

FOCUS REVIEW

Functional spaces in star and single-chain polymers via living radical polymerization

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This article reviews recent advances in the creation of functional spaces with core-functionalized star polymers and single-chain folding/crosslinked polymers via living radical polymerization. Various core-functionalized star polymers were efficiently prepared with functional linking agents and monomers to perform unique functions. For example, they can serve as nanoreactors for active and robust catalysis in organic reactions and polymerization and as nanocapsules for selective and stimuli-responsive molecular recognition. Single-chain folding polymers were obtained from the self-folding of amphiphilic random copolymers bearing hydrophilic poly(ethylene glycol) chains and hydrophobic alkyl pendants in water, resulting in unimer micelles with dynamic hydrophobic domains. The folded structure could be further fixed via the intramolecular crosslinking of the hydrophobic interior. In addition, cation template-assisted cyclopolymerization and concurrent tandem living radical polymerization with *in situ* monomer transesterification were also developed for the one-pot synthesis of cyclopolymers with large in-chain cavities and gradient and sequence-controlled copolymers.

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INTRODUCTION

Polymers and macromolecules can provide three-dimensional compartments^{1–10} and place functional groups in a specific position¹¹ to serve as promising scaffolds for unique functional spaces. Proteins and enzymes naturally possess precision nanocavities within their globular tertiary structure where they perform selective recognition and catalysis in water. The tertiary structure consists of self-folding polymer chains with perfectly controlled primary structures. Recent advances in living radical polymerization and the initiating/catalytic systems have allowed us to tailor-make functional polymers with controlled primary structure and three-dimensional and/or branched architecture.^{12–22} Focusing on these features, we have recently developed functional polymer spaces (microgel-core star polymers, single-chain folding/crosslinked polymers)^{8–10} and functional polymer chains (cyclopolymers, sequence-controlled polymers) via ruthenium-catalyzed living radical polymerization.^{12,13} These polymers perform unique functions reflecting their primary structure and specific environment (Figure 1).

With functionalization and/or primary structure control, synthetic linear polymers can be typically transformed into the following globular, compartmentalized polymers: (1) microgel-core star polymers;^{8–10,23–25} (2) micelles, vesicles and polymersomes;^{3–6} and (3) unimer micelles and single-chain polymeric nanoparticles.^{26–28} Among these, microgel-core star polymers comprise crosslinked microgels that are covered and solubilized by multiple linear arm polymers to be regarded as ‘solubilized gels’.²⁹ Such star polymers are generally obtained from the intermolecular crosslinking of living polymers (or macroinitiators) with divinyl compounds in living

polymerization,^{29–35} whereas the microgel cores of divinyl compounds have been conventionally used as a connecting point of arm polymers. Beyond such classical understanding, we regard the microgel cores of star polymers as crosslinked but solubilized functional spaces^{8–10,36–46} that are distinct from dynamic, non-crosslinked spaces such as micelles via the physical self-assembly of amphiphilic block copolymers in solvents that are poor for one of the segments.^{3–5}

By contrast, amphiphilic or functional linear random copolymers in turn self-fold to form unimer micelles and single-chain polymeric nanoparticles with intramolecular non-covalent physical (for example, hydrophobic or hydrogen bonding) interaction and/or covalent chemical crosslinking in specific solvents.^{47–62} The folding spaces are not only attractive as an artificial mimic of proteins and enzymes but they can also be more precisely designed because the primary structure (for example, molecular weight, composition of monomers and functional groups) of linear polymers is directly related to folding spaces.

Here, we review recent advances in the synthesis and functions of microgel-core star polymers^{37–46} and single-chain folding/crosslinked polymers^{57–61} via living radical polymerization. In addition, smart synthetic strategies for cyclopolymers with large in-chain cavities⁶³ and sequence-controlled polymers^{64–66} are also briefly described.

RESULTS AND DISCUSSION

Core-functionalized star polymers

Design of microgels and arms. As a result of the high functionality tolerance and controllability of ruthenium catalysts,^{12,13} various

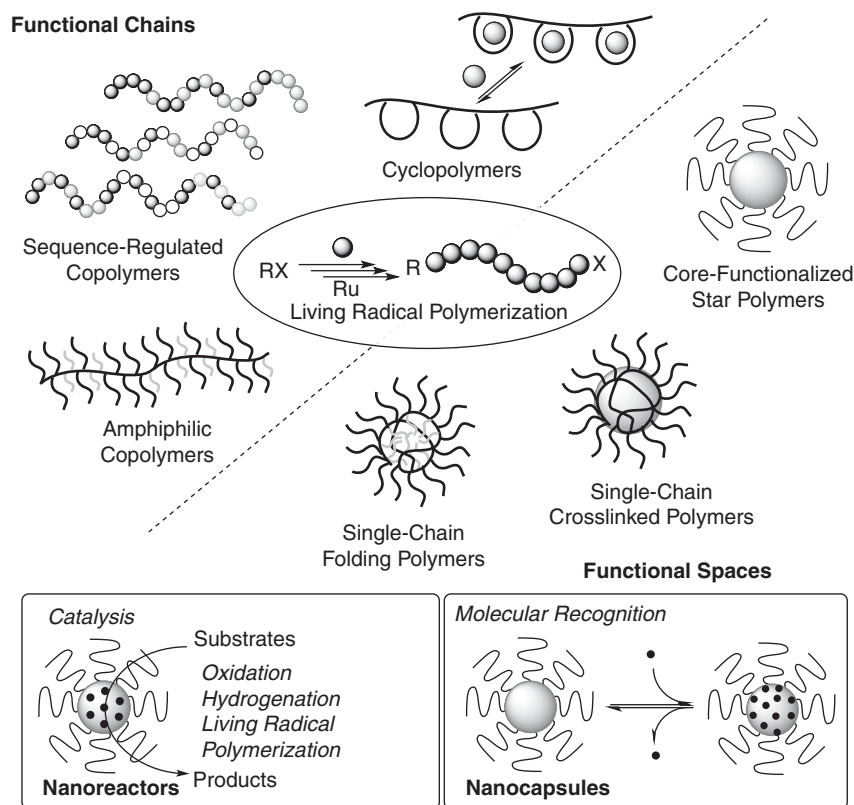


Figure 1 Design of functional polymer chains and spaces via ruthenium-catalyzed living radical polymerization.

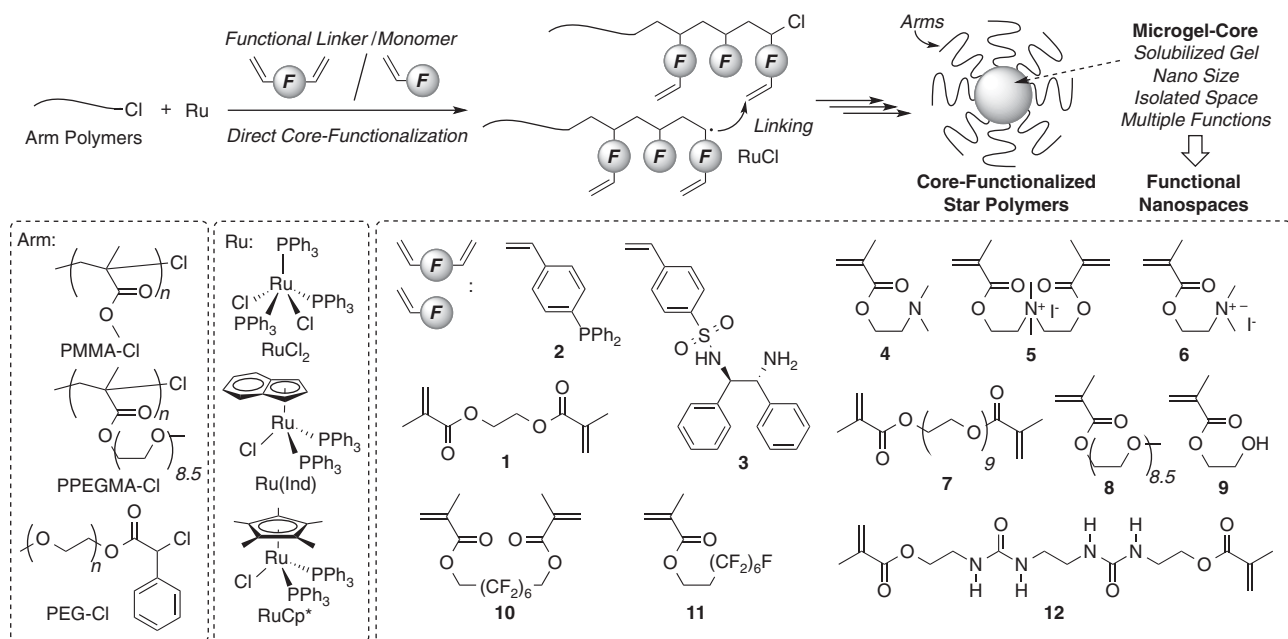


Figure 2 Core-functionalized star polymers obtained via ruthenium-catalyzed living radical polymerization of functional linkers and monomers (1–12) with chlorine-capped arm polymers (PMMA-Cl, PPEGMA-Cl and PEG-Cl).

core-functionalized star polymers have been directly synthesized by the ruthenium-mediated linking reaction of chlorine-capped linear arm polymers (living polymers or macroinitiators) with functional divinyl linkers/monomers carrying phosphines (2), amines (3, 4), quaternary ammonium salts (5, 6), poly(ethylene glycol) (7, 8),

hydroxyl groups (9), perfluorinated alkanes (10, 11) and urea groups (12); (Figure 2).^{8–10,37–46} Efficient preparation involves the following: (1) selection of catalytic systems ($\text{RuCl}_2(\text{PPh}_3)_3/n\text{-Bu}_3\text{N}$, $\text{Ru}(\text{Ind})\text{Cl}(\text{PPh}_3)_2/n\text{-Bu}_3\text{N}$, $\text{RuCp}^*\text{Cl}(\text{PPh}_3)_2/\text{amino alcohol}$ (for example, 4-dimethylaminobutanol)) and solvents (toluene, ethanol

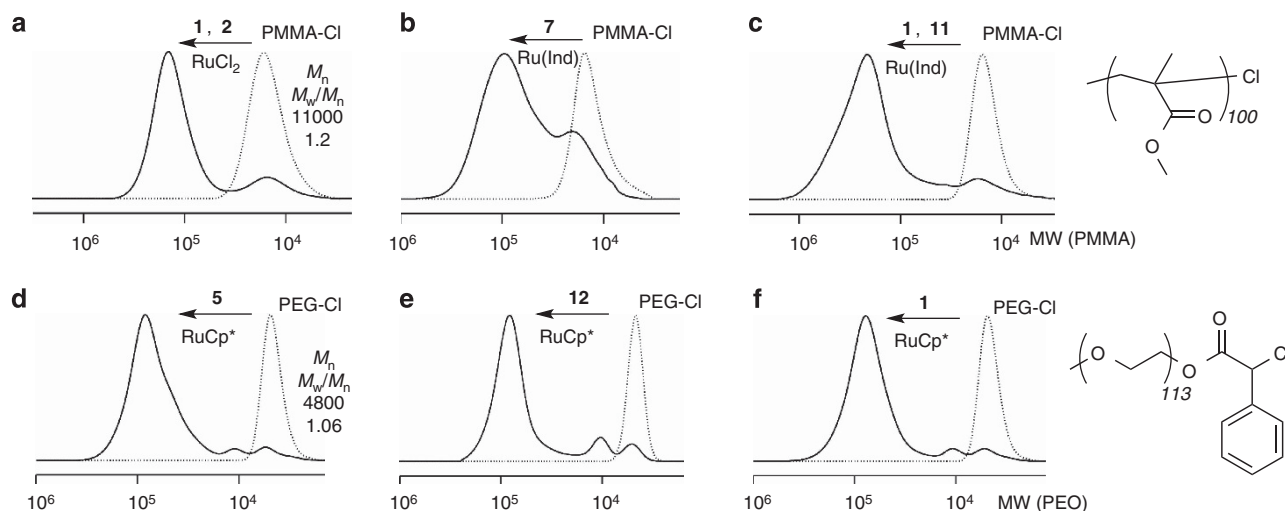


Figure 3 Synthesis of core-functionalized star polymers via Ru-catalyzed linking reactions of arm polymers (PMMA-Cl or PEG-Cl) with functional linkers and monomers ((a) **1**, **2**, (b) **7**, (c) **1**, **11**, (d) **5**, (e) **12**, (f) **1**): $[arm]_0/[linker]_0/[monomer]_0 = 1/10/0$ or (a) **5** or (c) **10**. Catalytic system: (a) $RuCl_2$ or (b, c) $Ru(Ind)$ in toluene at $80^\circ C$; (d-f) $RuCp^*$ in ethanol at $40^\circ C$.

and water) suitable for arm polymers and core-forming functional linkers/monomers; and (2) optimization of the feed ratio of core-forming linkers/monomers to arm chains ($[R-Cl]$).

Arm polymers provide the desired solubility to star polymers. Arm chains are typically obtained from one of two methods: (1) living radical polymerization of monomers (for example, methyl methacrylate (MMA),^{29,30,36–41,45} poly(ethylene glycol) methyl ether methacrylate (PEGMA: $M_n = 475$; ethylene oxide units = 8.5)^{42–44}) with a chlorine-based initiator (a chlorine-capped MMA dimer: H-(MMA)₂-Cl, ethyl 2-chloro-2-phenylacetate); and (2) esterification of polymer chains (for example, poly(ethylene glycol) methyl ether (PEG-OH: $M_n = 5000$; ethylene oxide units = 113)) with an acid chloride (2-chloro-2-phenylacetyl chloride).⁴⁶ The former yields hydrophobic poly(methyl methacrylate) arms (PMMA-Cl) and amphiphilic, thermosensitive poly[poly(ethylene glycol) methyl ether methacrylate] arms (PPEGMA-Cl), whereas the latter yields amphiphilic long poly(ethylene glycol) methyl ether arms (PEG-Cl; Figure 2). PMMA-arm star polymers are soluble in organic solvents including toluene, tetrahydrofuran, chloroform and *N,N*-dimethylformamide (DMF), whereas their PEG counterparts are soluble not only in such organic solvents but also in alcohols and water with thermoresponsive solubility.

Metal-bearing star polymer catalysts. Generally, polymer-supported metal catalysts should have high practicability and easy handling in catalysis (recovery and separation of catalysts and products, catalyst recycling).^{67,68} This objective is achieved with insoluble scaffolds such as silica gel and crosslinked polystyrene, whereas the insolubility often leads to low activity and selectivity. Soluble polymer-supported metal catalysts in turn maintain an activity level that is consistent with the original homogeneous counterparts, although they sometimes cause metal leaching during reactions and in the recovery processes. Thus, it is difficult for polymer-supported catalysts to satisfy both catalytic activity and practicability.

By contrast, metal-bearing microgel star polymers are expected to exhibit high activity and selectivity together with high stability and robustness because the metal complexes are tightly supported within solubilized microgels. Focusing on this aspect, we designed metal/linker-bearing microgel star polymers via ruthenium-catalyzed living

radical polymerization with ligand-bearing monomers (**2**, **3**).^{8–10,37–44} Importantly, this synthetic strategy affords a one-pot transformation of ruthenium polymerization catalysts into ruthenium-bearing star polymer catalysts, which is thus more efficient than conventional multistep procedures: (1) synthesis of ligand-bearing (co)polymers, followed by the post introduction of metals; and (2) synthesis of metal-bearing monomers, followed by (co)polymerization.

Typically, MMA was first polymerized with a chloride initiator and a ruthenium catalyst ($RuCl_2(PPh_3)_3/n-Bu_3N$) to yield chlorine-capped PMMA-Cl with a narrow molecular weight distribution (condition: $[MMA]_0/[initiator]_0/[RuCl_2(PPh_3)_3]_0/[n-Bu_3N]_0 = 2000/20/10/40$ mM, conv. = $\sim 90\%$, 48 h, $M_n = 11\,000$, $M_w/M_n = \sim 1.2$). Then, PMMA-Cl was directly crosslinked with ethylene glycol dimethacrylate (EGDMA: **1**) in the presence of a phosphine-bearing styrene derivative (**2**) in toluene ($[1]_0/[2]_0/[PMMA-Cl]_0 = 10/1.25-5/1$), leading to the production of phosphine and ruthenium-bearing microgel star polymers in high yield (80–90%; Figure 3a).^{37,38,40} During the arm-linking process, **2** is simultaneously coordinated to $RuCl_2(PPh_3)_3$ (polymerization catalyst) via a ligand exchange reaction to directly encapsulate the ruthenium complex into star polymer cores. A star polymer ($[2]_0/[PMMA-Cl]_0 = 5$) had an absolute weight-average molecular weight (M_w) of 650 000, 35 arm numbers (N_{arm}) and a radius of gyration (R_g) of 10 nm, as analyzed by multiangle laser light scattering coupled with size exclusion chromatography (SEC-MALLS).

M_w , N_{arm} , ligand and ruthenium content in star polymers are controllable by the feed ratio of monomers (**1** and **2**) to PMMA arms ($r_1 = [1]_0/[PMMA-Cl]_0$, $r_2 = [2]_0/[PMMA-Cl]_0$).³⁸ Arm length is simply tunable by the feed ratio of MMA to an initiator ($DP = [MMA]_0/[initiator]_0$). System optimization revealed that EGDMA ($r_1 = 10$) was effective for the linking of PMMA-Cl ($DP = 100$, $M_n = \sim 10\,000$). The ruthenium content in star polymers increased from 31 to $74\ \mu mol\ g^{-1}$ with increasing ligand feed ($r_2 = 1.25, 2.5, 5$), which was confirmed using ultraviolet-visible absorption spectroscopy (UV-vis) and inductively coupled plasma-atomic emission spectroscopy.³⁸ A star polymer with $r_2 = 5$ almost quantitatively encapsulates Ru polymerization catalysts into the core. Owing to the in-core Ru, Ru-star polymers cast on a glass plate were observed as black dots of $\sim 2-3$ nm with transmission electron microscopy.^{37,38}

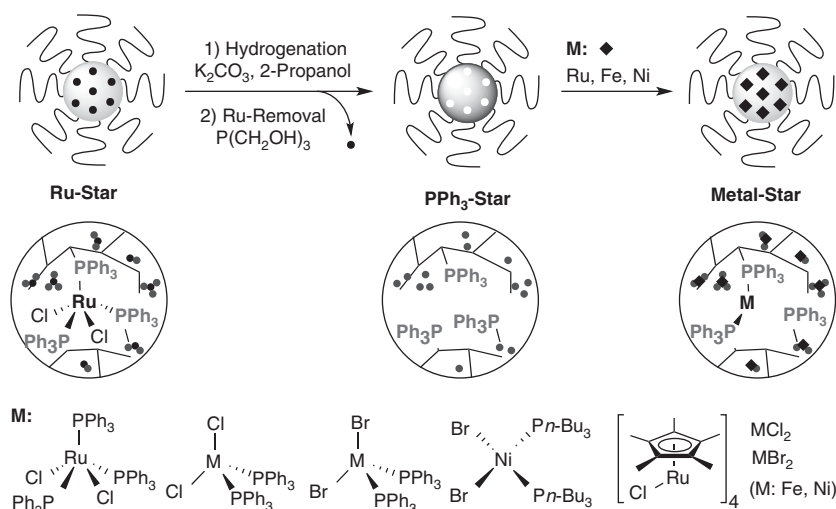


Figure 4 Star polymer catalysts (Metal-Star) were obtained via the metal interchange of ruthenium-bearing star polymers (Ru-Star) as follows: (1) hydrogenation of the RuCl_2 -Star core with K_2CO_3 and 2-propanol; (2) removal of core-bound Ru with $\text{P}(\text{CH}_2\text{OH})_3$; and (3) introduction of metals (M) to PPh_3 -Star.

Metal-bearing star polymers are further functionalized and modified with arms, ligands and metal interchange. PPEGMA arms provide amphiphilic and thermosensitive solubility to star polymers bearing hydrophobic microgels.⁴² Core-bound metals are interchangeable from an original ruthenium [$\text{RuCl}_2(\text{PPh}_3)_3$] to others (iron and nickel) via ligand exchange reaction.^{40,41} Core-bound ruthenium in Ru-Star can be removed with a hydrophilic and basic phosphine [$\text{P}(\text{CH}_2\text{OH})_3$], leading to empty star polymers with phosphine-bearing microgels (PPh_3 -Star; Figure 4). PPh_3 -Star can again enclose various metal salts and complexes (M: FeX_2 , NiX_2 , $\text{FeX}_2(\text{PPh}_3)_2$, $\text{NiX}_2(\text{PPh}_3)_2$, $\text{NiBr}_2(\text{P}n\text{-Bu}_3)_2$, $\text{X} = \text{Br}$ or Cl) to provide novel metal-bearing star polymer catalysts (Metal-Star).

However, PPh_3 -Star cores still contain chlorine terminals and unreacted pendant olefins that may induce undesired reactions such as gelation in radical-mediated catalysis. This possibility is avoided by the core hydrogenation of Ru-Star before Ru removal.^{40,41} The hydrogenation of in-core olefins and chlorine terminals is mediated by in-core ruthenium hydride (RuH_2) that is directly transformed from ruthenium chloride complexes (RuCl_2) with K_2CO_3 and 2-propanol.⁶⁹ Chiral ruthenium catalysts can also be directly created in microgels with a styrene derivative carrying a chiral diamine ligand (3).¹⁰

Function-condensed star polymer capsules. In addition to phosphine (2) and diamine (3), various functional groups (4–12) can be introduced into star polymer cores via ruthenium-mediated arm-linking reaction, yielding star polymer nanocapsules that efficiently and selectively capture guest molecules within the microgel cores.^{8–10,41,45,46} The key is to condense functional groups into microgels at a high local concentration.

A $\text{Ru}(\text{Ind})\text{Cl}(\text{PPh}_3)_2/n\text{-Bu}_3\text{N}$ catalytic system is widely applicable to chlorine-capped polymethacrylate arms (PMMA-Cl, PPEGMA-Cl) and functional (di)methacrylates (4, 7–11) (Figures 3b and c). Typically, fluororous microgel star polymers are obtained from the $\text{Ru}(\text{Ind})\text{Cl}(\text{PPh}_3)_2$ -catalyzed linking reaction of PMMA-Cl ($M_n = 13\,000$) with perfluorinated alkane methacrylates (10, 11) ($[\mathbf{1}]_0/[\mathbf{11}]_0/[\text{PMMA-Cl}]_0 = 10/10/1$, $M_w = 1\,200\,000$, 52 arms, $R_g = 12\text{ nm}$).⁴⁵ The number of core-bound perfluorinated alkanes (NCF_3) and fluorine atoms (NF) is controlled by the feed ratio of

perfluorinated monomers to arms ($\text{NCF}_3 = 0\text{--}760$, $\text{NF} = 2000\text{--}15\,000$). Importantly, the properties and mobility of fluorinated microgels are evaluated by ^{19}F nuclear magnetic resonance. The mobility of in-core perfluorinated pendants is dependent on solvents; the fluorine signal is broader in $\text{DMF-}d_7$ than in CDCl_3 , meaning that DMF promotes intramolecular aggregation of the perfluorinated alkanes with fluororous interaction. Confirmed by relaxation time (T_1) measurements with ^{19}F nuclear magnetic resonance, the thermal mobility of fluorinated pendants in star polymers was much lower than that in linear random counterparts.

Coupling of $\text{RuCp}^*\text{Cl}(\text{PPh}_3)_2$ with amino alcohol additives effectively induces the linking reaction of hydrophilic PEG-Cl arms with polar functional linkers/monomers carrying quaternary ammonium salts (5, 6)⁴⁶ and urea groups (12)¹⁰ (insoluble in organic solvents such as toluene) in ethanol, DMF, and water (Figures 3d and e). The resulting star polymers are water-soluble and have narrow molecular weight distribution (yield: $\sim 90\%$, $[\mathbf{5}$ or $\mathbf{12}]_0/[\text{PEG-Cl}]_0 = 10/1$, $M_w/M_n = 1.1\text{--}1.3$). It should be noted that $\text{RuCp}^*\text{Cl}(\text{PPh}_3)_2$ has high controllability of such polar functional monomers, which is comparable to that of a non-functional EGDMA (1, Figure 3f).

Catalysis. Ruthenium complexes are widely utilized as catalysts not only for living radical polymerization but also for organic reactions (for example, oxidation and reduction).⁷⁰ The catalytic activity of ruthenium-bearing star polymers was thus investigated in the oxidation of sec-alcohols,^{37,39} hydrogenation of ketones^{43,44} and living radical polymerization^{40,41} (Figure 5). Ru-bearing star polymer catalysts obtained from direct $\text{RuCl}_2(\text{PPh}_3)_3$ encapsulation with a ligand monomer (2) were employed for oxidation and hydrogenation, whereas metal-bearing counterparts were utilized for living radical polymerization via metal interchange (core hydrogenation, Ru removal, metal introduction).

$\text{Ru}/2$ -bearing star polymers with PMMA arms (Ru-Star) were effective in the oxidation of various sec-alcohols (for example, **A1–A4**) with K_2CO_3 in acetone at 65°C (Figure 5a).^{37,39} Typically, Ru-Star ($M_w = 388\,000$, 24 arms ($M_n = \sim 10\,000$), core 2: 60/star, core Ru: 15/star) homogeneously catalyzed the oxidation of 1-phenylethanol (**A1**) into acetophenone in high yield (90%, 8 h),

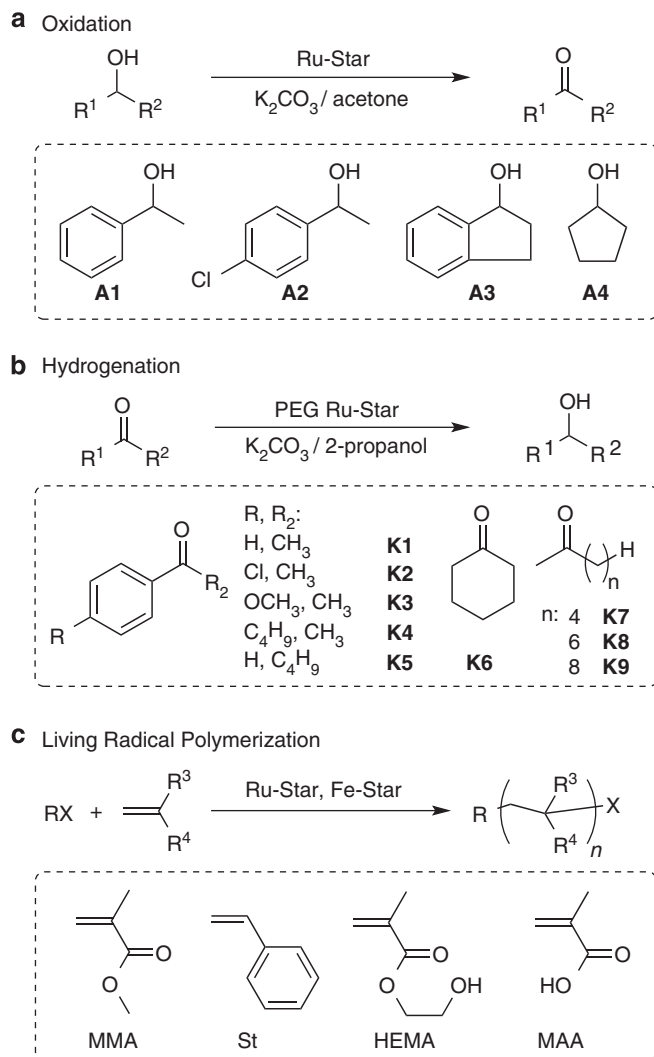


Figure 5 Catalysis with metal-bearing star polymers: (a) oxidation of sec-alcohols with Ru-Star in acetone; (b) hydrogenation of ketones with PEG Ru-Star in 2-propanol; and (c) living radical polymerization with Ru-Star or Fe-Star.

even at a low catalyst feed ratio to the substrate ($[\text{substrate}]_0/[\text{Ru}]_0 = 1000/1$, turnover frequency (h^{-1}) = ~ 110).³⁹ The activity was greater than that obtained with a Ru-supported polystyrene gel (64%, 8 h) and a Ru-supported MMA/2 linear random copolymer (52%, 8 h). Importantly, the catalytic activity of Ru-Star depends on the ratio of **2** (ligand) to Ru in the core ($[\text{core } \mathbf{2}]/[\text{core Ru}]$); turnover frequency (h^{-1}) increased from 110 to 300 with a decrease in the ratio $[\text{core } \mathbf{2}]/[\text{core Ru}]$ from 4 to 2.5. This result suggests that coordinatively unsaturated metal species efficiently induce catalysis. This activity was in turn independent of arm length and **1** (crosslinking unit), indicating that small substrates freely diffuse in Ru-bearing microgel spaces. Ru-Star can be reused three times without any retardation of activity or decomposition of polymer via recovery under air exposure. These results demonstrate that ruthenium-bearing star polymers are active, robust and stable catalysts for organic reactions.

Because of its amphiphilic solubility, Ru-Star with PPEGMA arms (PEG Ru-Star) functions as an active and recyclable catalyst for the transfer hydrogenation of ketones (for example, **K1**–**K9**) to sec-

alcohols in 2-propanol at 100 °C ($[\text{substrate}]_0/[\text{Ru}]_0 = 1000/1$, Figure 5b).⁴⁴ PEG Ru-Star showed high activity for various substrates, including acetophenone (**K1**: turnover frequency = $\sim 220 \text{ h}^{-1}$), p-chloroacetophenone (**K2**: $\sim 930 \text{ h}^{-1}$), cyclohexanone (**K6**: $\sim 980 \text{ h}^{-1}$) and 2-octanone (**K8**: $\sim 230 \text{ h}^{-1}$). In addition, PEG Ru-Star is recyclable three times in acetophenone and 2-octanone.

More intriguingly, PEG Ru-Star affords thermoregulated phase-transfer catalysis in the hydrogenation of 2-octanone (**K8**, hydrophobic, aliphatic substrate) in 2-propanol/ H_2O (1/1, v/v).⁴³ The reaction mixture is phase-separated into an organic (upper) layer of 2-propanol and 2-octanone and an aqueous (lower) layer. In the biphasic solution, PEG Ru-Star rapidly moves from the lower aqueous layer to the upper organic layer upon heating to efficiently catalyze the hydrogenation in dispersion at 100 °C. Upon cooling the reaction solution to room temperature after the reaction, PEG Ru-Star returns to the aqueous phase. Thus, easy product recovery and efficient catalyst recycling were achieved via thermoregulated phase transfer.

Star polymer catalysts can be further applicable to living radical polymerization of methacrylates and styrene (Figure 5c).^{40,41} A RuCp^* -bearing star polymer ($\text{RuCp}^*\text{-Star}$), obtained with hydrogenated $\text{PPh}_3\text{-Star}$ and $[\text{RuCp}^*\text{Cl}]_4$ (Cp^* : pentamethylcyclopentadienyl), efficiently induced living radical polymerization of MMA with a chloride initiator (conv. $\sim 90\%$) to yield well-controlled PMMA with a narrow molecular weight distribution (M_w/M_n : ~ 1.1) and high end functionality (end olefin: $< 3\%$).⁴⁰ This result indicates that microgel cores have enough void space for growing polymer terminals that can smoothly access core-bound ruthenium. The activity and controllability were better than those obtained with an in-core ruthenium analog $[\text{RuCp}^*\text{Cl}(\text{PPh}_3)_2]$. It should be noted that $\text{RuCp}^*\text{-Star}$ induces direct copolymerization of MMA and methacrylic acid (MAA) owing to efficient metal protection. Tolerance to acidic functions is further enhanced by multifunctionalization of $\text{RuCp}^*\text{-Star}$ cores with phosphine and amino groups; the Ru metal is efficiently activated and protected by the cooperative ligation of phosphine (**2**) and amine (**4**).⁴¹ The stability of iron catalysts was also improved with $\text{PPh}_3\text{-Star}$.⁴⁰

Molecular encapsulation and release. Function-condensed microgel star polymers (fluorinated core, PEG core and cation core) efficiently and selectively capture molecules within their cores and release them in response to a stimulus; this process is dependent on the core-bound functional groups (Figure 6). Typically, fluorinated star polymers with PMMA arms ($M_w = 2\,000\,000$, 86 arms ($M_n = \sim 13\,000$), core-F atom (**10** + **11**): 14 800/star, core- CF_3 (**11**): 760/star) can encapsulate polyfluorinated compounds, including perfluorooctane, perfluorohexane and perfluoromethylcyclohexane, via fluororous interaction in DMF (Figure 6a).⁴⁵ The efficiency for fluororous encapsulation was enhanced with an increased local concentration of perfluoroalkane pendants (**11**), whereas a perfluoroalkane spacer in dimethacrylate (**10**) is almost independent of fluororous interaction. A fluorinated star polymer selectively recognized perfluorooctane even in the presence of other fluorinated compounds (trifluoromethylbenzene: hydrophobic, trifluoroethanol: hydrophilic) and further released in-core perfluorooctane via the addition of CHCl_3 .

Ionic molecules (for example, Orange G: a hydrophilic dye with sulfonic acid sodium salt) are efficiently enclosed into PEG core or cation-core star polymers in various environments.⁴⁶ PEG (**7**)-core star polymers with PMMA arms solubilized Orange G in CHCl_3 (although it was originally insoluble in CHCl_3) via the recognition of the dye cation (sodium) with the core-PEG spacers and released it via

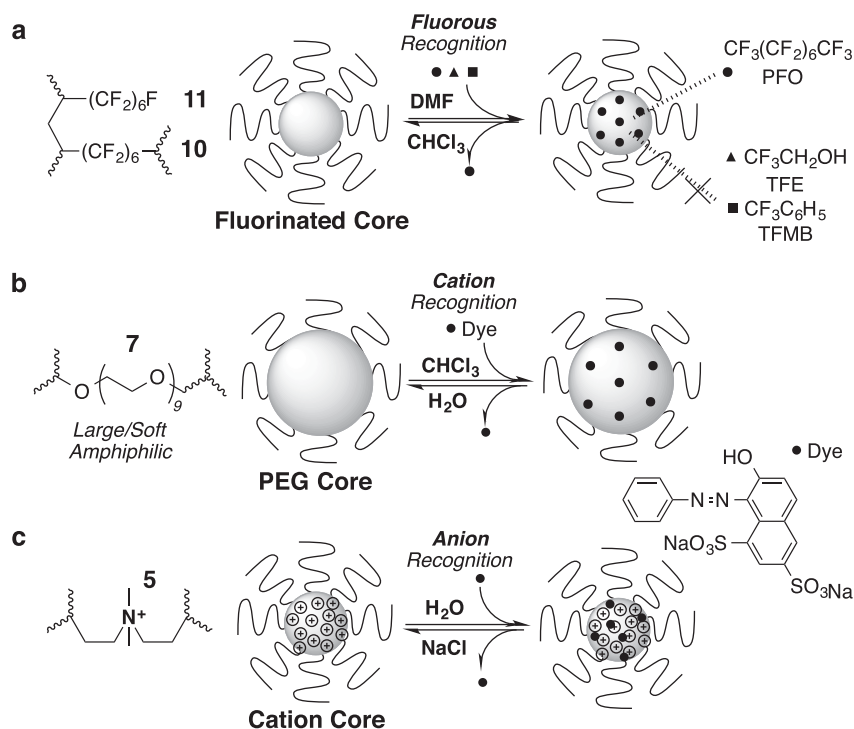


Figure 6 Selective encapsulation and stimuli-responsive release with star polymer nanocapsules: (a) fluorinated core star for perfluoroalkanes via fluoruous interaction; (b) PEG core star for an ionic dye via cation recognition in organic solvents; (c) cation core star for an ionic dye via ionic interaction in water.

the addition of H₂O (Figure 6b). By contrast, water-soluble cation core (quaternary ammonium salts: 5 or 1/6) star polymers with PEG arms successfully entrapped Orange G even in water via ionic interaction between the in-core ammonium cations and the dye sulfonate anions. The controlled release of core-bound dyes was also achieved via treatment with an aqueous solution of NaCl (Figure 6c).

Single-chain folding/crosslinked polymers

Amphiphilic and/or functional linear random copolymers are potentially good precursors that can self-fold (autonomously or in response to stimuli) with intramolecular physical association and/or chemical bond formation in organic solvents or water to yield unimer micelles and single-chain polymeric nanoparticles.^{26–28,48–62} In particular, PEGMA-based copolymers^{57–62} are attractive because of the following: (1) their primary structure (molecular weight, composition and sequence of monomers and/or functional groups, terminal structure) can be designed and controlled by living radical polymerization; (2) their water-soluble and amphiphilic properties afford autonomous self-folding in water; (3) multiple hydrophilic PEG pendants may effectively isolate a hydrophobic methacrylate main chain and stabilize the self-folded structure in water. Self-folding of PEGMA-based copolymers in water has been triggered by intramolecular hydrophobic^{60,61} and/or hydrogen-bonding^{57–59} interactions.

For self-folding with hydrophobic interactions,⁶⁰ amphiphilic PEGMA/RMA random copolymers were synthesized by Ru(Ind)Cl(PPh₃)₂/*n*-Bu₃N-catalyzed living radical copolymerization of PEGMA and hydrophobic alkyl methacrylates (RMA: e.g., dodecyl methacrylate (DMA), octadecyl methacrylate) with a chloride initiator ($M_n = 40\,000\text{--}50\,000$, $M_w/M_n = 1.2\text{--}1.4$, Figure 7a), where monomer composition ($l = [\text{PEGMA}]/[\text{initiator}]$, $m = [\text{RMA}]/[\text{initiator}]$, $l/m = 200/0\text{--}80/120$) and RMA alkyl pendants (R: -C_{*n*}H_{2*n*} or -C_{*n*}H_{2*n*+1}; $n = 1\text{--}18$) were systematically varied. Structural analysis

by SEC and light scattering revealed that the content and hydrophobicity of RMA is important for self-folding: (1) PEGMA/DMA random copolymers gradually folded to become compact in water with an increase in DMA content of up to 40 mol% and in turn induced multichain aggregation in the presence of DMA at 50 mol%; (2) self-folding structures of PEGMA/RMA (160/40) random copolymers gradually became compact with increasing RMA hydrophobicity (carbon number: *n*). In addition, these polymers can dynamically and reversibly fold in water and unfold via methanol addition; they are more mobile upon heating and finally induce lower critical solution temperature-type phase separation.

The dynamic structures of self-folding polymers can be further fixed, that is, ‘frozen’, via the intramolecular crosslinking of the hydrophobic pendant olefins that are accumulated within the unimer micelles in water (Figure 7b).¹⁰ The single-chain crosslinked polymers maintain a self-folding structure, even in organic solvents.

Supramolecular self-assembly of pendant units is also effective for self-folding of polymers. PEGMA/BTAMA random copolymers carrying chiral benzene-1,3,5-tricarboxamide (BTA) units folded in water via the helical self-assembly of the BTA pendants with intramolecular hydrogen bonding.^{57–59} Interestingly, PEGMA/BTAMA random copolymers bearing ruthenium complexes efficiently catalyzed the hydrogenation of cyclohexanone within the self-folded, hydrophobic space in water.⁵⁷ This approach is intriguing as an artificial mimic of enzyme function.⁶² The creation of a specific environment in single-chain folding/crosslinked polymers would be a promising strategy for selective and innovative catalysis.

Cyclopolymers and sequence-regulated copolymers

The placement of precision cavities and sequence-controlled units into polymer chains and spaces would also be important for unique and selective functions in addition to the construction of global functional spaces with core-functionalized star polymers and single-

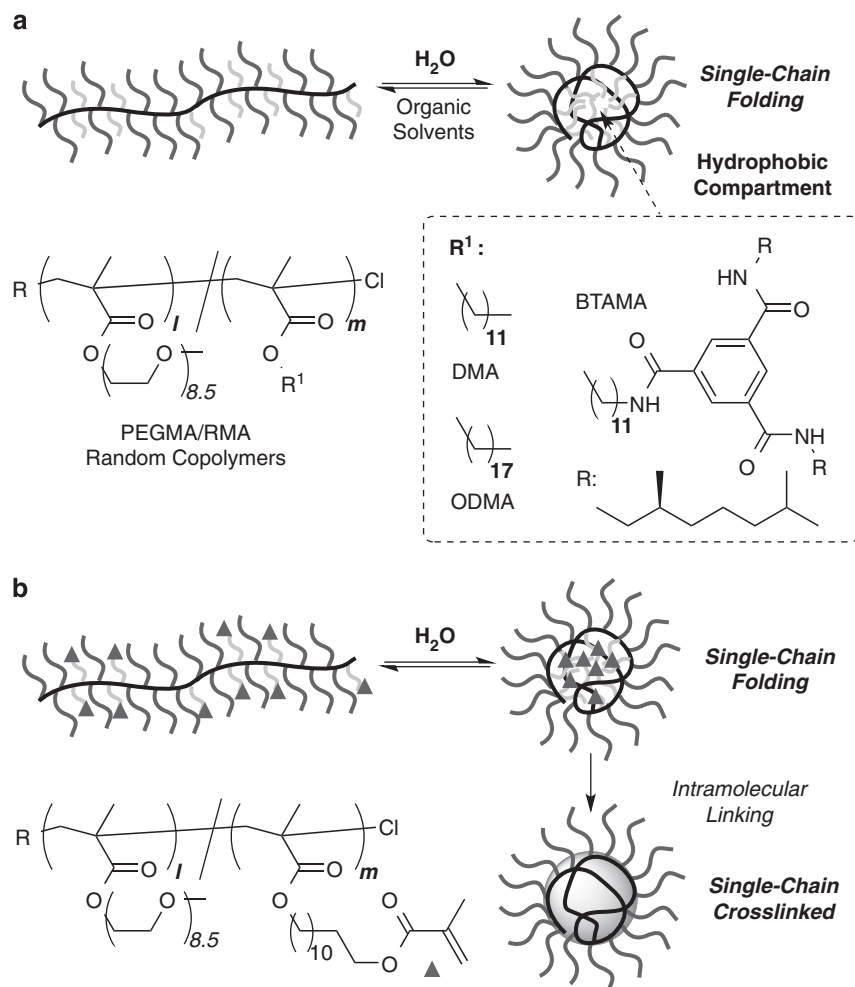


Figure 7 (a) Single-chain folding of amphiphilic random copolymers for unimolecular hydrophobic compartments in water. (b) Single-chain crosslinked polymers via the intramolecular linking of self-folding copolymers in water.

chain folding/crosslinked polymers. Recently, we have developed cation template-assisted cyclopolymerization of poly(ethylene glycol) dimethacrylate (PEGnDMA: $n = 4-8$) as a one-pot strategy to prepare cyclopolymer with large in-chain PEG rings, referred to as 'polymeric pseudo crown ethers' (Figure 8a).⁶³ Cyclopolymerization⁷¹⁻⁷⁶ involves an alternating process of intramolecular cyclization and intermolecular addition of divinyl monomers; the adjacent location of the two olefins is thereby essential to induce efficient cyclization without gelation.

In our system, a potassium cation template (KPF₆) was combined with hexa(ethylene glycol) dimethacrylate (PEG6DMA) to dynamically form a pseudocyclic conformation that places two olefins adjacent to each other.⁶³ The K⁺-template PEG6DMA was polymerized with RuCp*Cl(PPh₃)₂/*n*-Bu₃N in cyclohexanone at 40 °C to yield well-controlled cyclopolymer with 24-membered in-chain PEG rings and high cyclization efficiency (>97%; PPEG6DMA: $M_n = 8000-30\,000$; $M_w/M_n = 1.2-1.5$), whereas non-template PEG6DMA induced gelation. The K⁺ template was further effective for PEG5DMA (21-membered) and PEG8DMA (30-membered). Interestingly, PPEG6DMA showed unique cation recognition: (1) 1/1 recognition of Li⁺, Na⁺, K⁺, Rb⁺ with cyclic PEG units and 1/2 recognition of Cs⁺ with two adjacent cyclic PEG units; (2) selective recognition of Na⁺ over Li⁺ and Bu₄N⁺ as well as selective recognition of K⁺ over Na⁺. Thus, template-assisted

cyclopolymerization is effective for functional cyclopolymer with large in-chain rings compared with conventional cyclopolymerization of divinyl monomers with short and/or rigid spacers.⁷¹⁻⁷⁶

Various sequence-regulated copolymers, including gradient copolymers, are directly synthesized by concurrent tandem living radical polymerization with *in situ* transesterification of methacrylates (Figure 8b).⁶⁴⁻⁶⁶ The key is to polymerize MMA in the presence of metal alkoxide (Al(Oi-Pr)₃ or Ti(Oi-Pr)₄) and alcohols (ROH), in which metal alkoxide-catalyzed transesterification of MMA into RMA synchronizes with living polymerization to provide MMA/RMA gradient copolymers from MMA (initiating terminus) to RMA (growing terminus). Compared with conventional synthetic pathways for gradient copolymers (copolymerization of two monomers with different reactivity or copolymerization via second monomer addition),⁷⁷ this tandem catalysis has the following advantages: (1) catalytic control of gradient monomer composition; (2) efficient synthesis of various gradient copolymers from common alcohols; and (3) easy access to complicated, sequence-regulated copolymers (random-gradient, gradient-block). Owing to the gradual change in monomer composition, gradient copolymers showed physical properties that differed from those of their random and block counterparts. For example, an MMA/DMA gradient copolymer had an extremely broad range of glass transition temperatures (~170 °C).⁶⁶

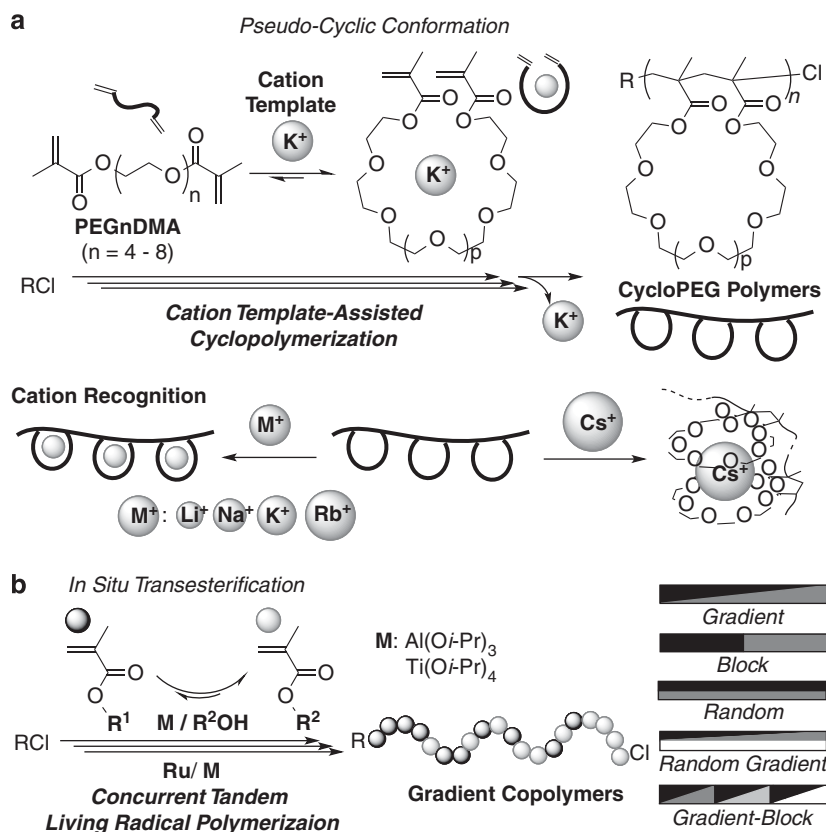


Figure 8 (a) Synthesis of cycloPEG polymers, referred to as 'polymeric pseudo crown ethers', via cation template-assisted cyclopolymerization of PEGnDMA ($n=4, 5, 6, 8$) for selective cation recognition. (b) Synthesis of sequence-regulated copolymers via concurrent tandem living radical polymerization with *in situ* transesterification of methacrylates.

CONCLUSION

Polymeric functional spaces were created in various core-functionalized star polymers and single-chain folding/crosslinked polymers via ruthenium-catalyzed living radical polymerization. Core-functionalized star polymers were synthesized by arm-linking reactions with functional linkers and monomers for unique functions: active, robust and recyclable catalysis (oxidation, hydrogenation and living radical polymerization); and stimuli-responsive and selective molecular recognition. Amphiphilic random copolymers efficiently folded in water with intramolecular hydrophobic and/or hydrogen-bonding interactions, resulting in single-chain compartments with hydrophobic interiors. In addition, cation template-assisted cyclopolymerization and concurrent tandem polymerization with *in situ* monomer transformation were also developed as smart strategies to directly produce cyclopolymers with large in-chain rings and sequence-controlled copolymers (for example, gradient copolymers). In the future, the construction of polymeric functional spaces with nanocavities and sequence-controlled units would open new vistas for innovative functional applications.

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