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FOCUS REVIEW

Synthetic approach for optically active polymers through the combination of asymmetric chirogenic polymerization and postpolymerization modification

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Abstract

A new type of asymmetric chirogenic polymerization by asymmetric allylic substitution catalyzed by planar–chiral ruthenium complexes was designed. The polymerization systems function in a highly stereoselective manner to afford optically active polymers with high selectivity. The asymmetric carbon in the main chain is precisely controlled. Each monomer unit of the polymer has a potentially reactive terminal olefin, which can be used for further transformations. Optically active polymers bearing chiral cyclic architecture were prepared by a combination of asymmetric allylic substitution and ring-closing metathesis reaction employing the terminal olefin of the side chains. Additionally, the efficient introduction of a wide range of substituents into the side chain of the optically active polymer without any racemization has been made possible by using the thiol–ene reaction. Poly-*N*-alkoxyamides obtained by our asymmetric polymerization can be transformed into nonnatural polypeptides containing an aromatic ring on the peptide backbone, called a poly "arylopeptide", through reductive cleavage of the N–O bond in *N*-alkoxyamide. The resulting polymer adopts a one-handed stable helical conformation in solution.

Introduction

Precise synthesis of optically active polymers is a challenging topic in polymer chemistry, because naturally occurring polymers, such as polypeptides, are formed by controlling the absolute stereogenic centers in the main chain [1–5]. The stereoselectivity of the main chain represents a significant foundation for three-dimensional structures with biological foundations. On this point, the synthesis of optically active polymers, which are controlled by the absolute chiral configuration of the main chain, has attracted a great deal of attention. The current goal is not only to understand the structures and properties of optically active polymers but also to develop a novel foundation for the polymeric synthesis of characteristic functional materials. Asymmetric chirogenic polymerization [6] is a promising method for synthesizing optically active polymers in which the stereogenic centers on the main chain can be controlled. Brookhart [7], Nozaki [8, 9], and Sen [10] reported the asymmetric alternating polymerization of α-olefins and CO using a Pd complex with chiral ligands. To date, several efficient asymmetric chirogenic polymerizations have been reported [11–14]. However, in most asymmetric chirogenic polymerization systems, the main chain structures of the polymer are less amenable to design. This is because chain polymerization, which is difficult to introduce in various designs, occurs on the main chain.

In the past decade, a number of asymmetric reactions have been reported [15]. If such enantioselective reactions can be applied to asymmetric polymerization and repetitive asymmetric reactions are maintained throughout the propagation step of the polymerization reaction, the synthesis of new polymers possessing various backbones and functionalities in the main chain would be possible. Thus, asymmetric reactions may facilitate the tailor-made synthesis of optically active polymers. Nevertheless, asymmetric chirogenic polymerization based on organic reactions has not been studied extensively to date. In common polymerization systems, highly enantioselective reactions cannot readily be maintained from the beginning to the end of

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polymerization, since it is difficult for asymmetric catalysts to recognize the reactive terminal moiety of the polymer due to steric hindrance.

Recently, we reported a new method for achieving asymmetric chirogenic polymerization based on our development of asymmetric allylic substitutions catalyzed by planar–chiral cyclopentadienyl–ruthenium (Cp'Ru) complexes [16–21]. This review focuses on our recent development of a novel synthetic approach for optically active polymers through the combination of asymmetric chirogenic polymerization and postpolymerization.

Asymmetric allylic substitutions catalyzed by Cp'Ru complexes

The catalysis of asymmetric allylic substitutions by organometallic complexes represents a powerful method for creating carbon–carbon and carbon–heteroatom bonds with high enantioselectivity [22–25]. Previously, we have shown that cyclopentadienyl–ruthenium (Cp'Ru) complexes are proficient catalysts for regio- and enantioselective allylic substitutions of monosubstituted allylic chlorides with types of nucleophile (Nu) containing carbon, oxygen, and nitrogen atoms (Fig. 1a). Therefore, since the Cp'Ru-catalyzed allylic substitutions exhibit high reactivity and selectivity, we seek to extend this system to an asymmetric chirogenic polymerization reaction via polycondensation.

Asymmetric chirogenic polymerization: asymmetric allylic substitutions catalyzed by a Cp'Ru complex

Previously, we reported the asymmetric allylic substitution with *N*-alkoxyamide as a nucleophile to afford carbon–nitrogen bonds with high enantioselectivity [19]. To this end, we designed an achiral AB-type bifunctional monomer (**1a**) bearing an allylic chloride and *N*-hexyloxybenzamide [26] (Fig. 1b-(a)). The polymerization of monomer **1a** was carried out based on previously reported methods employing (*S*)-**I** as the catalyst. The polymerization of monomer **1a** proceeded smoothly with almost quantitative monomer conversion after 36 h. Purification by column chromatography on silica gel provided the polymer **poly-1a** at a 70% yield ($M_n = 17{,}000$; $M_w/M_n = 1.5$). **Poly-1a** was then characterized by ^{1}H NMR analysis and compared to the branched allylic compound **3**; the analysis clearly showed that the polymerization proceeded with high regioselectivity ($x/y = 98/2$) and that the polymer was almost completely composed of chiral branched allylic structures (Fig. 2a). Therefore, the catalytic system employing **I** can be utilized to introduce regular arrangements of chiral carbons into the main chain of the resulting polymers.

The enantioselectivity of the asymmetric chirogenic polymerization was estimated by ultraviolet (UV) and circular dichroism (CD) spectroscopic techniques. The UV and CD spectra of **poly-1a** and model compound **4** (98% ee) are shown in Fig. 2b. The model compound exhibited a positive Cotton effect in the region of 240–260 nm in the CD spectrum, which is attributed to the π–π* transition of the benzene chromophore. The spectrum of **poly-1a** also displayed a CD spectral pattern quite similar to that of **4**. The CD spectra are reflective of the local conformation of **poly-1a**; therefore, the new stereocenters of **poly-1a** exhibit the same absolute configuration as those of **4**. Thus, the stereochemistry at the asymmetric carbon atoms of the polymer main chain is strictly controlled during asymmetric chirogenic polymerization.

The selectivity of the polymer was also estimated using another method. As will be described later, the polymer can be modified by chiral substitution with a 2,3,4,6-tetra-*O*-acylated-β-D-glucopyranose-1-thio group on the terminal olefinic moiety of the monomer unit using the thiol–ene reaction (Fig. 2c). The ^{1}H NMR spectra of **poly-1a-(7j)-((*rac*)-I)** ($M_n = 12\,000$; $M_w/M_n = 1.4$), which was synthesized from **poly-1a-((*rac*)-I)** ($M_n = 11000$; $M_w/M_n = 1.5$) polymerized using the racemic catalyst **(*rac*)-I**, exhibited two peaks at 4.57 (d, –SC*H*CH(OAc)–, 1 H) and 4.53 ppm (d, –SC*H*CH(OAc)–, 1 H) with a ratio of 1:1 in the region representing the methine proton on the C1 carbon of the pyranoside according to the chirality of the main chain (Fig. 2c-(a)). In contrast, **poly-1a-(7j)-((*S*)-I)** and **poly-1a-(7j)-((*R*)-I)**, which were polymerized using **(*S*)-I** and **(*R*)-I**, respectively, each exhibited only one peak in the corresponding region (at 4.53 or 4.57 ppm), indicating that the stereocenters of the polymer were strictly controlled during asymmetric chirogenic polymerization when an optically active catalyst was employed (Fig. 2c-(b), (c)). These results show that the planar–chiral Cp'Ru complex functions as a highly efficient catalyst for stereochemical control even in polymerization reactions.

The asymmetric polymerization reaction developed herein is applicable to a variety of monomers bearing different arylene backbones (**1b–d**) (Fig. 1b-(a)). All of these reactions also proceeded with high regio- and enantioselectivity to afford the desired polymer (**poly-1b–d**).

The polymerization mechanism is shown in Fig. 3; the reaction involves the oxidative addition of an allylic moiety to the (*S*)-**I** complex, affording a π-allyl intermediate with high diastereoselectivity at the chiral metal center and planar chirality at the π-allyl ligand. Subsequent inside attack of the nucleophile via the Ru complex and substitution of the chloride with the nucleophile affords a branched allylic compound with high enantioselectivity. Thus, it is likely that the asymmetric chirogenic polymerization proceeds through the same pathway described above with control over the metal-center chirality during polymerization, making control of the chirality of the metal-center essential for the success of the polymerization.

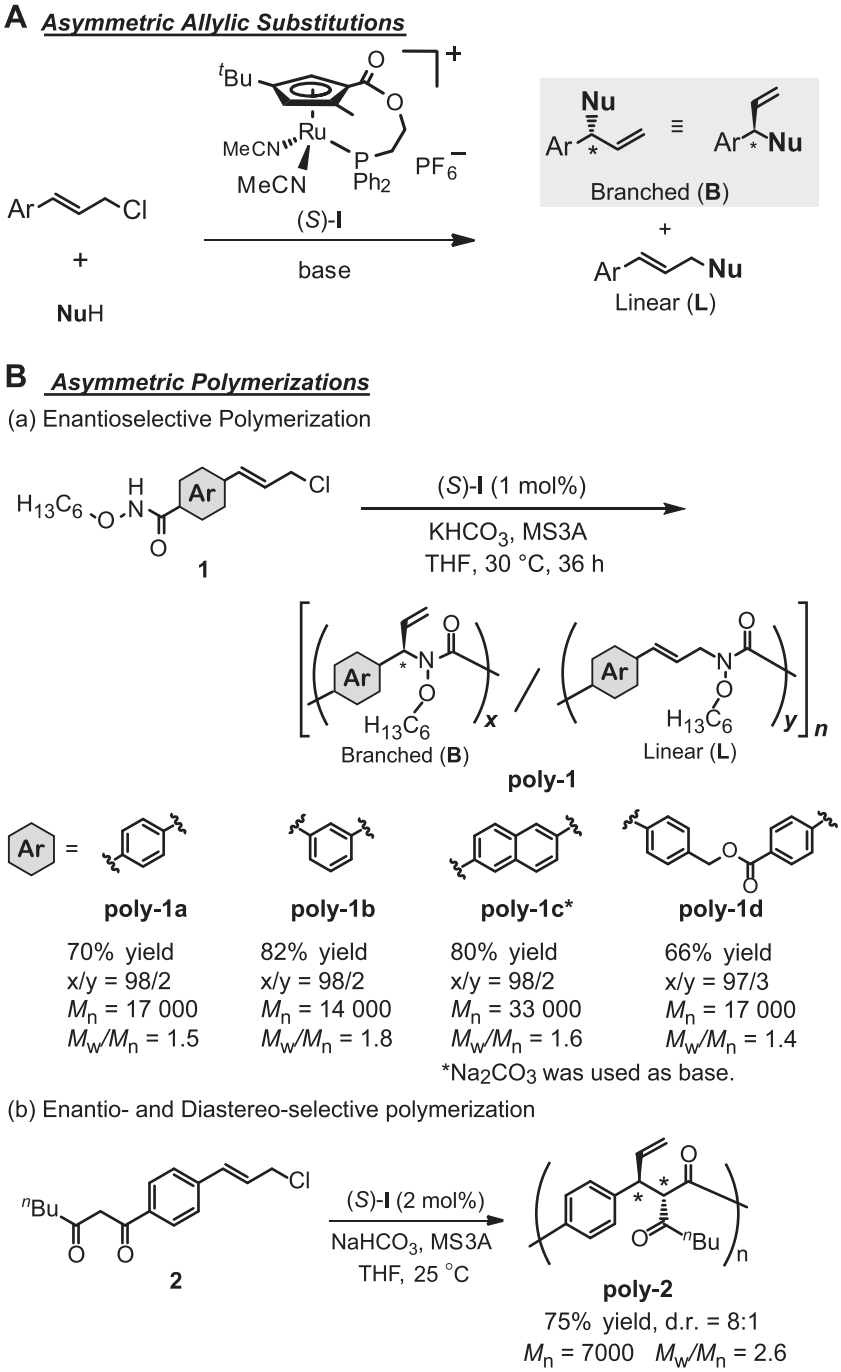


Fig. 1 **a** Asymmetric allylic substitutions catalyzed by the Cp'Ru complex. **b** Asymmetric chirogenic polymerization using asymmetric allylic substitutions catalyzed by (*S*)-**I**

Enantio- and diastereoselective polymerization: asymmetric allylic alkylation catalyzed by a Cp'Ru complex

Asymmetric allylic alkylation is one of the most promising methods for the construction of carbon–carbon bonds. Therefore, the application of these reaction systems for the synthesis of optically active polymers is of great interest. However, when the aforementioned asymmetric chirogenic polymerization reaction is applied to carbon nucleophiles, the carbon nucleophile exhibits a prochiral difference from a nitrogen nucleophile; therefore, it is necessary to control the two vicinal stereocenters in the monomer unit. However, the control of vicinal stereocenters through allylic substitutions in organic synthesis is challenging [27–33]. Previously, asymmetric allylic alkylation catalyzed by **I** was reported [16]. The reaction proceeded with quantitative conversion under mild conditions yielding vicinal stereocenters with regio-, diastereo-, and enantioselectivity. The asymmetric alkylation

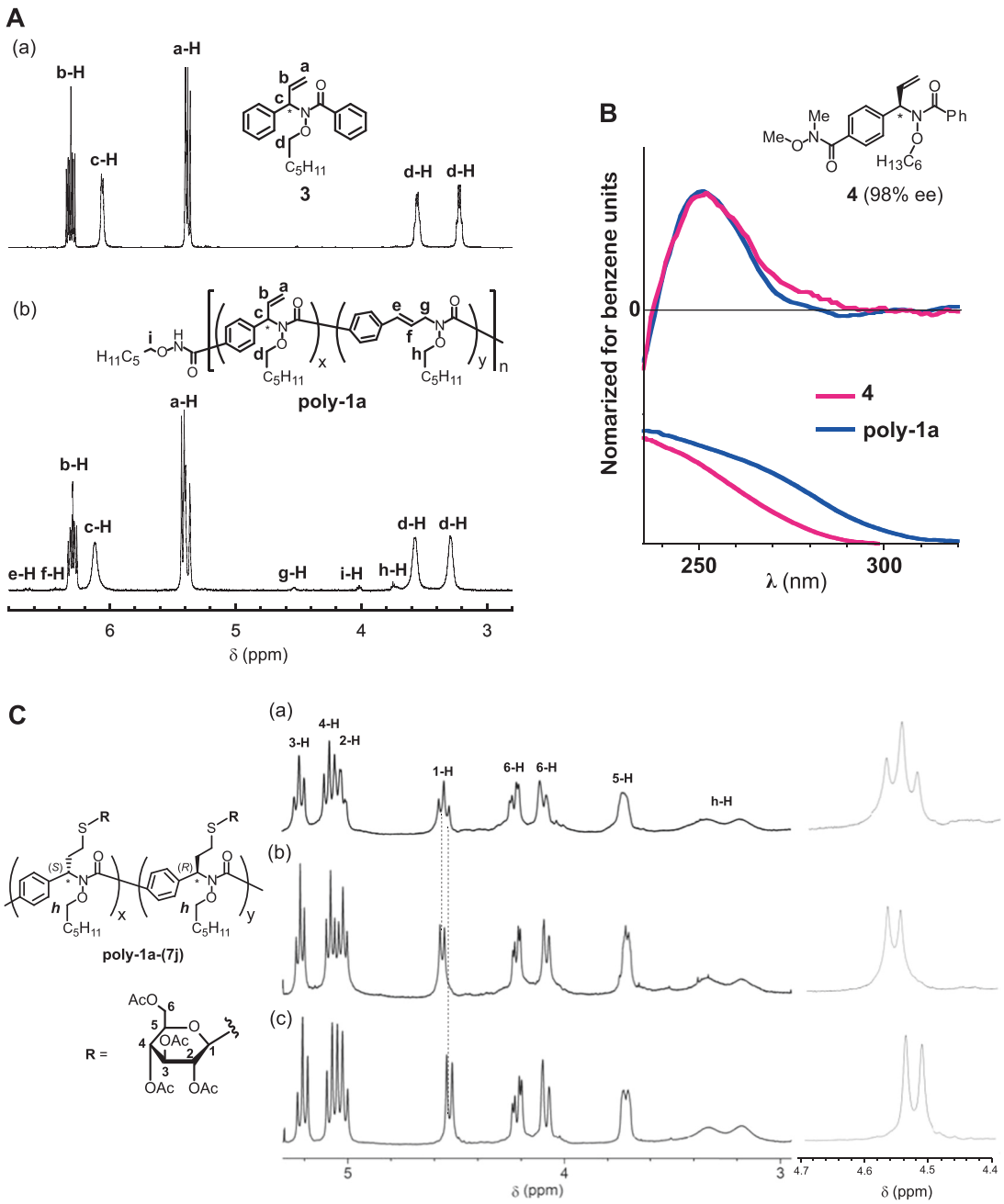


Fig. 2 Characterization of **poly-1a**. **a** ^{1}H NMR (500 MHz, in $CDCl_3$ at 298 K) spectra of **a** model compound and **b poly-1a**. **b** CD and UV spectra of **poly-1a** and model compound **4** (in $CHCl_3$ at 298 K). The vertical axis is normalized to the benzene unit. **c** ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) spectra of **a poly-1a-(7j)-((rac)-I)**, **b poly-1a-(7j)-((*R*)-I)**, and **c poly-2a-(7j)-((*S*)-I)**

reaction was attempted for asymmetric chirogenic polymerization [34].

An achiral AB-type bifunctional monomer **2** bearing allylic chloride and prochiral β-diketone moieties was designed and synthesized (Fig. 1b-(b)). The polymerization was conducted under optimized conditions, proceeding with almost quantitative monomer conversion to afford the desired polymer. After purification, **poly-2** was obtained in 75% yield ($M_n = 7000$, $M_w/M_n = 2.6$). The chemical structure of **poly-2** was confirmed by NMR analysis, which indicated that the polymerization of **2** catalyzed by (*S*)-**I** proceeded with high regioselectivity. Additionally, the diastereoselectivity was estimated by comparison to the model compound, which gave a diastereo-ratio (dr) = 8:1. Therefore, the polymerization of monomer **2** proceeded with high diastereoselectivity, greater than that of the model reaction (dr = 4:1). The enantioselectivity of the resulting polymer was estimated using UV and CD spectrometry, which were assigned by density functional theory (DFT) and time-dependent (TD)-DFT. The results indicated that

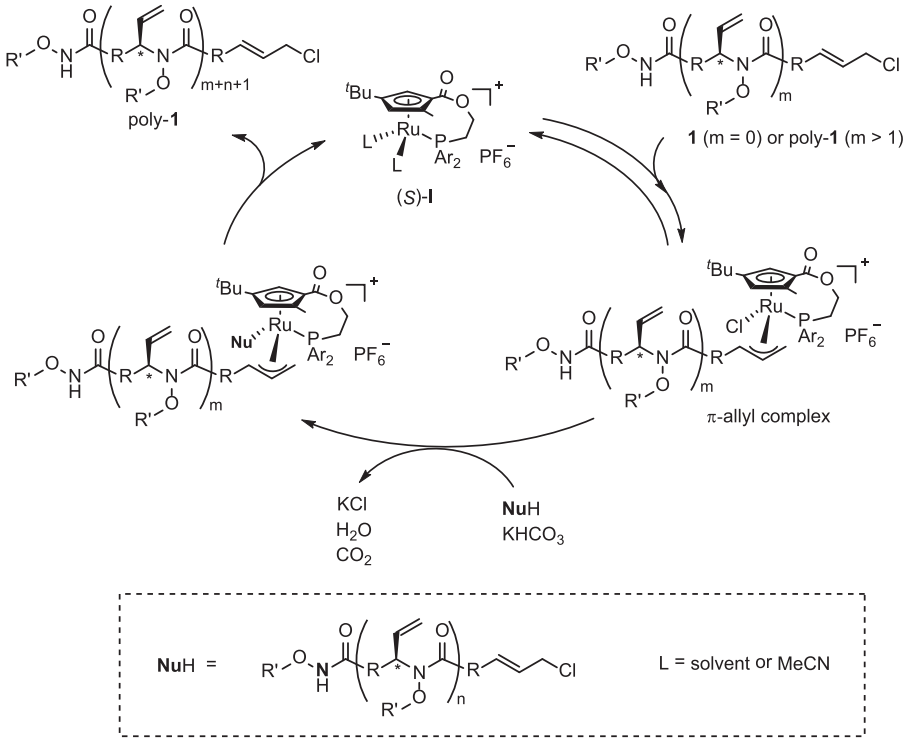


Fig. 3 Plausible reaction mechanism of asymmetric chirogenic polymerization using (*S*)-**I**

the polymerization proceeded in a highly enantioselective manner to afford an optically active polymer.

Synthesis of optically active polymer using postpolymerization

In our asymmetric polymerization method, the spacer group and the side chain of the *N*-alkoxide group can be modified. Additionally, the resulting optically active polymers retain one reactive terminal double bond per monomeric unit, which can be used for further transformations. Recently, the postpolymerization modification method for preparing new functional polymers has become a powerful tool in polymer synthesis [35–41]. This method can be used to obtain a series of polymers from a single parent polymer. Therefore, upon the postpolymerization conversion of terminal olefins, our polymerization methods are expected to expand the versatility of optically active polymer synthesis. Herein, new methods for the synthesis of optically active polymers through the combination of asymmetric polymerization and postpolymerization modification are described.

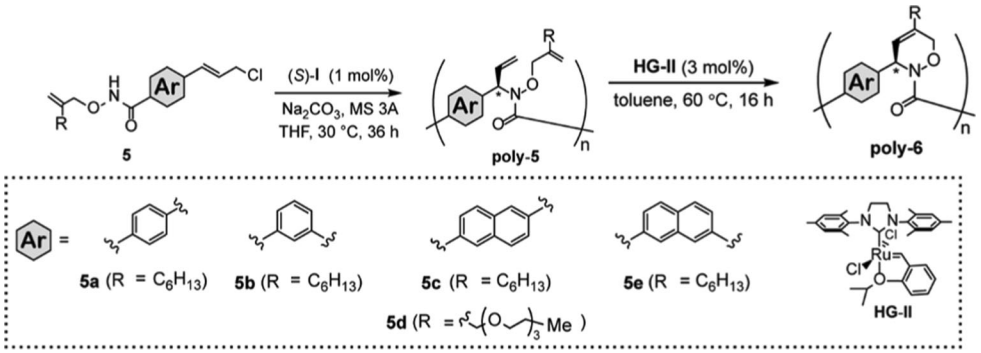
Synthesis of optically active polymer bearing chiral cyclic architecture

Natural polymers, such as nucleic acids, starch, and cellulose, possess chiral cyclic structures in their main chains. Such cyclic structures restrict the conformation of the main chain bonds to form the appropriate chiral foundation. Therefore, intelligently designing the main chain to restrict the local conformation, as well as to control the resulting stereocenters, plays an important role in the continued development of artificial chiral foundations, although it is quite difficult to synthesize optically active polymers bearing such chiral cyclic architecture in the main chain.

Previously, we focused on the ring-closing metathesis (RCM) reaction as a candidate for the transformation of terminal olefins. This reaction is a powerful tool in organic synthesis for the preparation of cyclic compounds [42, 43]. We accomplished the synthesis of optically active γ- and δ-lactones using a combination of asymmetric allylic carboxylation and RCM reaction [21]. Based on these results, we designed a new synthetic approach for the synthesis of optically active polymers bearing chiral cyclic architecture in the main chain using a combination of asymmetric allylic amidation and RCM reactions [44].

An achiral AB-type monomer (**5a**) bearing an allylic chloride and an *N*-alkoxyamide group possessing an olefinic moiety was designed. Upon polymerization, the resulting polymer presents two olefinic moieties per monomer unit for postpolymerization RCM. The asymmetric chirogenic polymerization catalyzed by (*S*)-**I** was carried out under optimized conditions. After 36 h, **5a** was quantitatively converted to afford the corresponding polymer **poly-5a** in 80% yield, maintaining the unreacted terminal olefin on the *N*-alkoxide moiety (Table 1a). The resulting polymer was analyzed by ^{1}H NMR, CD, and UV spectroscopic methods, which indicated that the polymerization proceeded in a

Table 1 (A) Asymmetric chirogenic polymerization using asymmetric allylic substitution of monomer **5** catalyzed by (*S*)-**I**[a]. (B) Ring-closing metathesis reaction of **poly-5**[b]



A

Entry	5	Yield (%)[c]	M_n[d,e]	n[f]	M_w/M_{dn}
1	**5a**	80	19 000	63	1.7
2	**5b**	55	12 000	40	1.6
3	**5c**	75	18 000	50	1.3
4	**5d**	58	13 000	29	1.5
5	**5e**	63	11 000	31	1.5

B

Entry	Poly-5[g]	Yield (%)[h]	M_n[i,j]	n[k]	M_w/M_n[i]
1	**poly-5a**	>90 (60)	17 000	61	1.5
2	**poly-5b**	>90 (63)	11 000	40	1.4
3	**poly-5c**	98 (63)	16 000	49	1.5
4	**poly-5d**	>99	11 000	27	1.7
5[l]	**poly-5e**	>99 (93)	9000	28	1.7

[a](S)-**I** (5.0 μmol), **5** (0.5 mmol) and Na_2CO_3 (0.60 mmol) in THF, stirred for 36 h

[b]**Poly-5** (0.25 mmol), **HG-II** (7.5 mmol), solvent (1.0 mL), 16 h

[c]Isolated yield

[d]Calculated from SEC measurement using a Viscotek TDA 305 triple detection system

[e]After purification with silica gel chromatography eluted by dichloromethane to remove catalyst

[f]Degree of polymerization was calculated by the use of M_n

[g]The precursor polymer (**poly-5**) was used as in the left Table

[h]The NMR yield was determined by observing the transition of the ^{1}H NMR signal from the precursor polymer (**poly-5**) to the modified polymer (**poly-6**). Isolated yield is shown in parentheses

[i]Calculated by SEC measurement using a Viscotek TDA 305 triple detection system

[j]After preparative purification, the SEC was eluted with $CHCl_3$ to remove catalyst

[k]Degree of polymerization was calculated using M_n

[l]1,2-Dichloroethane was used instead of toluene

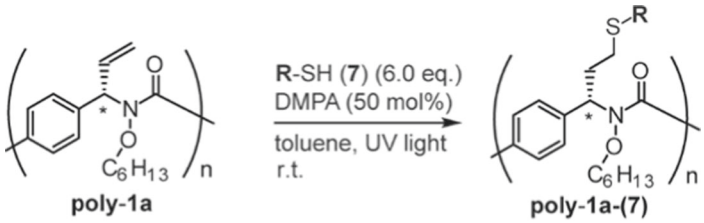
highly regio- and enantioselective manner to afford an optically active polymer. The absolute molecular mass of the resulting polymer was determined by a Viscotek TDA 305 triple detection system. Additionally, monomers bearing 1,3-phenylene (**5b**), 2,6-naphthylene (**5c** and **5d**), or 2,7-naphthylene (**5e**) as a spacer group (Ar) were also polymerized with quantitative monomer conversion and high regioselectivities.

The resulting polymer (**poly-5a**) underwent RCM using a Hoveyda–Grubbs II catalyst under optimized conditions (Table 1b). The olefinic components of **poly-5a** were fully consumed through the RCM. After purification to remove the catalyst, the polymer **poly-6a** ($M_n = 17000$; $M_w/M_n = 1.5$) was obtained in a 60% yield. Since the degree of polymerization (n) calculated by the absolute molecular mass was not affected after RCM (**poly-5a**: $n = 63$; **poly-6a**: $n = 61$), the evidence indicated that the intermolecular reaction of the polymer dominated. Additionally, the postpolymerization conversion is applicable to various monomer residues, potentially affording optically active polymers possessing several types of main chain and side chain structures.

Postpolymerization modification of the side chain in optically active polymers by thiol–ene reaction

The thiol–ene reaction is one of the most reliable methods for postpolymerization modification and has facilitated the functionalization of unsaturated aliphatic hydrocarbons of polymer side chains with complete chemo- and regioselectivity [45–52]. Additionally, the thiol–ene reaction can tolerate many functional groups under mild conditions. These advantages suit our envisaged synthetic approach [53].

Table 2 Modification of the side chain in poly-1 by the thiol–ene reaction[a]



Entry	Thiol R–SH	7	NMR yield (%)[b]
1	$C_{12}H_{25}$–SH	**7a**	>98 (90)
2	$F_3C(CF_2)_7SH$	**7b**	>98 (88)
3	$(O)_3SH$	**7c**	>98% (94)
4	$(EtO)_3Si$SH	**7d**	>98 [c]
5[d]	HOSH	**7e**	98 (88)
6[e]	HOOCSH	**7f**	>98 (90)
7	BocNHSH	**7 g**	>98 (88)
8	$^{i}Pr_2N$SH·HCl	**7 h**	96 (85)
9	H_2NSH	**7i**	>98 [c]
10	AcO-sugar-SH	**7j**	>98 (92)
11[d]	MeO-Ph-SH	**7k**	96 (85)
12	Ph-SH	**7 l**	trace

[a][C=C of **poly-1a**]/[**7**]/[DMPA] = 1.0/6.0/0.5

[b]The NMR yield was determined from the integral intensity of the ^{1}H NMR signals of the crude product. The isolated yield is given in parentheses

[c]Excess thiol was hard to separate by conventional methods. The isolated yield was not determined

[d]After the general procedure, 6.0 eq. of thiol and 0.5 eq. of DMPA were added to the reaction mixture, which was then irradiated for 14 h

[e]The reaction mixture was irradiated for 14 h

The thiol–ene reaction of **poly-1a** ($M_n = 16\ 000$; $M_w/M_n = 1.4$) with 1-dodecanethiol (**7a**) was conducted in the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) as a photoinitiator (entry 1 in Table 2). The reaction mixture was irradiated at room temperature using a 500 W high-pressure mercury lamp (centered at

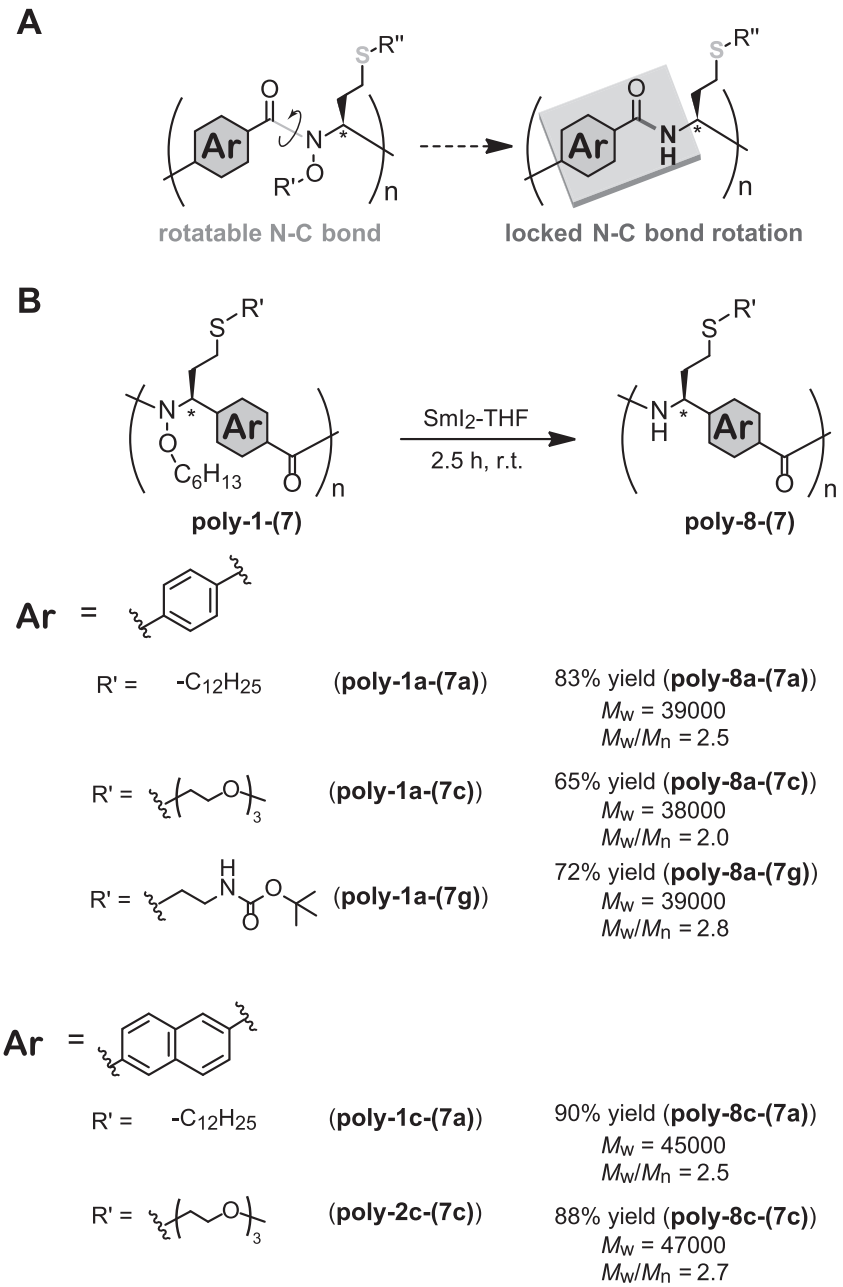


Fig. 4 Novel synthetic approach to poly-arylopeptides using reductive cleavage of N–O bond of **poly-1**

350 nm). The reaction proceeded with quantitative conversion to give **poly-1a-(7a)** ($M_n = 27000$; $n = 58$), which is appended with a dodecylthio group at the terminal olefin moiety of **poly-1**. After purification, the functionalized polymer was obtained in 90% isolated yield. These postpolymerization modification conditions can be applied with various thiols (**7b–l**) (entries 2–12). All of the tested reactions proceeded with almost quantitative conversion regardless of the polarity or bulkiness of the substituents, and the solubility of each resulting optically active polymer **poly-1a-(7)** can be altered depending on the substituent that is introduced.

Synthesis of helical poly-arylopeptide through reductive cleavage of N–O bond

Chiral helical polymers have received a great deal of attention in polymer chemistry because naturally occurring polymers often form sophisticated helical structures. In artificial polymers, the precise synthesis of helical polymers has also been reported for the preparation of potential functional materials [54–56]. Although we have explained the synthesis of various types of optically active polymers based on asymmetric chirogenic polymerization, the poly-*N*-alkoxyamide polymers (**poly-1** and **poly-1-(7)**), unlike

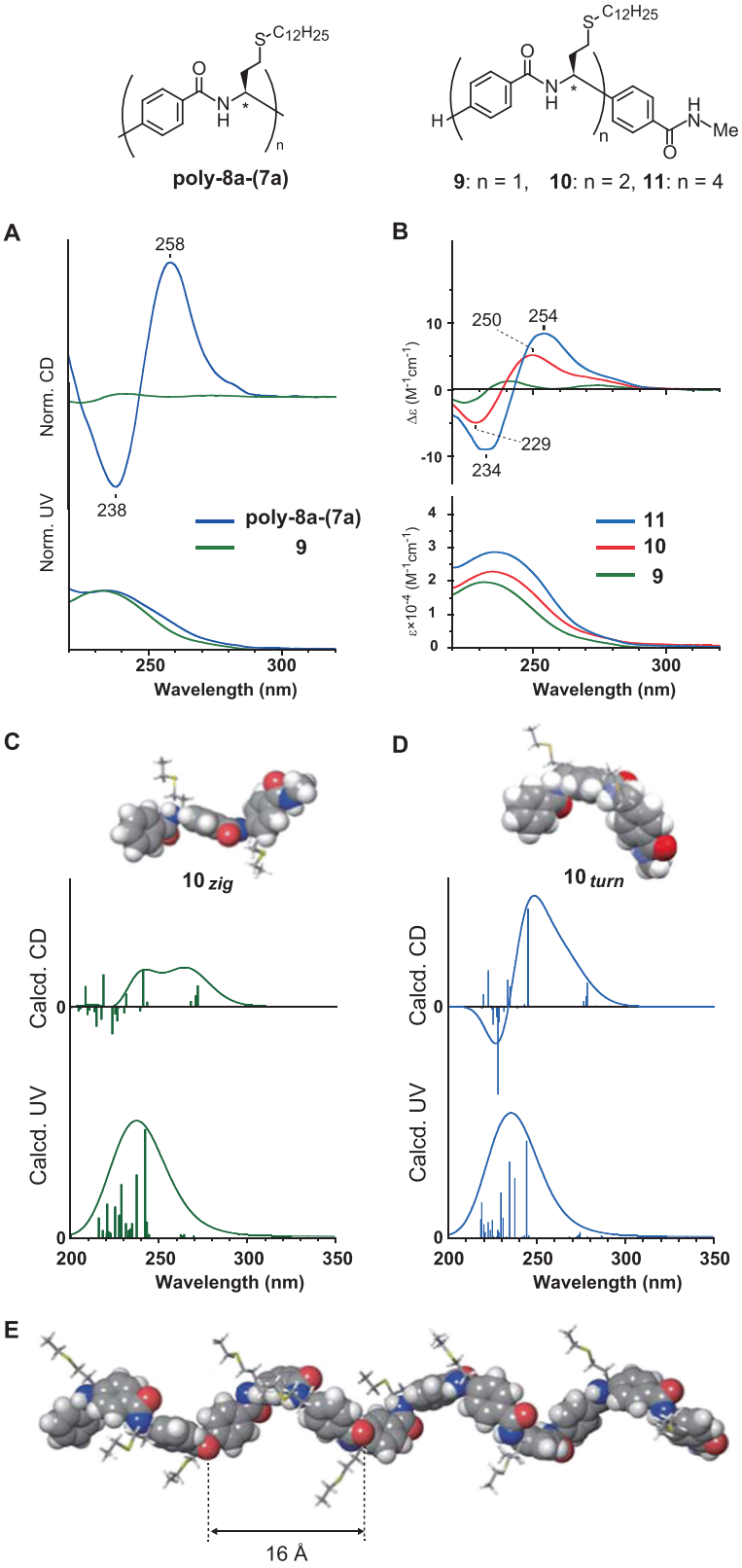


Fig. 5 CD and UV spectra of **a poly-8a-(7a)** and **9** in THF at 25 °C (The vertical axis is normalized on the basis of the absorption at 236 nm) and **b 9**-**11** at THF at 25 °C. Simulated CD and UV spectra of **c** $\mathbf{10}_{zig}$, and **d** $\mathbf{10}_{turn}$ by TD-DFT calculation (B3LYP/6-31**). **e** Plausible helical conformation of **poly-8a′** ($n = 12$, R = Et) based on the conformation of $\mathbf{10}_{turn}$

proteins, do not form stable secondary structures in solution even though the asymmetric centers of the monomer unit are strictly controlled. This is because the rotational barrier of the N–C bond of the *N*-alkoxyamide moiety is relatively low compared to that of peptides. If the flexible alkoxyamide bonds of the polymer main chain could be

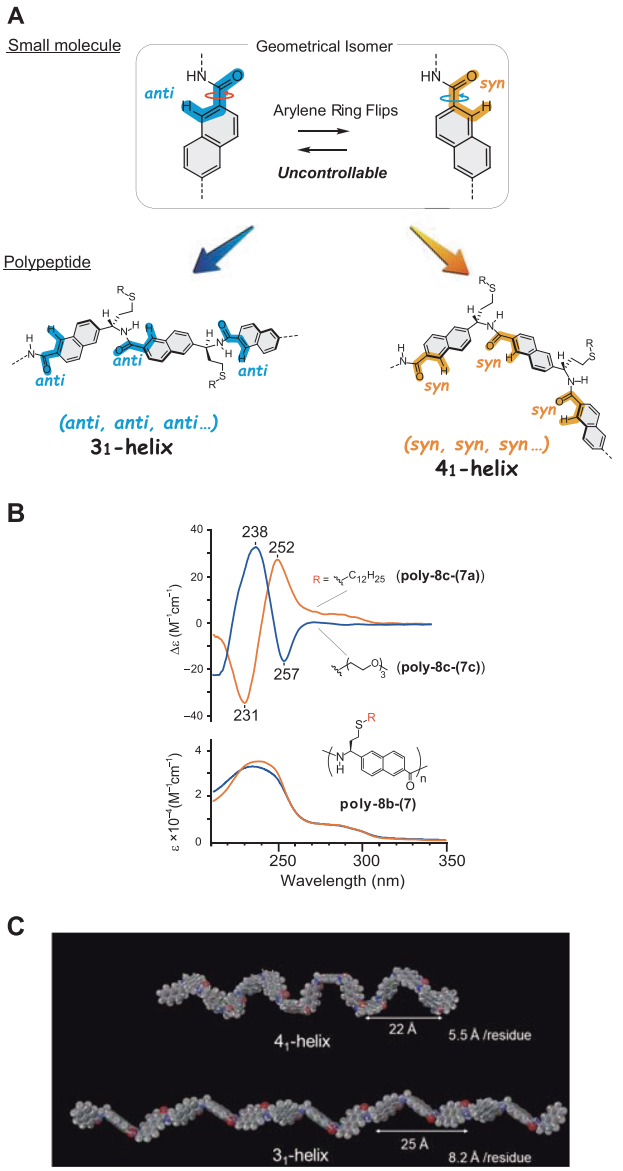


Fig. 6 **a** Geometrical properties of 2,6-naphthylene amide and this concept. **b** CD spectra of **poly-8b-(7a)** and **poly-8b-(7c)** in THF 25 °C. Concentration: [**poly-8b-(7a)**] = 0.32 mM and [**poly-8b-(7c)**] = 0.30 mM. **c** Two plausible helical conformations of **poly-8b** ($n = 15$) based on the *syn* and *anti* results. The upper structure corresponds to **poly-8b-(7a)**, and the lower structure corresponds to **poly-8b-(7c)**. Side chains are omitted for clarity

converted to planar amide bonds, one would expect the creation of a secondary structure (Fig. 4a). Thus, a new synthetic approach to nonnatural helical polypeptides using our previously presented asymmetric polymerization method and N–O bond reduction is presented here (Fig. 4) [57].

In organic synthesis, the *N*-alkoxyamide group is used as a precursor to the amide moiety; they can be transformed without racemization by the reductive cleavage of the N–O bonds [58–63]. Through optimization studies, samarium diiodide was chosen as the N–O bond reducing reagent [62, 63]. The treatment of **poly-1a-(7a)** ($M_w = 51000$; $M_w/M_n = 2.5$; $n = 110$) with SmI_2 in THF resulted in quantitative conversion of the *N*-alkoxyamide moieties into amide groups without racemization (Fig. 4b). The resulting polymer, **poly-8a-(7a)** ($M_w = 39000$; $M_w/M_n = 2.6$), was completely characterized by ^{1}H NMR and IR spectroscopy as well as size exclusion chromatography. This is the application of the SmI_2 complex in postpolymerization modification. To distinguish the resulting polyamides from simple polyamides, **poly-8-(7)** was classified as a polyarylopeptide. This designation was used because the monomer units of the polymer were composed of amino acids containing arylene spacers, and the polymer directionality of the main chain mimics that of natural polypeptides. This synthetic method was applied to various types of **poly-1a-(7)** polymers with different side chains, including oligoetherthio and *N*-(tert-butoxycarbonyl)aminoethylthio substituents.

The polymer conformation of **poly-8a-(7a)** was investigated by UV and CD spectroscopic methods. The CD spectrum of **poly-8a-(7a)** showed a large bisignate Cotton effect that differed from that of the corresponding monomer, **9** ($n = 1$) (Fig. 5a). As additional chirality was present, derived from the asymmetric carbons of the main chain, a one-handed helical structure was suggested for **poly-8a-(7a)**. In the case of dimer **10** ($n = 2$), a new bisignate Cotton effect was observed, similar to that of **poly-8a-(7a)**, which was shifted to a longer wavelength as the monomer unit was elongated (from $n = 2$ to $n = 4$ (**11**)) (Fig. 5b). To reveal the origin of the Cotton effect of **poly-8a-(7a)**, DFT and TD-DFT calculations were carried out for **10** based on the crystal structure of the model compound [64]. In this case, since the carbonyl group and benzene rings are generally regarded as coplanar, two possible conformations based on the optimized structure of **9** can be assumed according to the orientation of the vicinal unit: the turn (**10**$_{turn}$) and zigzag (**10**$_{zig}$) types. The calculated UV and CD spectra of **10**$_{turn}$ were in close agreement with the observed spectra of **10** (Fig. 5c, d). The results indicated that longer oligomer lengths form a stable *turn*-type conformation. The proposed structure of **poly-8a-(7a)** was constructed based on the optimized structure of **10**$_{turn}$, which exhibited a right-handed (*P*) 3_1-helical structure (Fig. 5e).

Side chain-driven dual structural system of polyarylopeptide; selective helical formation derived from aromatic ring flips on the backbone

To develop a dual structural architecture, we used 2,6-naphthalene rings as the axially unsymmetrical spacer in the main chain [65]. Aromatic-ring flips give the *syn* and *anti* geometrical isomers of the 2,6-naphthalene spacer where, in

solution, the energy barrier between the isomers is negligible. In this work, the minute energy difference between the two isomers is amplified by incorporating 2,6-naphthalene spacers into the polypeptide backbones, which creates a thermodynamic driving force for the formation of two distinct secondary structures, (i.e., 3_1- and 4_1-helices) biased toward one geometrical isomer depending on the side chain (Fig. 6a).

The CD spectra of **poly-8c-(7a)** and **poly-8c-(7c)** in THF at 25 °C revealed very different Cotton effects (Fig. 6b). The CD spectrum of **poly-8c-(7a)** showed a plus-to-minus bisignate Cotton effect between 252 and 231 nm, which was similar to that of **poly-8a-(7a)**. Conversely, **poly-8c-(7c)** presented a CD spectrum with a minus-to-plus bisignate curve exhibiting a negative Cotton effect at 257 nm and a positive Cotton effect at 238 nm. These results indicated that **poly-8c-(7a)** and **poly-8c-(7c)** adopted different specific structures in solution, whereas **poly-8a-(7)**, which contains *p*-phenylene spacers with no geometrical isomers, formed a stable 3_1-helix regardless of the side chain. Based on the DFT and TD-DFT calculations, it was found that the dodecyl side chain induced successive *syn* units (*syn*, *syn*, *syn*, etc), while the oligoether group induced successive *anti* units (*anti*, *anti*, *anti*, etc), leading to the proposal of two global conformations (Fig. 6c). **Poly-8c-(7a)** exhibited a right-handed 4_1-helix due to the successive formation of *syn* units, while **poly-8c-(7c)** formed a right-handed 3_1-helix in THF. This geometrical control of the local structure is due to the relative thermodynamic stability of the polymers.

Conclusions

This review summarizes a new method for achieving asymmetric chirogenic polymerization based on asymmetric allylic substitutions catalyzed by a planar–chiral Cp'Ru complex. The presented polymerizations proceed with high regio- and enantioselectivity. The presence of asymmetric carbons in the main chain of the resulting polymers was precisely controlled. These results indicated that the planar–chiral Cp'Ru complex functions as a highly efficient catalyst to control stereochemistry, even in polymerization reactions. Additionally, the resulting polymer exhibited terminal double bonds at each monomer unit in the main chain, which can be easily modified using RCM and thiol–ene reactions as a postpolymerization method to enable the quantitative conversion of the main chain or modification of the side chains. Furthermore, we applied our polymerization system to the synthesis of poly-arylopeptides, which involved the use of asymmetric chirogenic polymerization and reductive cleavage of the N–O bonds in the *N*-alkoxyamide of the main chain. This method does not require enantiomerically pure amino acids; the use of a condensation reaction and stepwise synthetic chemistry affords a long peptide chain with controlled asymmetric centers.

Because these polymerization reactions are polycondensation reactions, optically active polymers possessing various main chain structures can be synthesized by polymerizing monomers exhibiting various main chain skeletons. In addition, by incorporating postpolymerization conversion, the flexible design of three-dimensional structures based on the precise tailored synthesis of the primary structures is expected. These studies are based on our organic and organometallic chemistry investigations and our understanding of the reaction mechanisms and reactive species involved and their application to the polymerization reactions. From this work, the future development of asymmetric chirogenic polymerization reactions based on new catalyst design and the synthesis of optically active polymers with unique physical properties are expected.

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Compliance with ethical standards

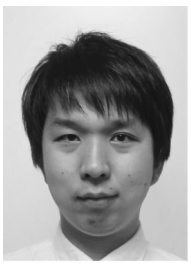
Conflict of interest The author declares that he has no conflict of interest.

References

1. Ito S, Nozaki K. Catalytic Asymmetric Synthesis, 3rd ed; Ojima, I, editor. New York: John Wiley; 2010. p. 931–85.
2. Jacobsen EN, Pfaltz A, Yamamoto H. Comprehensive Asymmetric Catalysis, Vol III. New York: Springer; 1999. p. 1329–50.
3. Nakano T, Okamoto Y. Synthetic helical polymers: conformation and function. Chem Rev. 2001;101:4013–38.
4. Okamoto Y, Nakano T. Asymmetric polymerization. Chem Rev. 1994;94:349–72.
5. Wulff G. On the chirality of polyvinyl compounds .8. Main-chain chirality and optical-activity in polymers consisting of C-C Chains. Angew Chem-Int Ed Engl. 1989;28:21–37.
6. Jones RG, Wilks ES, Metanomski WV, Kahovec J, Hess M, Stepto R, et al. Compendium of polymer terminology and nomenclature: IUPAC recommendations 2008. The Royal Society of Chemistry: Cambridge; 2009.
7. Brookhart M, Wagner MI, Balavoine GGA, Haddou HA. Polymers with main-chain chirality—synthesis of highly isotactic, optically-active poly(4-Tert-Butylstyrene-Alt-Co) using Pd(Ii)

catalysts based on C-2-symmetrical bisoxazoline ligands. J Am Chem Soc 1994;116:3641–2.
8. Nozaki K, Komaki H, Kawashima Y, Hiyama T, Matsubara T. Predominant 1,2-insertion of styrene in the Pd-catalyzed alternating copolymerization with carbon monoxide. J Am Chem Soc 2001;123:534–44.
9. Nozaki K, Sato N, Takaya H. Highly enantioselective alternating copolymerization of propene with carbon-monoxide catalyzed by a chiral phosphine-phosphite complex of palladium(Ii). J Am Chem Soc 1995;117:9911–2.
10. Jiang ZZ, Sen A. Palladium(Ii)-catalyzed isospecific alternating copolymerization of aliphatic alpha-olefins with carbon-monoxide and isospecific alternating isomerization cooligomerization of a 1,2-disubstituted olefin with carbon-monoxide—synthesis of novel, optically-active, isotactic 1,4-polyketones and 1,5-polyketones. J Am Chem Soc 1995;117:4455–67.
11. Coates GW, Waymouth RM. Enantioselective Cyclopolymerization: optically-active poly(methylene-1,3-cyclopentane). J Am Chem Soc. 1991;113:6270–1.
12. Coates GW, Waymouth RM. Enantioselective cyclopolymerization of 1,5-hexadiene catalyzed by chiral zirconocenes—a novel strategy for the synthesis of optically-active polymers with chirality in the main chain. J Am Chem Soc 1993;115:91–8.
13. Nagai D, Sudo A, Endo T. Anionic alternating copolymerization of ketene and aldehyde: control of enantioselectivity by bisoxazoline-type ligand for synthesis of optically active polyesters. Macromolecules. 2006;39:8898–900.
14. Nozaki K, Nakano K, Hiyama T. Optically active polycarbonates: asymmetric alternating copolymerization of cyclohexene oxide and carbon dioxide. J Am Chem Soc 1999;121:11008–9.
15. Ojima I, Catalytic Asymmetric Synthesis, 3rd ed. New York: A John Wiley & Sons, Inc.; 2013.
16. Kanbayashi N, Hosoda K, Kato M, Takii K, Okamura T, Onitsuka K. Enantio- and diastereoselective asymmetric allylic alkylation catalyzed by a planar-chiral cyclopentadienyl ruthenium complex. Chem Commun. 2015;51:10895–8.
17. Kanbayashi N, Onitsuka K. Enantioselective synthesis of allylic esters via asymmetric allylic substitution with metal carboxylates using planar-chiral cyclopentadienyl ruthenium catalysts. J Am Chem Soc 2010;132:1206–7.
18. Kanbayashi N, Onitsuka K. Ruthenium-catalyzed regio- and enantioselective allylic substitution with water: direct synthesis of chiral allylic alcohols. Angew Chem Int Ed. 2011;50:5197–9.
19. Kanbayashi N, Takenaka K, Okamura T, Onitsuka K. Asymmetric auto-tandem catalysis with a planar-chiral ruthenium complex: sequential allylic amidation and atom-transfer radical cyclization. Angew Chem Int Ed. 2013;52:4897–901.
20. Kanbayashi N, Yamazawa A, Takii K, Okamura T, Onitsuka K. Planar-chiral cyclopentadienyl-ruthenium-catalyzed regio- and enantioselective asymmetric allylic alkylation of silyl enolates under unusually mild conditions. Adv Synth Catal. 2016; 358:555–60.
21. Takii K, Kanbayashi N, Onitsuka K. Modular synthesis of optically active lactones by Ru-catalyzed asymmetric allylic carboxylation and ring-closing metathesis reaction. Chem Commun. 2012;48:3872–4.
22. Kazmaier U. Transition metal catalyzed enantioselective allylic substitution in organic synthesis. New York: Springer; 2011.
23. Lu Z, Ma SM. Metal-catalyzed enantioselective allylation in asymmetric synthesis. Angew Chem Int Ed. 2008;47:258–97.
24. Mohr JT, Stoltz BM. Enantioselective Tsuji allylations. Chem – Asian J. 2007;2:1476–91.
25. Trost BM, Machacek MR, Aponick A. Predicting the stereochemistry of diphenylphosphino benzoic acid (DPPBA)-based palladium-catalyzed asymmetric allylic alkylation reactions: a working model. Acc Chem Res. 2006;39:747–60.
26. Kanbayashi N, Okamura T, Onitsuka K. New method for asymmetric polymerization: asymmetric allylic substitution catalyzed by a planar-chiral ruthenium complex. Macromolecules. 2014; 47:4178–85.
27. Chen JP, Ding CH, Liu W, Hou XL, Dai LX. Palladium-catalyzed regio-, diastereo-, and enantioselective allylic alkylation of acylsilanes with monosubstituted allyl substrates. J Am Chem Soc 2010;132:15493–5.
28. Chen W, Chen M, Hartwig JF. Diastereo- and enantioselective iridium-catalyzed allylation of cyclic ketone enolates: synergetic effect of ligands and barium enolates. J Am Chem Soc 2014;136:15825–8.
29. Krautwald S, Sarlah D, Schafroth MA, Carreira EM. Enantio- and diastereodivergent dual catalysis: alpha-allylation of branched aldehydes. Science. 2013;340:1065–8.
30. Liu WB, Reeves CM, Stoltz BM. Enantio-, diastereo-, and regioselective iridium-catalyzed asymmetric allylic alkylation of acyclic beta-ketoesters. J Am Chem Soc 2013;135:17298–301.
31. Liu WB, Reeves CM, Virgil SC, Stoltz BM. Construction of vicinal tertiary and all-carbon quaternary stereocenters via Ir-catalyzed regio-, diastereo-, and enantioselective allylic alkylation and applications in sequential Pd catalysis. J Am Chem Soc 2013;135:10626–9.
32. Trost BM, Miller JR, Hoffman CM Jr. A highly enantio- and diastereoselective molybdenum-catalyzed asymmetric allylic alkylation of cyanoesters. J Am Chem Soc 2011;133:8165–7.
33. Zheng WH, Zheng BH, Zhang Y, Hou XL. Highly regio-, diastereo-, and enantioselective Pd-catalyzed allylic alkylation of acyclic ketone enolates with monosubstituted allyl substrates. J Am Chem Soc 2007;129:7718–9.
34. Kanbayashi N, Hosoda K, Okamura TA, Aoshima S, Onitsuka K. Enantio-and diastereoselective polymerization: asymmetric allylic alkylation catalyzed by a planar-chiral cp'ru complex. Polym Chem. 2016;7:3691–9.
35. Gauthier MA, Gibson MI, Klok H-A. Synthesis of functional polymers by post-polymerization modification. Angew Chem Int Ed. 2009;48:48–58.
36. Iha RK, Wooley KL, Nyström AM, Burke DJ, Kade MJ, Hawker CJ. Applications of orthogonal "Click" chemistries in the synthesis of functional soft materials. Chem Rev. 2009;109: 5620–86.
37. Kakuchi R, Theato P. Three-component reactions for post-polymerization modifications. ACS Macro Lett. 2013;2:419–22.
38. Kakuchi R, Theato P. Efficient multicomponent postpolymerization modification based on kabachnik-fields reaction. ACS Macro Lett. 2014;3:329–32.
39. Ono RJ, Liu SQ, Venkataraman S, Chin W, Yang YY, Hedrick JL. Benzyl chloride-functionalized polycarbonates: a versatile platform for the synthesis of functional biodegradable polycarbonates. Macromolecules. 2014;47:7725–31.
40. Patrick Theato H-AK. Functional Polymers by Post-Polymerization Modification: Concepts, Guidelines, and Applications. New York: Wiley-VCH; 2013.
41. Zhao Y, Wu H, Zhang Y, Wang X, Yang B, Zhang Q, et al. Postpolymerization modification of poly(dihydropyrimidin-2(1h)-thione)s via the thiourea–haloalkane reaction to prepare functional polymers. ACS Macro Lett. 2015;4:843–7.
42. Monfette S, Fogg DE. Equilibrium ring-closing metathesis. Chem Rev. 2009;109:3783–816.
43. Vougioukalakis GC, Grubbs RH. Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts. Chem Rev. 2010;110:1746–87.
44. Kanbayashi N, Okamura T, Onitsuka K. New synthetic approach for optically active polymer bearing chiral cyclic architecture: combination of asymmetric allylic amidation and ring-closing metathesis reaction. Macromolecules. 2015;48:8437–44.

45. Chae C-G, Shah PN, Min J, Seo H-B, Lee J-S. Synthesis of novel amphiphilic polyisocyanate block copolymer with hydroxyl side group. Macromolecules. 2014;47:1563–9.
46. Dondoni A. The emergence of thiol–ene coupling as a click process for materials and bioorganic chemistry. Angew Chem Int Ed. 2008;47:8995–7.
47. Gress A, Völkel A, Schlaad H. Thio-click modification of poly[2-(3-butenyl)-2-oxazoline]. Macromolecules. 2007;40:7928–33.
48. Hoyle CE, Bowman CN. Thiol–ene click chemistry. Angew Chem Int Ed. 2010;49:1540–73.
49. Killops KL, Campos LM, Hawker CJ. Robust, efficient, and orthogonal synthesis of dendrimers via Thiol-ene "Click" chemistry. J Am Chem Soc 2008;130:5062–4.
50. Lowe AB. Thiol-ene "click" reactions and recent applications in polymer and materials synthesis. Polym Chem. 2010;1:17–36.
51. Lowe AB. Thiol-ene "click" reactions and recent applications in polymer and materials synthesis: a first update. Polym Chem. 2014;5:4820–70.
52. Vidal F, Gowda RR, Chen EYX. Chemoselective, stereospecific, and living polymerization of polar divinyl monomers by chiral zirconocenium catalysts. J Am Chem Soc. 2015;137:9469–80.
53. Kanbayashi N, Miyamoto S, Ishido Y, Okamura T, Onitsuka K. Post-polymerization modification of the side chain in optically active polymers by thiol-ene reaction. Polym Chem. 2017;8:985–94.
54. Cornelissen JJLM, Rowan AE, Nolte RJM, Sommerdijk NAJM. Chiral architectures from macromolecular building blocks. Chem Rev. 2001;101:4039–70.
55. Yashima E, Maeda K, Iida H, Furusho Y, Nagai K. Helical polymers: synthesis, structures, and functions. Chem Rev. 2009;109:6102–211.
56. Yashima E, Ousaka N, Taura D, Shimomura K, Ikai T, Maeda K. Supramolecular helical systems: helical assemblies of small molecules, foldamers, and polymers with chiral amplification and their functions. Chem Rev. 2016;116:13752–990.
57. Ishido Y, Kanbayashi N, Okamura T, Onitsuka K. Side-chain-driven dual structural system of poly-arylopeptide: selective helical formation derived from aromatic ring flips on the backbone. ACS Macro Lett. 2019;8:694–9.
58. Cesario C, Tardibono LP, Miller MJ. Titanocene(III) chloride-mediated reductions of oxazines, hydroxamic acids, and N-Hydroxy carbamates. J Org Chem. 2009;74:448–51.
59. Keck GE, McHardy SF, Murry JA. Total synthesis of (+)-7-deoxypancratistatin: a radical cyclization approach. J Am Chem Soc. 1995;117:7289–90.
60. Mattingly PG, Miller MJ. Titanium trichloride reduction of substituted N-hydroxy-2-azetidinones and other hydroxamic acids. J Org Chem. 1980;45:410–5.
61. Miller MJ, Mattingly PG, Morrison MA, Kerwin JF. Synthesis of. beta.-lactams from substituted hydroxamic acids. J Am Chem Soc 1980;102:7026–32.
62. Szostak M, Spain M, Procter DJ. Recent advances in the chemoselective reduction of functional groups mediated by samarium (ii) iodide: a single electron transfer approach. Chem Soc Rev. 2013;42:9155–83.
63. Chiara JL, Destabel C, Gallego P, Marco-Contelles J. Cleavage of N−O bonds promoted by samarium diiodide: reduction of free or N-acylated O-alkylhydroxylamines. J Org Chem. 1996;61:359–60.
64. CCDC 1554046: Experimental crystal structure determination. 2017. https://doi.org/10.5517/ccdc.csd.cc1p53jh
65. Ishido Y, Kanbayashi N, Okamura T, Onitsuka K. Side-chain-driven dual structural system of poly-arylopeptide: selective helical formation derived from aromatic ring flips on the backbone. ACS Macro Lett. 2019;8:694–9.



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