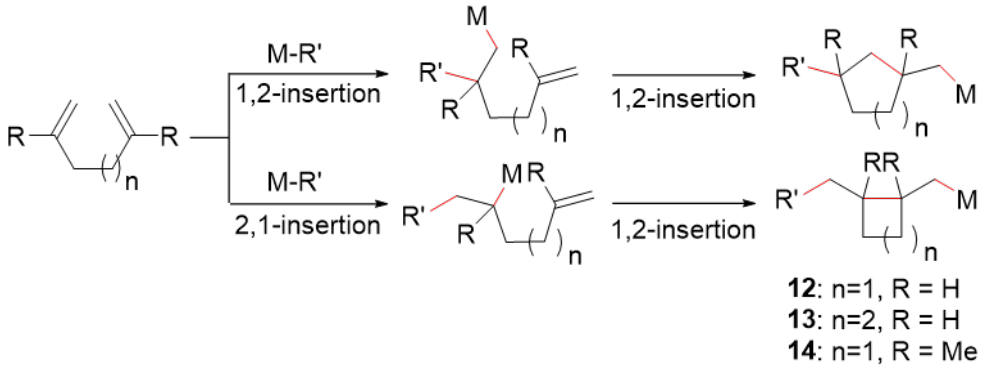
Scheme 16. Anionic RORCCP of diepoxides (**A**) **11a** and (**B**) **11b** to afford polysaccharide with different repeating units.

4. Transition metal-catalyzed cascade polymerization.

Transition metal catalysis is another powerful approach to enable chain-growth cascade polymerization. Among all the transition metal complexes, catalysts consisting of Group IV metals (titanium, zirconium, and hafnium) and palladium were used to mediate cascade polymerization via the coordination-insertion mechanism. In addition, ruthenium carbene complexes (*e.g.*, first-, second-, and third-generation Grubbs catalysts) demonstrated superior reactivity, regioselectivity, and functional group compatibility in metathesis cascade polymerization. It is noteworthy that readers are referred to Section 2 for the discussions related to metal-catalyzed radical cascade polymerization.

4.1. Coordination-insertion cascade polymerization.

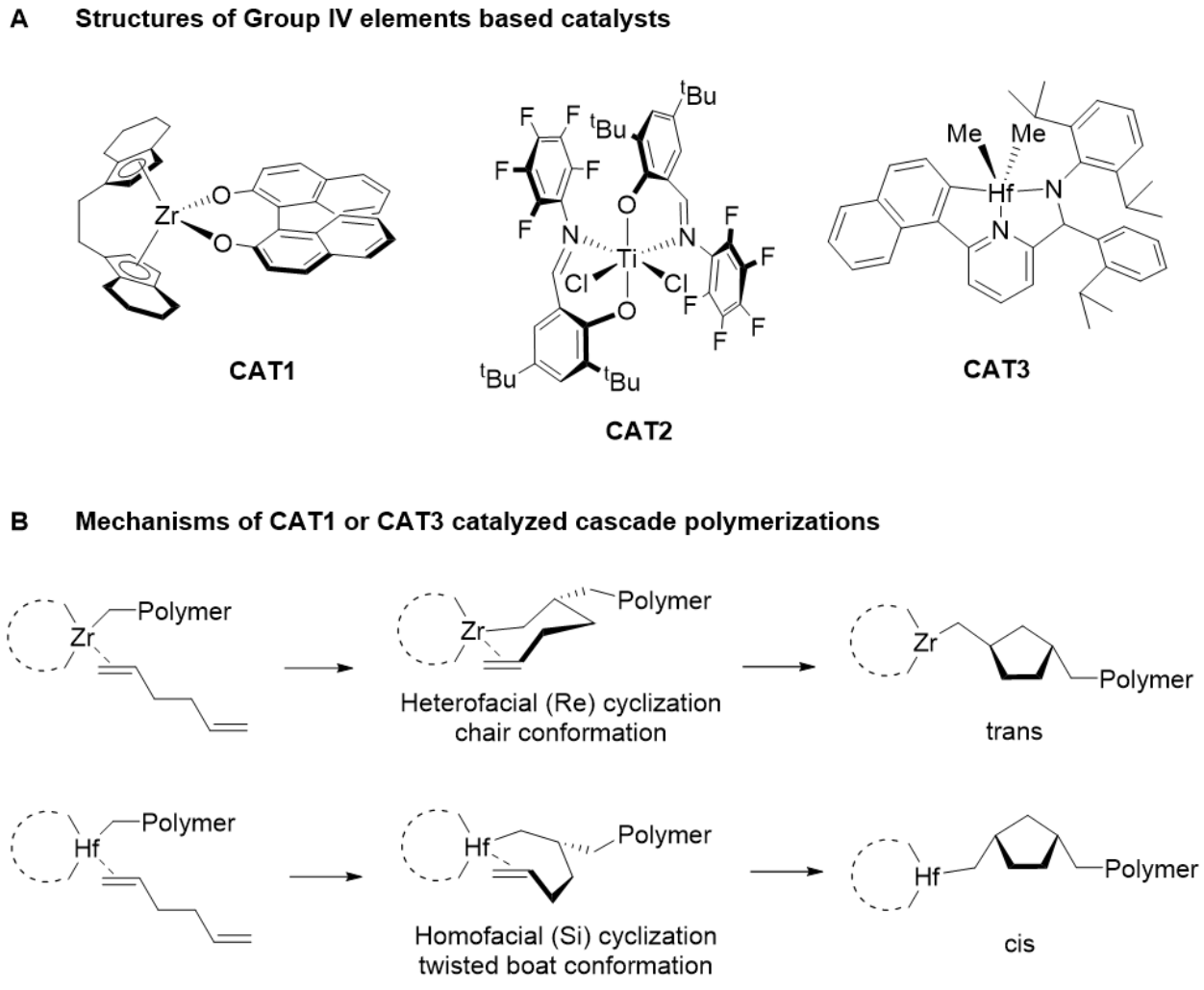
Coordination-insertion cascade polymerization of α-diolefins (**12-14**) can proceed via either an 1,2-insertion mechanism or an 2,1-insertion mechanism. The ring size of the generated cycloalkane in the polymer main chain depends on the insertion mode of the vinyl groups (**Scheme 17**).



Scheme 17. General mechanisms of coordination-insertion cascade polymerization of α-diolefins.

The development of coordination-insertion cascade polymerization can date back to the 1950s when Ziegler–Natta catalysts were discovered.[106,107] In 1958, Stille et al. first developed a cascade cyclopolymerization of α-diolefins to generate cyclic repeating units catalyzed by titanium tetrachloride in combination with aluminum triisobutyl as the cocatalyst.[108] While not a particularly efficient reaction, this work laid the foundation for the development of future cascade polymerization systems. In the 1990s, Waymouth et al. reported the cascade polymerization of **12** using chiral zirconium complex (**CAT1**) as catalyst and methylaluminoxane (MAO) as the cocatalyst (**Scheme 18A**).[109] High molecular weight polymers (M_n up to 38 kg/mol) with uniform cyclized repeating units (cyclization > 99%) and conversion over 90% were readily achieved, although stereoregularity decreased with the increasing of polymer molecular weight. In 2002, cascade polymerization of **12** catalyzed by a titanium complex (**CAT2**) and MAO was reported by Coates et al. [110] Compared with zirconium complexes, titanium complexes easily generated polymers with much higher molecular weight (M_n up to 268 kg/mol) and low dispersity ($Đ$ = 1.27) within 20 minutes. However, the poor regioselectivity (1, 2-insertion/2, 1-insertion = 63/37) resulted in a mixture of cyclopentane and cyclobutane repeating units in the polymer backbone, with the latter further rearranged into 3-vinyl-tetramethylenes. Li et al. described a fast, *cis*-

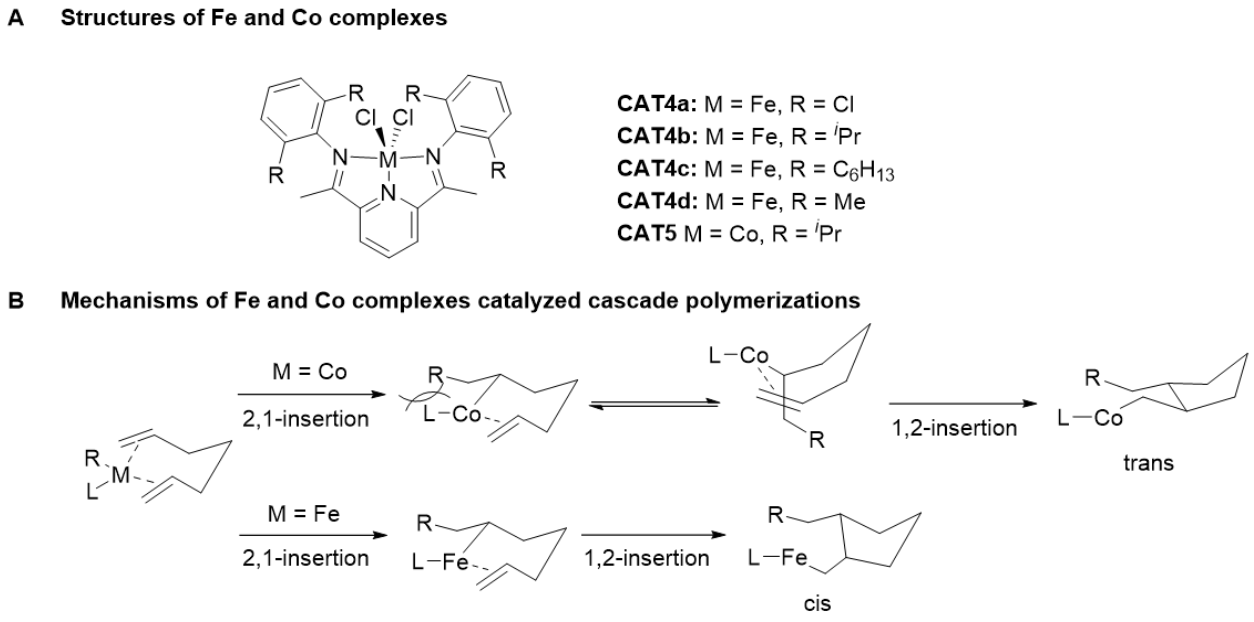
selective cyclopolymerization of **12** using hafnium complex (**CAT3**) as catalyst and borane as the cocatalyst.[111] However, the conversion did not exceed more than 70% and *Đ* was usually higher than 2.5. In these works, both of zirconium and hafnium catalysts could achieve *cis*/*trans* selectivity, which was mainly determined by the conformation of the coordination-insertion intermediates formed by the catalysts and the monomer. The formation of the *trans* conformation requires heterofacial insertion while the *cis* conformation needs the homefacial topology in the insertion step. For instance, the intermediate obtained by **CAT1** favors the *trans*-chair conformation, leading to *trans*-repeating units in the resulting polymer. In contrast, the intermediate formed by **CAT3** favors the *cis*-twist boat conformation, resulting in *cis*-repeating units (**Scheme 18B**).



Scheme 18. (**A**) Structures of Group IV elements based catalysts. (**B**) The *cis*/*trans* selectivity achieved by **CAT1-** and **CAT3**-catalyzed cascade polymerization.

Beyond Group IV elements, other early transition metal complexes have also been used to catalyze chain-growth cascade polymerization. Iron (**CAT4a**) and cobalt (**CAT5**) complexes were developed by Osakada et al. to mediate the polymerization of **13** in the presence of modified methylaluminoxane (**Scheme 19A**).[112] Even with similar ligand structures, iron and cobalt complexes exhibited the opposite *cis*/*trans* selectivity: the iron catalysts generated polymers rich in *cis*-1,2-cyclopenthylene repeating unit, while the cobalt catalysts generated polymers with

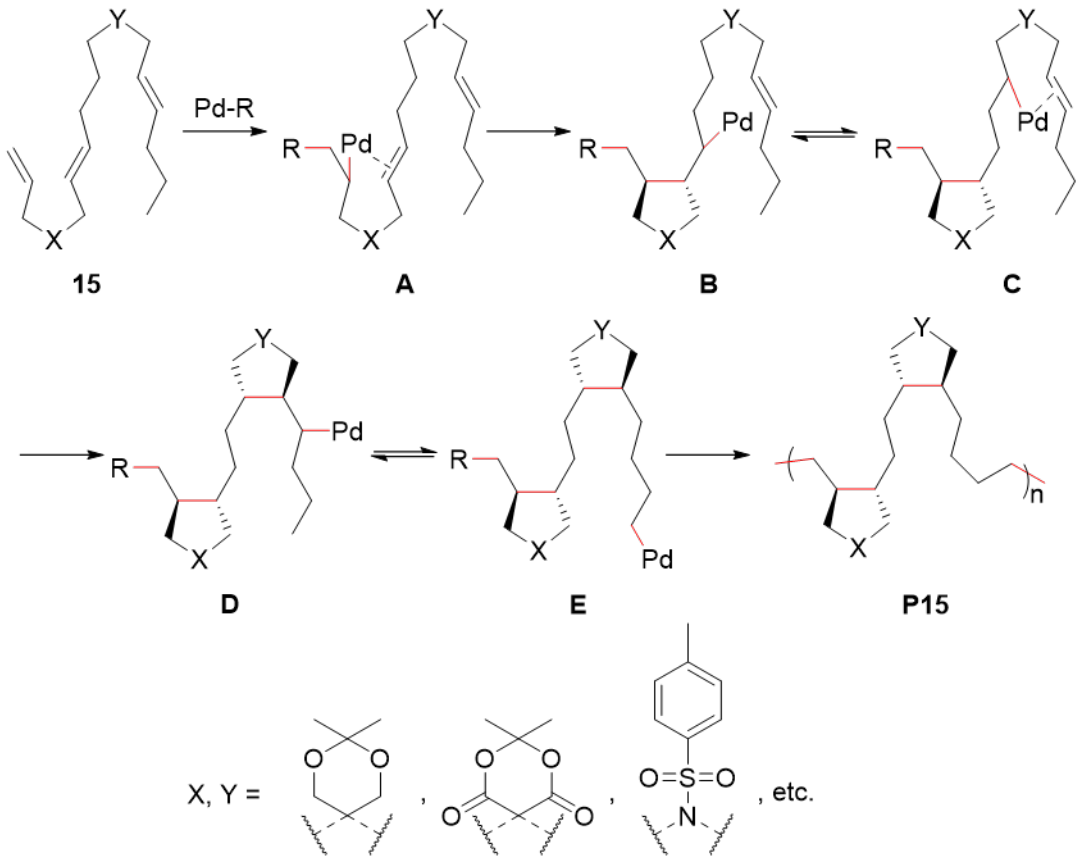
trans-5-membered rings with high selectivity. Both of the iron and cobalt complexes underwent 2,1-insertion of a vinyl group of the monomer into the metal-carbon bond to yield intermediates with chair conformation. While the cobalt complex underwent a *cis-trans* conversion prior to cyclization due to the steric effect, the iron complexes directly formed the *cis*-1,2-cyclopenthylene repeating unit (**Scheme 19B**). A major limitation of this approach is the low molecular weight (M_n = 14 kg/mol) and high dispersity ($Đ > 1.7$) of the resulting polymer.



Scheme 19. (**A**) Structures of iron and cobalt complexes. (**B**) Mechanisms of iron and cobalt complex-catalyzed cascade polymerizations.

Compared to early transition metal catalysts, palladium complexes have demonstrated improved compatibility with heteroatoms in the monomer, thereby expanding the structural and functional scopes of the resulting polymers. An impressive example is the double ring-closing cascade polymerization developed by Osadaka et al. in 2015 (**Scheme 20**).[113] Palladium insertion of the terminal olefin of the monomer **15** produced a secondary alkyl-palladium intermediate **A**.

The subsequent cyclization via intramolecular palladium migration to an adjacent vinylene group of the monomer yielded intermediate **B**, which quickly underwent chain-walking to form **C**. Subsequent intramolecular palladium migration/cyclization formed **D**, and further chain-walking generated **E** with the terminal C–Pd bond, which underwent chain propagation to yield the polymer **P15**. The high selectivity for racemo diads was achieved by the limited rotation of the C–C bonds during the rapid chain-walking process from B to C, as the monomer structure bears bulky substituents. Although the obtained polymer molecular weights were usually lower than 15 kg/mol, and the dispersity increased with the increasing of conversion ($Đ$ > 1.7 with conversion > 80%), this work demonstrated a unique method of generating cycloalkane units on the polymer backbone.



Scheme 20. Cascade polymerization of trienes catalyzed by palladium complexes.

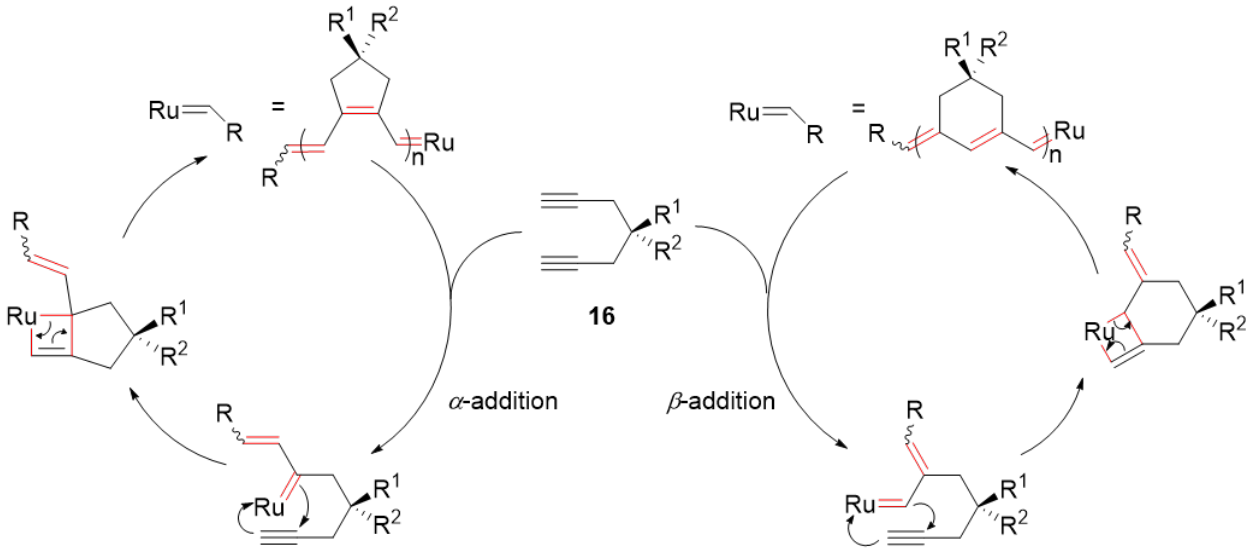
4.2. Metathesis cascade polymerization

Thermodynamically, chain-growth polymerization requires a driving force to compensate for the loss of the translational entropy of monomers. For example, an enthalpic driving force is provided by the release of the ring strain in monomers during the ring-opening metathesis polymerization (ROMP). However, with rational design, monomers with less reactive alkenes or alkynes can be polymerized with high rates and low dispersity via metathesis cascade polymerization, which not only enables the otherwise energetically disfavored polymerization but also creates polymers with complex main-chain structures. One of the most important factors that influence the cascade polymerization efficiency is the Thorpe–Ingold effect, which dictates that linear reactants bearing bulky substituents greatly favor intramolecular cyclization.[31]

Tungsten and molybdenum complexes were first explored for metathesis cascade polymerization. In the 1990s, metathesis cyclopolymerization of 1,6-heptadiyne derivatives catalyzed by tungsten and molybdenum catalysts were reported.[114] In 2003, the cyclopolymerization of the same type of monomer with high *5-exo-dig* selectivity was developed by Nuyken and Buchmeiser based on a molybdenum catalyst.[115] Polymers with high M_n (120 kg/mol) were readily prepared despite having high dispersity ($Đ > 1.60$). Major limitations of the tungsten and molybdenum catalysts include their high sensitivity to moisture and oxygen and limited functional group compatibility.

In 2011, Choi et al. reported a ring-closing metathesis cascade polymerization (RCMP) of 1,6-heptadiyne derivatives (**16**) mediated by the third-generation Grubbs catalyst (**Scheme 21**).[116] Two possible pathways were proposed for this cascade polymerization: an initial α-addition to form a ruthenium carbene intermediate followed by a *5-exo-dig* cyclization, or an initial β-addition

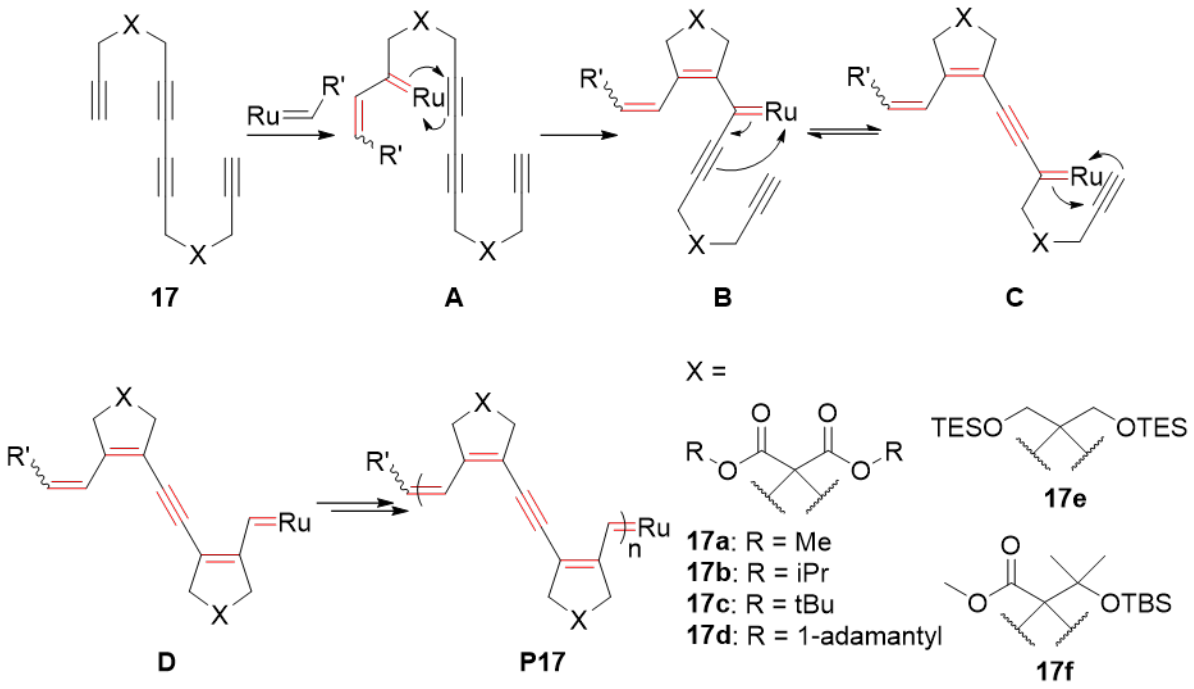
followed by a *6-endo-dig* cyclization of the ruthenium carbene. As shown in **Scheme 21**, in both pathways the addition of chain-end ruthenium carbene to one alkyne of the monomer facilitates the subsequent intramolecular cyclization. The newly formed ruthenium carbene chain-end further undergoes chain propagation to finally generate a fully conjugated polymer. Through detailed analysis of the selectivity of α-addition and β-addition, the authors demonstrated that the electronic properties made a major impact on regioselectivity, and steric interaction between ligand and monomer may also influence it.[117] In this work, semiconducting polymers with M_n up to 58 kg/mol and $Đ < 1.5$ were produced. A macromonomer consisting of a G3-dendron were also polymerized, providing a new method for synthesizing insulated molecular wires.



Scheme 21. Cascade polymerization of **16**.

Inspired by the small molecule metallotropic 1,3-shift developed by Lee et al.,[118] in 2017 the Choi group moved one step further by incorporating a metallotropic 1,3-shift transformation in RCMP (**Scheme 22**).[119] This impressive cascade process started with α-addition of ruthenium complex **A**. The resulting disubstituted carbene went through intramolecular ring-closing

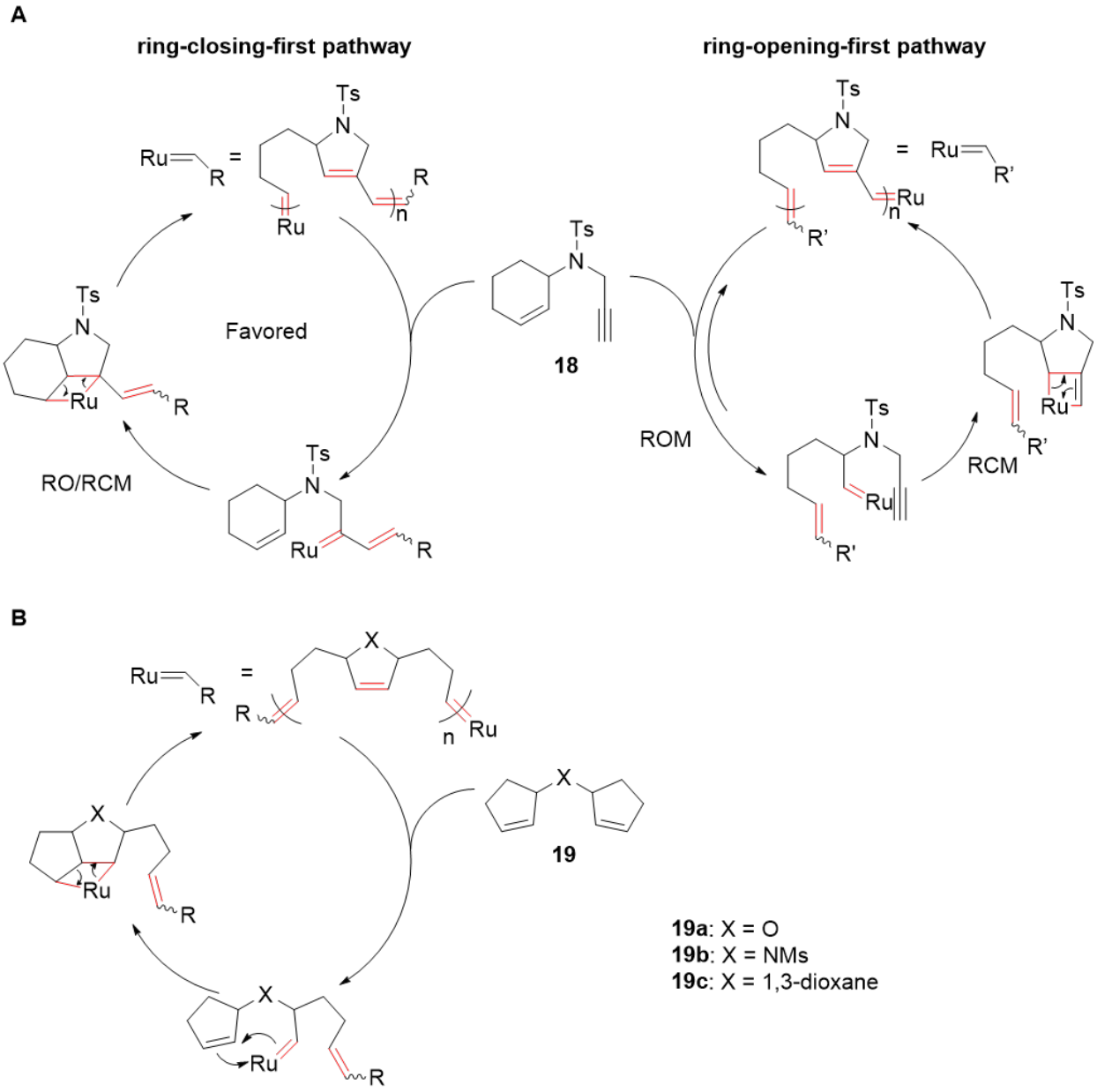
metathesis to form intermediate **B**. Ruthenium carbene in **B** underwent a metallotropic 1,3-shift to form **C**, which enabled the second intramolecular ring-closing metathesis to generate **D**. A fully conjugated polymer **P17** with two 5-membered rings were obtained via this mechanism. By adding a weakly coordinating ligand, 3,5-dichloropyridine to hinder catalyst decomposition, well controlled M_n (up to 36 kg/mol), low dispersity ($Đ$ < 1.4), and block copolymerization were realized, highlighting the versatility of this chemistry.



Scheme 22. RCMP with metallotropic 1, 3-shift mechanism.

Again inspired by small molecule cascade reaction,[120,121] the Choi group developed a cascade ring-closing/ring-opening metathesis polymerization (RCROMP) technique in 2012 (**Scheme 23A**).[122] In this cascade polymerization system, cyclohexene and terminal alkyne, were coupled to form an enyne via a sulfonamide spacer (**18**).[123,124] Two possible reaction pathways were proposed

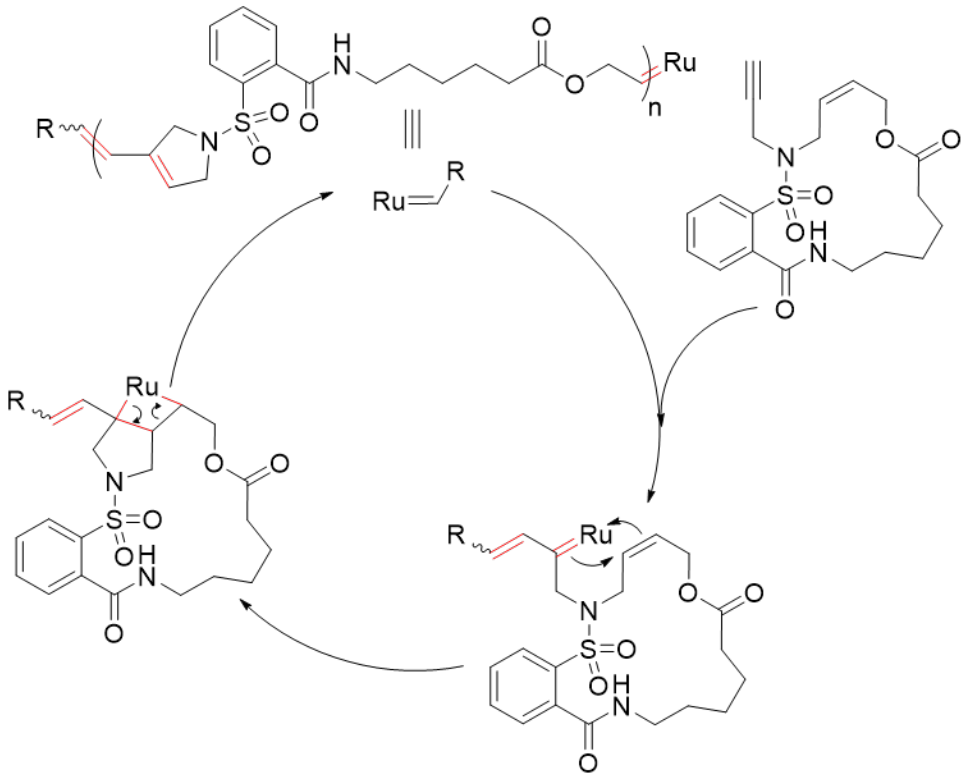
by starting the metathesis cascade from either the terminal alkyne (the ring-closing-first pathway) or cyclohexene (the ring-opening-first pathway). In the ring-closing-first pathway, the catalyst metathesizes with the terminal alkyne, enabling the newly formed ruthenium carbene to undergo the second ring-closing/ring-opening metathesis with the adjacent cyclohexene. In the ring-opening-first pathway, the catalyst conducts ring-opening metathesis with cyclohexene at first, followed by the second ring-closing metathesis between the newly generated ruthenium carbene and the adjacent terminal alkyne to form the chain-propagation species. The ring-closing first pathway was proposed to be the favored one, as compared with 3-substituted cyclohexene, the terminal alkyne is kinetically more accessible. There was also evidence that Grubbs catalyst with an N-heterocyclic carbene ligand has higher reactivity towards alkynes than alkenes.[122] Furthermore, the initiation of ruthenium carbene with terminal alkyne is irreversible, while the ROM of 3-substituted cyclohexene is a reversible process.[122] This mechanism was further supported by the NMR analysis.[123] A closely related design that follows the ring-opening-first pathway was reported by the Choi group shortly after, in which the catalyst first opens the cyclopentene ring and the ruthenium carbene intermediate generated further metathesizes with the adjacent cyclopentene intramolecularly (**Scheme 23B**).[125] The novel monomer design features high cascade efficiency and gives access to a new class of polymers with main-chain cyclic structures.



Scheme 23. (**A**) RCROMP of **18** via a ring-closing-first or a ring-opening-first pathway. (**B**) RCROMP of **19**.

A creative application of RCROMP is the metathesis-triggered ring-opening polymerization developed by Gutekunst and Hawker in 2016. The authors implemented Choi's enyne motif into the ring-opening trigger design, such that the ring-closing/ring-opening metathesis cascade of the

enyne motif could provide the driving force for the ring-opening polymerization of unstrained macrocyclic monomers (**Scheme 24**).[126] Polymers with various functionalities within the backbone were readily produced with excellent M_n control (up to 36 kg/mol) and low dispersity ($Đ$ < 1.4). Other recent applications of the metathesis cascade of enynes include main-chain degradable polymers reported by Gutekunst[127] and Choi,[128] and polymer chain-end functionalization developed by Gutekunst[129] and Kilbinger.[130]



Scheme 24. RCROMP of unstrained macrocyclic monomers.

5. Summary and Outlook

The efficiency and atom economy of cascade reactions have made revolutionary impacts on the synthetic organic chemistry and the enzymatic biosynthesis of natural products. Incorporating

cascade reactions into the monomer and catalyst design for the chain-growth polymerization, evidenced by the examples in this Perspective, is a new frontier in polymer science with the potential to develop new chemistry and new materials. Mechanistically, cascade reactions and chain-growth polymerization reactions share many commonalities, with radical, nucleophilic, ionic, and transition metal-catalyzed cascade reactions matching perfectly with the corresponding chain-growth polymerization techniques. Given the increasing integration of modern organic chemistry with polymer science, such an intrinsic compatibility of the cascade reaction and chain-growth polymerization will almost certainly lead to more chain-growth cascade polymerization approaches in the future.

The recent emergence of external stimuli-controlled polymerization has not only laid the foundation for the synthesis of novel polymer structures, but also enabled the spatial and temporal control over how they can be made. Combining the stimuli-controlled polymerization techniques with chain-growth cascade polymerization would create opportunities for the on-demand access to the new properties they provide. For example, eATRP,[131] Photo-ATRP,[132,133] photoelectron transfer (PET)-RAFT,[134] Sono-ATRP,[135] and photocontrolled cationic polymerization[136] techniques can all be applied to controlling the propagation of chain-growth cascade polymerization.

The further development of chain-growth cascade polymerization also requires better catalyst design. As demonstrated in works on metathesis cascade polymerization, catalysts play a profound role in defining the reaction pathway, efficiency, and product structures. New catalyst design can also have major impacts on stereospecific cascade polymerization, an area with few examples to date. Toward this end, Leibfarth's work on stereoselective catalytic cationic polymerization has demonstrated the power of uniting enantioselective catalysis with polymer chemistry.[11]

Finally, new materials with novel structures and desirable properties will emerge from the development of new chain-growth cascade polymerization. For example, polyVCP and polyCAS were developed as low shrinkage materials. Polymerization of CKA generated polyesters with degradable main-chain functionalities. Fully conjugated polymers prepared by RCMP holds a great potential as organic semiconductors. Furthermore, the current environmental crisis caused by conventional plastics has called for new sustainable polymers. Compared to conventional chain-growth polymerization techniques, cascade polymerization has the unique advantage to enable the incorporation of large and complex bio-based and/or degradable functionalities into the polymer backbone. For example, radical and ionic cascade polymerization have been extensively studied to generate degradable polymers and polymers that can undergo efficient depolymerization.[79,80,84,92,93] Gains in fundamental knowledge of chain-growth cascade polymerization and creative monomer and catalyst designs will undoubtedly lead to new materials with tailor-made properties.

List of Acronyms

ATRP	atom transfer radical polymerization
CAS	cyclic allylic sulfide
CTA	chain-transfer agents
CVS	cyclic vinyl sulfone
DCE	dichloroethane
DEDPM	diethyl dipropargylmalonate
ECVCP	bis(ethoxycarbonyl)-2-vinylcyclopropane
iRCCP	ionic ring-closing cascade polymerization
iRORCCP	ionic ring-opening/ring-closing cascade polymerization
MAO	methylaluminoxane
NMP	nitroxide-mediated polymerization
NCA	*N*-carboxyanhydride
NTA	*N*-thiocarboxyanhydride
nROCP	nucleophilic ring-opening cascade polymerization
O-ATRP	organocatalyzed atom transfer radical polymerization
OCA	*O*-carboxyanhydrides
OEG	Oligo ethylene glycol
o-PA	*o*-phthalaldehyde
PC	photoredox catalyst
PET	photoelectron transfer
PPA	Poly(phthalaldehyde)
PS-(M)AA	poly-styrene-(meth)acrylic acid copolymers
RAFT	reversible addition-fragmentation chain-transfer polymerization
RCMP	ring-closing metathesis cascade polymerization
RCROMP	ring-closing/ring-opening metathesis polymerization
ROMP	ring-opening metathesis polymerization
rRCROCP	radical cascade ring-closing/ring-opening polymerization
rRCCP	radical ring-closing cascade polymerization
rROCP	radical ring-opening cascade polymerization
SCM	sulfide cyclic methacrylate
SOC	spiro-ortho-carbonate
VCB	vinyl cyclobutane
VCH	vinyl cyclohexadiene
VCP	vinyl cyclopropane
VO	vinyl oxirane

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Notes

The authors declare no conflict of interests.

Biography

Jingsong Yuan (left) received his BSc degree in Chemistry from Peking University in 2014 and PhD degree from the same university in 2019 under the supervision of Prof. Hua Lu, where he worked on ring-opening polymerizations. He is now a postdoctoral fellow at Boston College working with Prof. Jia Niu towards the development of novel cascade polymerization techniques.

Wenqi Wang (second from the left) was born in Changchun, China. He received his BSc degree in Chemistry at the University of California, Santa Barbara in 2018. He then moved to Boston to pursue his PhD at Boston College with Prof. Jia Niu. His research is focused on ring-opening polymerization of macrocyclic monomers.

Zefeng Zhou (second from the right) was born and raised in Xiamen, China. He earned his BSc in Chemistry from Xiamen University in 2018. He is currently pursuing his PhD in chemistry at Boston College under the direction of Prof. Jia Niu. His research involves developing novel methods for the synthesis of polymers responsive to various external stimuli, including force, heat, and light.

Jia Niu (right) received his BSc (2005) and MSc (2008) degrees from Tsinghua University (Beijing, China) under the direction of Professor Xi Zhang, PhD degree (2014) from Harvard University under the direction of Professor David R. Liu, followed by a postdoctoral training at University of California, Santa Barbara with Professor Craig J. Hawker and Professor H. Tom Soh from 2014 to 2017. In 2017 he became an Assistant Professor of Chemistry at Boston College. His research focuses on the development of novel precision macromolecules with tailor-made structures and sequences, and applying them to address pressing needs in biomedicine, materials, and environmental sciences.

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