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INVITED REVIEW

Recent advances in ring-opening metathesis polymerization, and application to synthesis of functional materials

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This article reviews the development of catalysts for ring-opening metathesis polymerization (ROMP), synthesis of polymers bearing amino acids and peptides by ROMP of functionalized norbornenes, formation of aggregates and micelles, and applications of the polymers to medical materials. It also describes the control of monomer unit sequences, that is, living polymerization to synthesize block copolymers, and alternating copolymerization that is achieved on the basis of acid–base interactions.
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INTRODUCTION

Olefin metathesis reactions are metal-mediated carbon–carbon (C–C) double bond exchange processes,[1,2] which were discovered in the mid 1950s. Chauvin proposed the commonly accepted mechanism for metathesis involving a metallacyclobutane, as illustrated in Scheme 1.[3] Initially, olefin metathesis was regarded as an odd reaction, but now it has undoubtedly established the position as one of the most important C–C bond formation reactions applicable to synthesis of a wide variety of useful products. In the early stages, transition metal chlorides were used as catalysts for the reaction, but the transition metal carbene complex catalysts designed by Schrock and Grubbs have remarkably advanced mechanistic analysis and control of catalytic activity by the choice of ligands. In 2005, Chauvin, Grubbs and Schrock were awarded the Nobel Prize in chemistry for development of the metathesis method in organic synthesis.

Olefin metathesis polymerization is an application of metathesis reactions to polymer synthesis and includes ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) polycondensation (Scheme 2). ADMET has been extensively developed by Wagener since 1987[4] for the synthesis of polyolefins having regularly spaced functional group branches and high thermal stability and crystallinity.[5,6] ADMET is also useful for synthesizing polymeric materials containing in-chain functionality. Although the general structures of the polymers obtained by ROMP and ADMET are illustratable in the same fashion as shown in Scheme 2, a completely different treatment is necessary from the viewpoint of polymerization kinetics. The former involves chain polymerization, whereas the latter is a step-growth polymerization process.

ROMP provides a wide range of polymers with unique architectures and useful functions. ROMP converts cyclic olefins into linear polymers containing olefins in the main chain, as illustrated in Scheme 3. The initiation step involves coordination of a cyclic olefin to a metal alkylidene complex. Subsequent [2+2] cycloaddition produces a metallacyclobutane intermediate to form a growing polymer chain. This intermediate undergoes cycloreversion to afford a new metal alkylidene. Analogous steps are repeated during the propagation stage until polymerization ceases, that is, the monomer is completely consumed, the reaction reaches equilibrium or the reaction is terminated. ROMP is commonly quenched by an addition of ethyl vinyl ether, which reacts with the metal carbene species of a growing polymer chain end and removes the metal from the polymer. Omitting this procedure leads to degradation of the product polymer and causes metal residue contamination in the isolated material.

In ROMP, polymerization releases the ring strain in the cyclic olefin monomer (negative ΔH°), with an accompanying decrease in entropy. The most common monomers used in ROMP are cyclic olefins having considerable ring strain ($>5\,\mathrm{kcal\,mol^{-1}}$), such as cyclobutene, cyclopentene, *cis*-cyclooctene and norbornene.[7] ROMP is commonly accompanied by intermolecular and intramolecular chain-transfer reactions as illustrated in Scheme 4. In the intermolecular chain transfer, a polymer chain having an active metal alkylidene on its terminus reacts with a double bond in another polymer chain. The individual polymer chains increase or decrease in molecular weight accordingly, keeping the total number of polymer chains unchanged. In the intramolecular chain-transfer reaction (backbiting), the carbene terminus of a polymer chain reacts with itself to form a polymer chain

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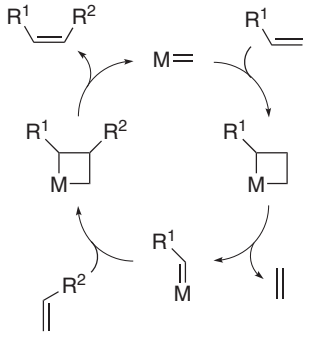
with a reduced molecular weight and release a cyclic oligomer. Intermolecular and/or intramolecular chain transfers both increase the polydispersity of the polymer product.

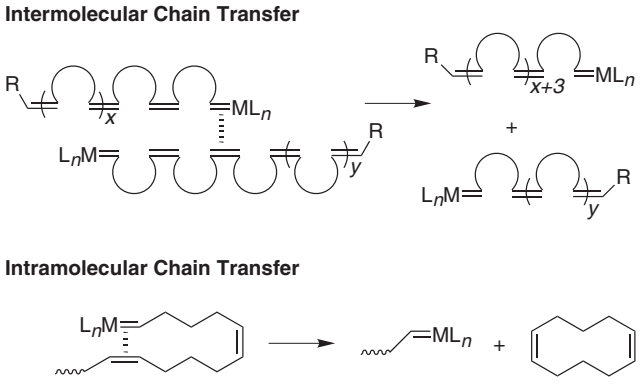
Strained cyclic olefins having no bulky groups around the double bonds are used as ROMP monomers (Scheme 5). Norbornene and its derivatives are the most commonly used due to their high ROMP activity and easy incorporation of substituents on the ring. More than 20 000 papers concerning olefin metathesis have been published so far, including 2000 ROMP-related original papers and 100 reviews. The most recent complete literature surveys include the *Handbook of Metathesis*,[8] a review of living ROMP by Bielawski and Grubbs,[9] and Buchmeiser's review of polymer-supported well-defined metathesis catalysts.[10] This manuscript overviews the development of transition metal complexes as olefin metathesis catalysts, as well as recent researches on amino acid- and peptide-functionalized polymer synthesis by ROMP intended for application to bio-related materials.

PROGRESS OF TRANSITION METAL CATALYSTS FOR ROMP

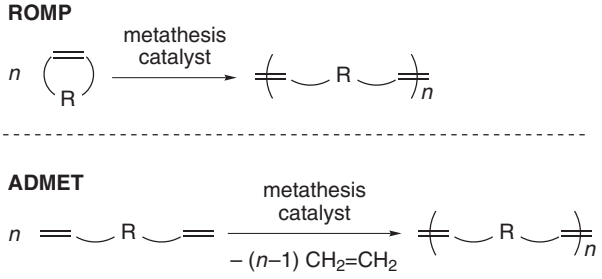
Metathesis reactions catalyzed by transition metal chlorides are heterogeneous, and the active species are ambiguous, and thus, it is difficult to control the molecular weights of polymers formed by ROMP using transition metal chlorides. Transition metal complexes



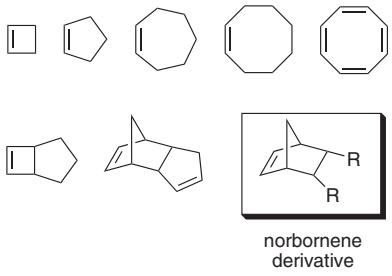
Scheme 1 Mechanism of olefin metathesis reaction.



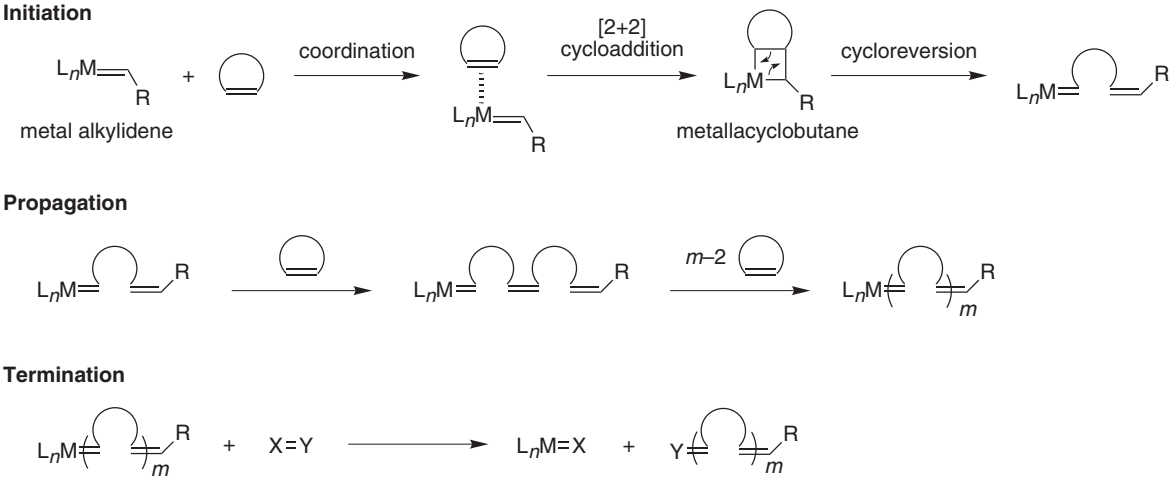
Scheme 4 Chain-transfer reactions accompanied in ROMP.



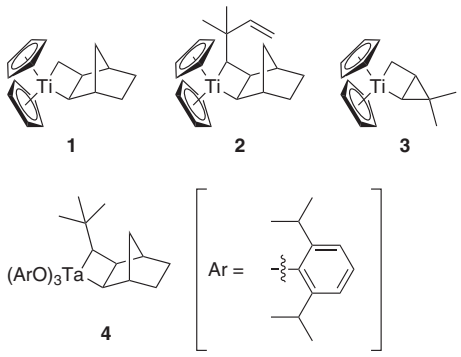
Scheme 2 Representative metathesis polymerizations.



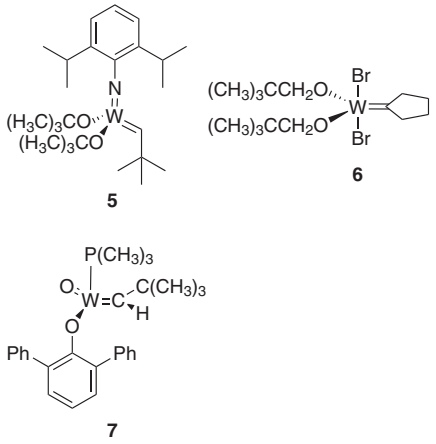
Scheme 5 Representative ROMP monomers.



Scheme 3 Mechanism of ROMP.



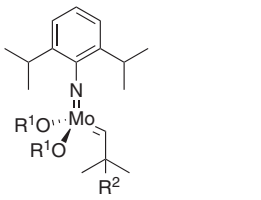
Scheme 6 Titanacyclobutane and tantalacyclobutane complexes.



Scheme 7 Tungsten–carbene complexes.

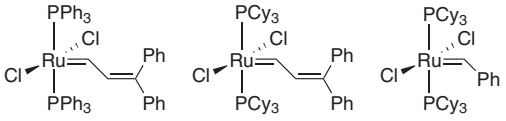
with organic ligands are preferable, because the reactions proceed homogenously and are easier to control. The active species are clearly defined and modification of catalytic activity is possible by ligand design. Titanacyclobutane complexes **1** and **2** (Scheme 6) are the first examples of single-component catalysts capable of catalyzing living ROMP. These catalysts provide polymers with small polydispersity indices (PDIs),[11] wherein the molecular weight linearly increases with the amount of monomer consumed. Block copolymers with narrow PDIs can be prepared using titanacyclobutane complex **3**,[12] which also allows synthesis of polymers with advanced topologies.[13] Tantalacyclobutane complex **4** also polymerizes norbornene in a living fashion.[14] However, titanium and tantalum complex catalysts face limited applicability in ROMP because they are incompatible with most heteroatom-containing functional groups.

Tungsten (W) chloride-based catalysts polymerize strained cyclic olefins in a nonliving fashion. On the other hand, well-defined W–carbene complex **5** (Scheme 7) catalyzes the living ROMP of norbornene,[15] and W-based catalysts are tolerant to ester groups. The initiation and propagation rate constants have been examined in the ROMP of variously substituted ester-containing norbornenes using W–carbene complex **6**.[16] Oxo–W alkylidene complex **7** catalyzes the living ROMP of 2,3-dicarbomethoxynorbornadiene to give a polymer with a high *cis*-olefin content (>95%) in the backbone and high isotacticity (>95%).[17]



$R^1 = C(CH_3)_3$, $CCF_3(CH_3)_2$, $C(CF_3)_2CH_3$
$R^2 = CH_3$, Ph

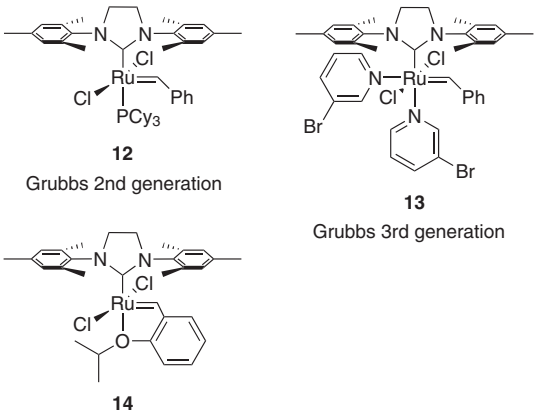
Scheme 8 Molybdenum complexes.



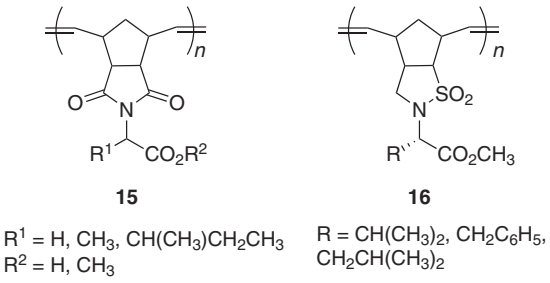
Scheme 9 Representative ruthenium–carbene complexes.

Molybdenum (Mo)-based alkylidene complexes **8** are also usable in ROMP (Scheme 8).[18] These catalysts are stable toward decomposition and tolerant to a much broader range of monomers functionalized with ester, amide, imide, ketal, ether, cyano, trifluoromethyl and halogen groups. Some complexes polymerize norbornene to give polymers with small PDIs. Star block copolymers are synthesized by the reaction of a crosslinking agent with a living polynorbornene.[19] The high functional group tolerance, as well as the high activity of the Mo-based catalysts, enables the preparation of synthetic analogs to biological polymers through ROMP of *endo*-5-norbornene-2,3-dicarboximides obtained from amino acid methyl esters.[20,21] Another advantage of Mo catalysts is their ability to provide stereoregular polymers. The 2,3-disubstituted-2,5-norbornadienes polymerize in a living fashion to give highly tactic polymers with >98% *trans*-olefin geometry.[22]

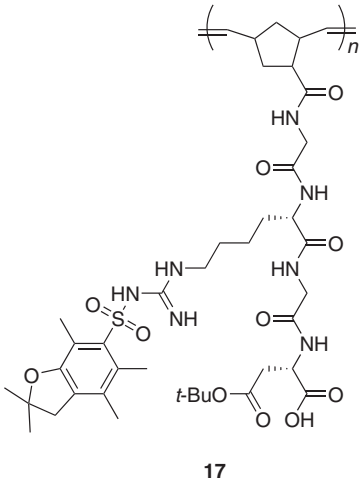
Owing to the low oxophilicity of ruthenium (Ru), its complexes are more tolerant toward polar functional groups compared with complexes of Ti, Ta, W and Mo.[9] It is likely that the $RuCl_3$-catalyzed ring-opening polymerization of norbornene reported in 1965 was the first example of norbornene ROMP, although a mechanism other than metathesis was mentioned.[23] A decade later, the Ru-catalyzed ring-opening polymerization of norbornene was recognized to proceed via the metathesis mechanism.[24,25] In 1988, $RuCl_3$ cyclootadiene was found to catalyze ROMP of variously functionalized 7-oxanorbornenes, but the degree of polymerization could not be controlled.[26] In 1992, the first well-defined, single-component Ru complex **9** catalyzing ROMP of norbornene was reported (Scheme 9).[27] Complex **9** is tolerant to a wide variety of functionalities, and it is active in ROMP of a cyclobutene derivative as well.[28] Use of PCy_3 (Cy=cyclohexyl), a bulky and electron-rich phosphine, leads to highly active catalyst **10**,[29] which is stable in organic solvents in the presence of water, alcohol and acetic acid, or in a diethyl ether solution of HCl. As a result, they have allowed the synthesis of end-functionalized poly(norbornene)s[30] and block copolymers.[31] Nowadays, various metathesis-active Ru–carbene complexes are available. Among them, the most successful is complex



Scheme 10 Ruthenium–carbene complexes bearing NHC ligands.



Scheme 11 Amino acid containing polymers synthesized by ROMP.



Scheme 12 Cell adhesion polymer synthesized by ROMP.

11, the Grubbs first-generation catalyst synthesized from $(PPh_3)_3RuCl_2$ by the reaction with diazobenzylidene and subsequent phosphine exchange.[32,33] Catalyst **11** has significantly widened the scope of monomers and substrates for metathesis chemistry using Ru complexes.

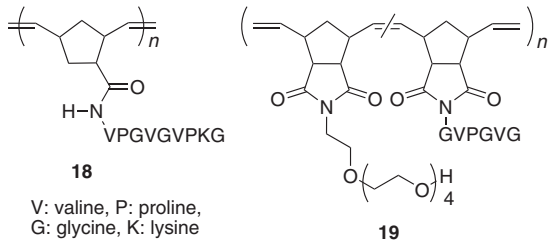
Nitrogen-heterocyclic carbene (NHC) ligands are better sigma donors and are less labile than phosphines.[34] Thus, NHC-coordinated Ru complexes are more stable than the corresponding complexes with PPh_3 or PCy_3 ligands only. A series of Ru complexes with NHC ligands, including **12–14** (Scheme 10), were synthesized with the intention of providing more active catalysts. Complex **12**, the Grubbs second-generation catalyst, possesses an exceptionally high activity in ROMP, because the NHC ligand efficiently enhances the dissociation of the *trans*-phosphine ligand from the Ru center to give the metathesis-active species.[35] However, **12** provides polymers with uncontrolled molecular weights and large PDIs. Thus, **13**, the Grubbs third-generation catalyst, has been developed as a new class of Ru-based metathesis catalysts.[36] Complex **13** contains a strongly ligating NHC and weakly coordinating brominated pyridines, and features high activity in ROMP, based on the labile nature of the pyridine ligand.[37] It catalyzes living ROMP of norbornene and its derivatives to give polymers with small PDIs (<1.10) due to high initiation rates, and is used for preparation of block copolymers.[38] Complex **14** is highly stable due to the bridged styrenyl ether structure, and is easily recovered from metathesis reaction mixtures.[39] Water-soluble Ru catalysts bearing NHC ligands show high activities in aqueous ROMP.[40]

SYNTHESIS OF AMINO ACID- AND PEPTIDE-BASED POLYMERS BY ROMP

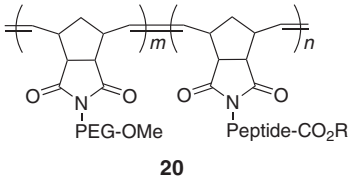
Amino acids are essential sources of biomimetic synthetic polymers. Various attempts have been made to synthesize protein-like polymers containing amino acids and peptides.[41] Some of these form self-assemblies,[42,43] and find pharmaceutical and biological applications.[44] As amino acid- and peptide-based polymers are biocompatible and biodegradable, they are expected to help build a society with an environmentally sound material cycle. These considerations are stimulating the synthesis of amino acid- and peptide-derived artificial polymeric materials and their application in medical fields. Synthesis of biologically active epitopes has attracted attention because of the diversity and complexity of naturally occurring ligands.[45] The polymerization requires compatibility with the polar functional groups of these bioactive ligands. Furthermore, living/controlled polymerization is preferable, as misconstruction can lead to undesired interactions and side effects when these biomimetic polymers are applied to biological processes. Ru complex catalysts for ROMP are tolerant to various functionalities, such as carboxy, hydroxy, amide and ester groups. Living ROMP allows synthesis of polymers and block copolymers with defined lengths, small PDIs, and unique structural features that contain biologically relevant functional groups.

Many biological processes are governed by macromolecular interactions such as binding of an enzyme to its substrate, in which multiple ligands interact with the substrate in the active site. Multivalent binding has an important role in regulating the specificity and avidity of other biological processes as well. To design artificial analogs to biologically active peptides, amino acid-functionalized 5-norbornene-2,3-dicarboximide monomers have been polymerized with Mo–carbene complexes **8** to obtain polymers **15** (Scheme 11).[21] The analogous polymers possessing amino acid-derived carboxy groups can also be synthesized by ROMP using Grubbs first-generation catalyst **11**,[46] without the need to protect the carboxy groups. Biologically active polymers **16** containing sulfonamide groups have been synthesized by ROMP with the Grubbs catalysts **11** and **12**.[47]

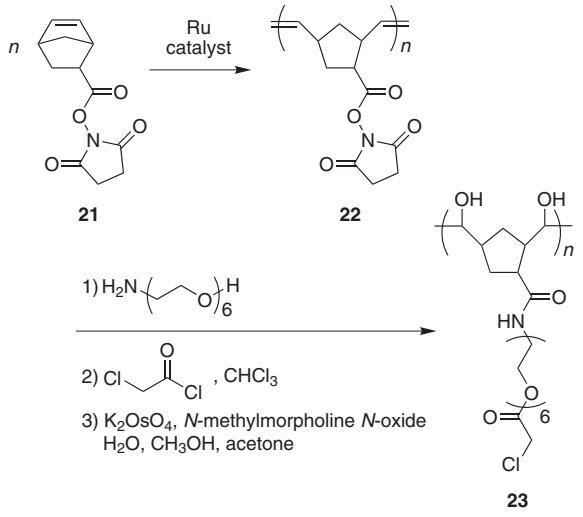
A tripeptide motif, the arginine–glycine–aspartic acid (RGD) sequence, occurs in cellular matrix proteins.[48] RGD peptides are cell adhesion molecules, and are used as drugs for inflammation and cancer metastasis. Polymer **17** containing RGD (Scheme 12)[49] and



Scheme 13 Elastin-like polymers synthesized by ROMP.



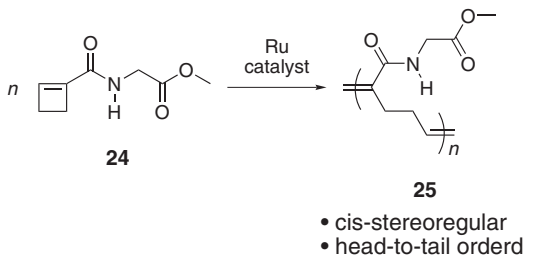
Scheme 14 Block copolymer of norbornenes bearing PEG and peptide units.



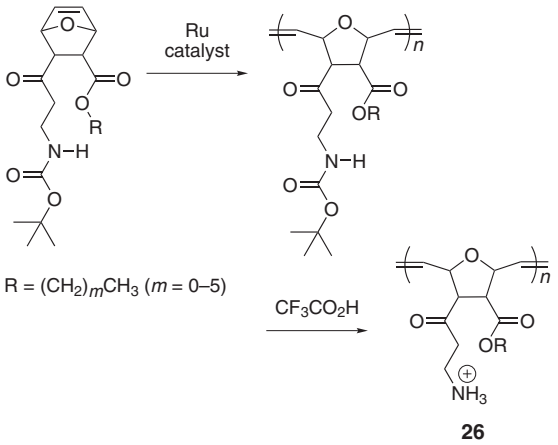
Scheme 15 Synthesis of a water-soluble activated polymer functionalizable with proteins or peptides.

analogous polymers[50] have been synthesized by ROMP. These polymers serve as inhibitors of fibroblast adhesion. As they show greater inhibition than the corresponding peptides, they are useful as drugs for disease-related applications such as tumor therapy.

Elastin is a protein that allows many tissues in the body to resume their shape after stretching or contracting. Elastin-like polymers are biocompatible and show uncommon self-assembling capabilities, which are tunable and expandable in many different ways by substituting the amino acids of the dominating repeating peptide.[51] They are useful as biologically compatible scaffolds for tissue repair and engineering. Bioactive polymers show high capacity to promote cell attachment, especially those based on RGD, which have cell attachment capabilities almost equivalent to those of human fibronectin.[52] ROMP-synthesized elastin-mimic oligomer **18** (Scheme 13)



Scheme 16 Regio- and stereoselective ROMP of a cyclobutene-glycine derivative.

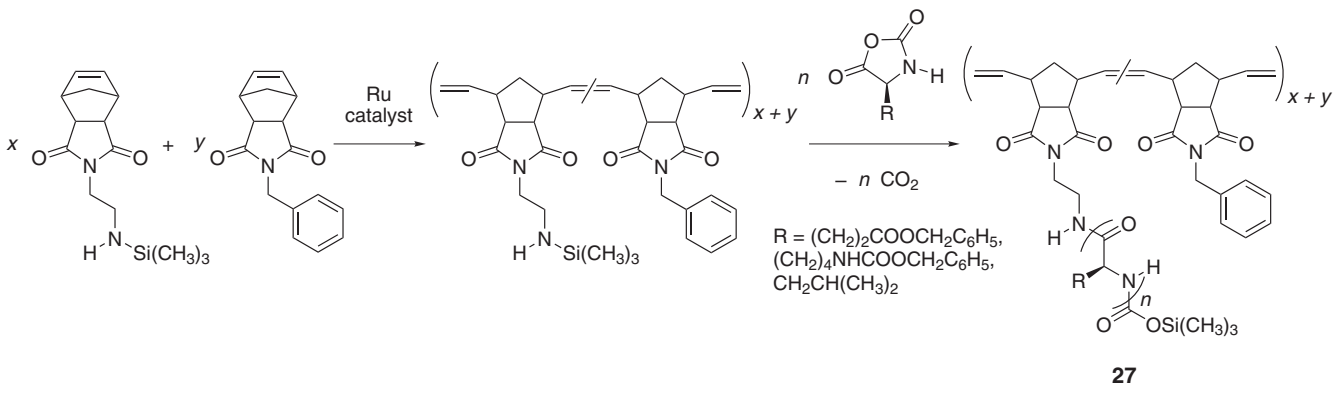


Scheme 17 Synthesis of 'lysine-like' polymer by ROMP.

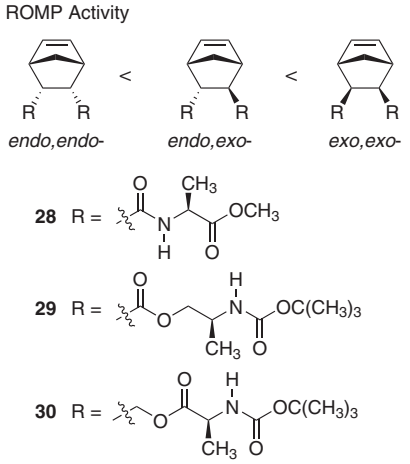
with peptide pendants shows stimuli responsiveness and supports cell survival and proliferation.[53] The lower critical solution temperatures of copolymer **19**, which is composed of an elastin-based monomer and a hydrophilic polyethylene glycol (PEG)-based monomer, are independent of molecular weights and tunable for target applications.[54]

Several attempts have been made to incorporate PEG units into ROMP copolymers, including postpolymerization loading of an amphiphilic ROMP copolymer with a high-density peptide sequence[55] with PEG incorporated as part of the hydrophilic block. The block copolymerization of a norbornene derivative having a short peptide with a norbornene having a PEG substituent gives block copolymer **20**, consisting of a segment with hydrophilic PEG side chains and a segment with more hydrophobic peptide side chains (Scheme 14).[56,57] The copolymer forms aggregates upon dispersion in water.

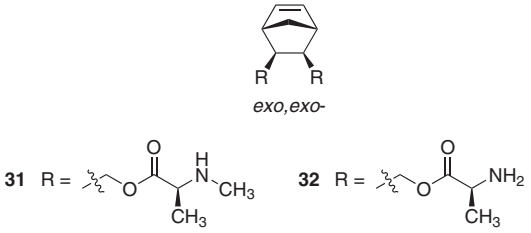
The ROMP of norbornene monomer **21** containing an activated ester linkage gives polynorbornene **22** having *N*-hydroxysuccinimide-derived activated ester moieties. Compound **22** is subsequently converted into water-soluble **23** having oligoethylene glycol side chains terminated with alkyl chlorides as handles for modification (Scheme 15).[55] This method allows the functionalization of polymers with proteins and peptides in a controlled orientation in aqueous media. The multivalent biofunctionalization of activated polymer **23** is demonstrated by the reactions with thioglycerol and a thiol-terminated peptide that binds to the heptameric subunit of anthrax toxin and inhibits toxin assembly. The multivalent inhibitor utilizing this polymer with a broad molecular weight distribution is effective



Scheme 18 Synthesis of polymers bearing brush-like polypeptides by integration of NCA polymerization with ROMP.



Scheme 19 ROMP activity of *endo,endo-*, *endo,exo-* and *exo,exo-*monomers.



Scheme 20 Norborene monomers having unprotected amino groups.

in vivo. The formation of protein–polymer conjugates has also been demonstrated, for example, the incorporation of bovin serum albumin (BSA) with a genetically engineered thiol in a ratio of one or two BSAs per polymer chain.

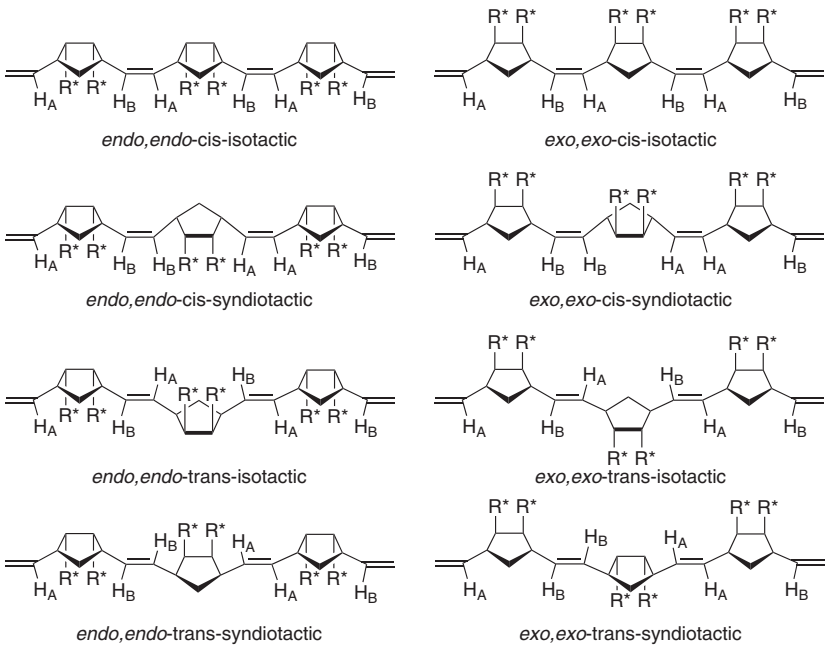
As stereocontrol of ROMP of substituted norbornenes is difficult to achieve, it is not easy to correlate the physical and biological properties of these polymers with specific structural features. Glycine-derived cyclobutene **24** gives a highly regio- and stereoselective head-to-tail ordered polymer **25** with no ambiguous tacticity issues (Scheme 16).[58]

Mimics of antimicrobial peptides based on polynorbornene derivatives have also been synthesized.[59] The polymers with facially amphiphilic antibacterial units have tunable antimicrobial activity depending on the ratio of hydrophobic and hydrophilic moieties in the monomer unit. The selectivity for bacteria versus human red blood cells is over 100.[60] A molecular construction kit approach was examined utilizing ROMP of a broad variety of facially amphiphilic oxanorbornene-derived monomers.[61] Polymers **26** having a 'lysine-like' primary amine as a hydrophilic component have been synthesized (Scheme 17). Some of the polymers are 50 times as selective for Gram-positive over Gram-negative bacteria, whereas some of them show the opposite preference. This unprecedented double selectivity (bacteria over mammalian and one bacterial type over another) is attributable to the monomer's 'facial amphiphilicity' (location of hydrophilic and hydrophobic groups on two opposite faces). The selectivity of the polymers appears to be affected by the overall hydrophilic/hydrophobic balance.

Brush-like copolymers **27** bearing polypeptide side chains have been synthesized via ROMP with controlled polymerization of *N*-carboxyanhydrides (NCAs) initiated by the trimethylsilylamino group at the side chain of the precursor copolymer (Scheme 18).[62] The polymer backbone is first prepared by ROMP of a norbornene having a trimethylsilyl-protected amino group, and then this polymer is used as a macromolecular initiator for subsequent NCA polymerization. The polymers form aggregates with sizes around 60–150 nm. A monomer having nonprotected amino group does not undergo ROMP due to catalyst deactivation by the amine group.

ROMP OF NORBORNENE DERIVATIVES BEARING TWO AMINO ACID ARMS

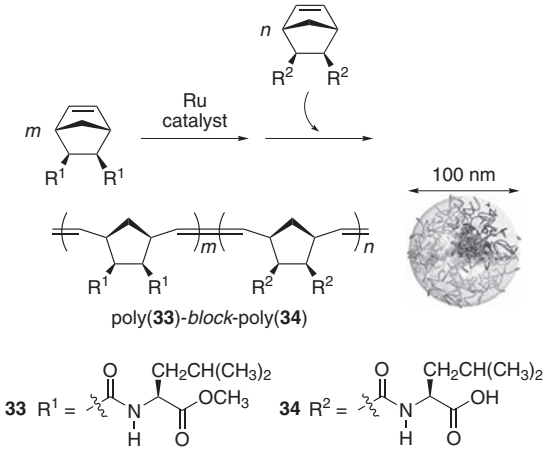
As mentioned above, ROMP of amino acid- and peptide-functionalized norbornene monomers has a high probability for synthesizing biologically and medically useful materials. As *endo,endo-*, *endo,exo-* and *exo,exo-*5-norbornene-2,3-dicarboxylic acids are commercially available, it is easy to synthesize norbornene monomers bearing two amino acid arms with different stereo structures. It is of interest to examine the relationship between the polymerization behavior and *endo-*/*exo-*structures. Novel norbornene derivative **28** (Scheme 19) having *endo,endo*-bis-L-alanine methyl ester moieties was synthesized and subjected to ROMP. Monomer **28** did not homopolymerize; instead, it copolymerized with norbornene.[63] On the other hand, *endo,exo*-**28** and *exo,exo*-**28** homopolymerized to give polymers with moderate



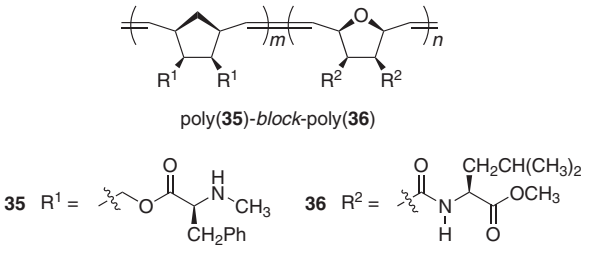
Scheme 21 Possible regular structures of poly(*endo,endo*-2,3-disubstituted norbornene) (left) and poly(*exo,exo*-2,3-disubstituted norbornene) (right): R*, chiral group; H_A and H_B, two sets of nonequivalent olefinic protons distinguishable by ^1H nuclear magnetic resonance spectroscopy.

molecular weights. The polymerization rates were affected by the stereo structure of the monomers; *exo,exo*-**28** underwent ROMP faster to give higher yields of the polymers than the *endo,exo*-**28**. It is likely that the *endo*-substituents of norbornene hinder the coordination of the double bond to the Ru center of the catalyst. The order of polymerization rates is *endo,endo-* < *endo,exo-* <*exo,exo-* (Scheme 19). It is assumed that this reflects the steric factor of the intermediate coordinating the monomer, and/or the stability of metallacyclobutene. Another reason for low reactivity of an *endo,endo*-isomer might be deactivation of the catalyst by chelation of the metal center with the double bond and the *endo*-functional groups. Among various Ru catalysts, Grubbs second-generation catalyst **12** is the most effective for a series of amino acid-based monomers. A polymer gel was synthesized by the copolymerization of the *exo,exo*-monomer and a bifunctional norbornene diester. The gel recognizes chirality; it adsorbs (*R*)-amino acid derivatives more than the (*S*)-isomers.[64] Comparing the amino acid-functionalized norbornene diamide monomers, diester derivatives **29** and **30** satisfactorily undergo homo-ROMP irrespective of *endo*- or *exo*-substitution.[65] The polymerization rates are significantly affected by solvents, but the trend with the solvent polarity and/or donor character is unclear.

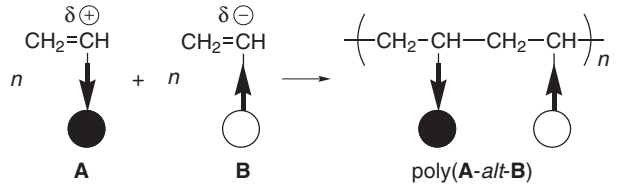
Although Ru–carbene complexes are highly tolerant to various functional groups, they cannot efficiently polymerize norbornene monomers bearing amino or cyano groups, because of strong coordination to the Ru leading to a large decrease of catalytic activity. Interestingly however, amino acid-derived *exo,exo*-norbornene monomer **31** (Scheme 20) having unprotected methylamino groups undergoes ROMP to give the polymer in good yield.[66] The key for successful polymerization is the presence of appropriate spacers between the amino groups and the norbornene skeleton, and possibly intramolecular hydrogen bonding between the amino and carbonyl groups, which presumably prevents the amino groups from deactivating the catalyst. The methyl groups at the nitrogen atoms are also important, because analogous monomer **32** having primary amino groups shows



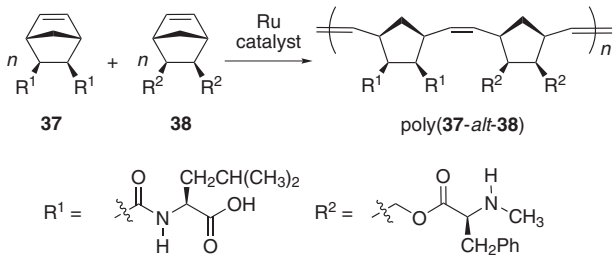
Scheme 22 Block copolymerization of amino acid-functionalized norbornene diester and dicarboxylic acid monomers.



Scheme 23 Block copolymer consisting of hydrophobic and hydrophilic blocks.



Scheme 24 Alternating copolymerization of electron-withdrawing and -donating monomers.



Scheme 25 Alternating copolymerization of norbornene dicarboxylic acid and diamino monomers.

no polymerizability. The *endo,endo*-isomers polymerize less efficiently than the *exo,exo*-ones. The successful polymerization of **31** extends the possibility of application of ROMP-based polymers to biocompatible and pH-responsive materials.

Polymers formed by ROMP of norbornene monomers *endo,endo*- and *exo,exo*-disubstituted with chiral groups have four stereoregularities in triads as shown in Scheme 21. Spectroscopic analysis by ^{1}H–^{1}H correlated spectroscopy nuclear magnetic resonance revealed that the polymer of **31** is syndiotactic-rich.[66] Molecular mechanics simulation suggested that this selectivity is kinetically caused by stability of metallacyclobutane intermediates rather than the thermodynamical stability of the product structures.

Block copolymers with different functionalities are prepared by utilizing the living nature of ROMP. Amphiphilic block copolymers are of interest because of their ability to self-assemble and form nanoscale structures.[67–69] When a diblock copolymer is dissolved in a selective solvent, which is good for one block but poor for the other, it associates to form micelles.[70,71] There have been several reports of amino acid-based amphiphile materials, such as pH-sensitive amphiphile vesicles applicable to a drug delivery systems[72] and polyacetylene with leucine pendant groups.[73]

Amino acid-derived hydrophobic and hydrophilic norbornene monomers **33** and **34** were synthesized and subjected to homo, random and block ROMP (Scheme 22).[74] The hydrophobicity increases with increasing ester monomer content, as confirmed by nuclear magnetic resonance spectroscopic measurements in various solvents and water contact angle measurements of the polymer films. The block copolymers form micelles in acetone (selective solvent), consisting of a hydrophobic shell of poly(**33**) and a hydrophilic core of poly(**34**).

A block copolymer consisting of a hydrophobic norbornene unit having unprotected amino groups and a hydrophilic part containing 7-oxanorbornene having ester groups (poly(**35**)-*block*-poly(**36**); Scheme 23) has also been synthesized.[75] The block copolymer is pH-responsive, and self-assembles in water (pH=7) but disassembles under acidic and basic conditions. It forms micelles with diameters of about 80 nm in H_2O and reverse micelles with diameters of about 45 nm in CH_2Cl_2. Another combination of carboxy and amine monomers also resulted in a block copolymer, whih formed micelles sensitive to pH.[75]

The precise control of polymer structure is an issue of great importance, not only in polymer chemistry but also in materials science, because of the improvement in properties of the resulting materials. Alternating copolymerization is another method of synthesizing sequence-controlled copolymers. This is commonly achieved by employing a combination of electron-accepting monomers, such as maleic anhydride and vinylidene cyanide, with electron-donating monomers, such as styrene and vinyl acetate (Scheme 24).[76] This is also possible in the case of a combination of an electron-donating monomer and an acrylate–Lewis acid complex. In every case, the key factor is a large difference in the electronic states of the polymerizable groups of the two comonomers.

In the case of ROMP, however, it is difficult to introduce electron-accepting or -withdrawing groups close to the double bond of cyclic olefin monomers. Therefore, other approaches have been used to attain alternating ring-opening metathesis copolymerization. For example, racemic 1-methylnorbornene undergoes ROMP alternatingly between the two enantiomeric monomers catalyzed with $ReCl_5$, but no homopolymerization takes place due to steric effects.[77] Alternating ring-opening metathesis copolymerization is also achieved by the combination of a small amount of highly polymerizable norbornene and a large amount of less polymerizable cyclopentene using $RuCl_3$–phenol[78,79] and Grubbs Ru complex–Lewis acid[80] as catalysts, wherein the 'cage effect' has an important role. Appropriately designed dual-site Ru–carbene complexes catalyze the alternating copolymerization of norbornene and a large excess of cyclooctene, wherein one site of the complex shows chemoselectivity while the other site does not.[81–83] The combination of polar 2,3-difunctionalized 7-oxanorbornene derivatives and nonpolar cyclic olefins, including cyclooctene, also works satisfactorily.[84,85] The alternating copolymers form well-controlled micrometer-scale aggregates by complementary noncovalent interactions when diaminopyridine and thymine side chains are introduced.

Cyclobutene 1-carboxylic esters and cyclohexene derivatives undergo alternating ring-opening metathesis copolymerization.[86] This success derives from the combination of two monomers, neither of which forms a homopolymer under ROMP conditions. A unique alternating ROMP is achieved using a combination of norbornene monomer **37** having carboxy groups and monomer **38** having amino groups (Scheme 25).[87] The possible key factor favoring alternating copolymerization is acid–base interaction between the monomers, leading to enhancement of local monomer concentration, and acid–base interaction between the metal carbene propagating species and the incoming monomers. This is the first successful example of an alternating ring-opening metathesis copolymerization between two kinds of norbornene monomers substituted with different functional groups. This achievement is expected to contribute not only to the development of well-defined ROMP chemistry but also to the enhancement of properties of ROMP-based polymers.

CONCLUSIONS

This article has described the development of olefin metathesis catalysts, ROMP behavior of monomers having amino acid and peptide moieties, and applications to bio-related materials. Although the recent remarkable progress of molecular design of ROMP catalysts and monomers has made it possible to provide unique and useful polymeric materials, more precise control over tacticity, *cis*/*trans* geometry of olefinic moieties in the main chain of the formed polymers, and induction of chirality is still needed. ROMP occupies

an important position in industry as well as in academic fields. In addition to the medical uses mentioned in this paper, amorphous cycloolefin polymers produced by ROMP followed by hydrogenation feature high transparency and thermal stability with low birefringence and water absorptivity. They are used as plastic lenses for laser printers and optical disk drives.

The most commonly used transition metal for ROMP catalysts is Ru, which is also used in the metallic form as a memory layer for hard disk drives. The production of Ru is significant (approximately 30 tons per year), but it is two orders of magnitude smaller than that of gold. Progress in the technology for recycling and reusing Ru catalysts is expected to economize on this important precious metal resource.

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