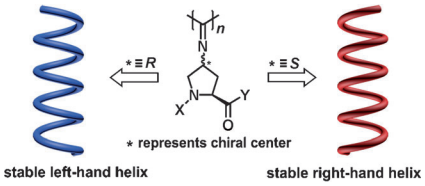
FULL PAPER

Twisted sisters: Polyisocyanides with various proline-based pendant groups were synthesized and their chiroptical properties investigated. These chiral polymers show unprecedented stable helical conformations in different solvents at various temperatures, even in the absence of strong hydrogen-bonding interactions between the pendant groups (see picture).



Chiral Polymers

Anqiu Xu, Guixia Hu, Yulong Hu, Xiuqiang Zhang, Kun Liu, Guichao Kuang, Afang Zhang** ———— ▮▮▮▮–▮▮▮▮

Remarkable Structure Effects on Chiroptical Properties of Polyisocyanides Carrying Proline Pendants

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Remarkable Structure Effects on Chiroptical Properties of Polyisocyanides Carrying Proline Pendants

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Abstract: Chiral polymers with simple chemical structures and high helical conformation stabilities are important for their applications as chiral supports and asymmetrical catalysts. We report herein the synthesis of a series of aliphatic polyisocyanides carrying proline pendants of different chiralities, and an investigation of the effects of the chemical structures of these pendants on the chiroptical properties of the polymers. The configuration of the chiral center at the 4-position of the proline pendants was changed from *S* to *R* to check its effect on the handedness of the helical conformation. To examine the effects of steric hindrance on the stabilities of the helical conformation for these aliphatic representatives, proline pendants with various substituents at both the carboxyl and amine terminals were designed. To further examine the steric effects of the proline pendants, aromatic counterparts were also prepared. In the latter case, the effects of hydrogen bonds between pendant units on the enhancement and stabilities of the helical conformation were investigated by switching from the ester to an amide linkage. The Cotton effects and signal intensities of both aliphatic and aromatic polyisocyanides from circular dichroism spectroscopy were compared based on the bulkiness of the pendant groups, solvent polarities, and solution temperatures. It was found that highly stable helical conformations of polyisocyanides could be imposed by small bulky monoproline pendants.

Keywords: chiroptical properties · helical structures · polyisocyanides · polymers · proline

Introduction

Ordered secondary structures in biomacromolecules, such as proteins and DNA, which have directed sophisticated functions in living systems, stimulate advances across many scientific disciplines.[1] Inspired by elegant features in nature, the development of various strategies to investigate polymers with rationally designed synthetic architectures and ordered secondary structures has been attracting interest from chemists in recent decades.[2] Helical polymers are among the most interesting representatives of optically active polymers and significant progress in this area has been made in pioneering reports.[3] These polymers can be realized by achiral polymerization of optically active monomers or through helix-sense-selective polymerization of achiral and chiral monomers or chiral supramolecular polymerization.[3,4] They have been developed to mimic biological helices and employed to display versatile functions, such as chiral recognition,[5] chiral separations,[6] and asymmetric catalysis.[7] For all of these applications, the amplified chirality and stability of helical conformation of these polymers play crucial roles. Generally speaking, the amplification of chirality and enhancement of helical conformation stability can be rationalized by strong hydrogen bonding, hydrophobic interactions, and/or steric hindrance.[3,8] Different from helical polymers carrying linear pendants that show variable conformation stabilities, depending on the bulkiness and hydrogen-bonding interactions of the side groups,[9] those carrying highly branched pendants normally display enhanced conformation stabilities.[10] In extreme cases, dendronized polymers carrying chiral and large branched pendants show thermally stable helical conformations.[11] Although investigations into helical polymers have resulted in a great boom in recent decades, the development of efficient strategies to amplify helical conformations and to further elucidate the relationship between their chemical structures and helical conformation stability remains challenging.

Polyisocyanides are an intriguing class of helical polymers, which were first investigated by the groups of Millich, Nolte, and Drenth.[12] They contain an all-carbon backbone and pendant groups at each carbon atom, which lead to limited rotational freedom of the C–C bonds, and thus, make these polymers relatively rigid. They were revealed to form a 4_1 helical conformation when the carbon atoms were substituted with chiral pendants. Improved understanding of the helical structures of polyisocyanides came from a combination of experimental and theoretical analyses. In general, bulky

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chiral substituents and intramolecular hydrogen bonds between the pendant amide residues are two most important factors to form and stabilize the helical conformation with preferred handedness for polyisocyanides. Recently, polymerization temperature and solvent polarities were also found to play a role in controlling the helical sense of polyisocyanides.[9c,13] Polyisocyanides with chiral amino acid pendant or bulky peptide moieties have gained great attention because they can assure versatile secondary structure formation and, at the same time, may allow the development of a variety of biocompatible and biodegradable chiral materials.[14] Those with a single amino acid pendant can also show helical structures with predominantly one-handed screw sense, but these helical structures are tunable by temperature and solvent polarities, even when a long linear alkyl chain is attached to the terminus of the amino acid moiety; thus, showing less stability to environmental stimuli.[15] Through the substitution of single amino acid moieties with peptide pendants, for example, alanine dipeptide pendants, the resulting polyisocyanopeptides were able to form remarkably stable β helices, which were supposed to be stabilized by strong hydrogen bonds between the pendant dipeptides.[16]

L-Proline is a nonessential, neutral, genetically coded amino acid. It is the only protein-forming amino acid with a secondary amino group. Pioneering work from the group of List has shown that this specific structure makes L-proline act as an efficient organocatalyst for asymmetric aldol and Mannich reactions.[17] Owing to conformational restrictions imposed by the pyrrolidine ring, the proline moiety also plays an important role within peptides and proteins by acting as a turn inducer, although the amide linkage from the secondary amine cannot form strong hydrogen bonds.[18] Thus, it is not surprising that proline is used in the synthesis of chiral and helical polymers. For example, L-proline was utilized to synthesize helical poly(phenyl acetylene) by Yashima et al. whose chirality is responsive in polar solvents.[19] Both proline-based molecular brushes[20] and dendronized polymers[11a,c] reported by our group demonstrate that a highly stable helical conformation can be achieved with proline moieties. Considering that the substituted pyrrolidine ring of proline may act as the simplest branched structure, we report herein the synthesis of a series of aliphatic and aromatic polyisocyanides with proline moieties as pendant groups (Figure 1). To examine the effects of steric hindrance at the 1- or 2-position of the proline ring on the conformation and stabilities of the resulting polymers, proline pendants with different structures were designed. The handedness of the polymers was examined by changing the stereogenic center at the 4-position of prolines. To further examine the steric effects of the proline pendants on the chiroptical properties of less hindered aromatic representatives, poly(phenyl isocyanide)s were also prepared. By switching the ester to amide linkage between the pendants and the backbone, the effects of hydrogen bonds between the pend-

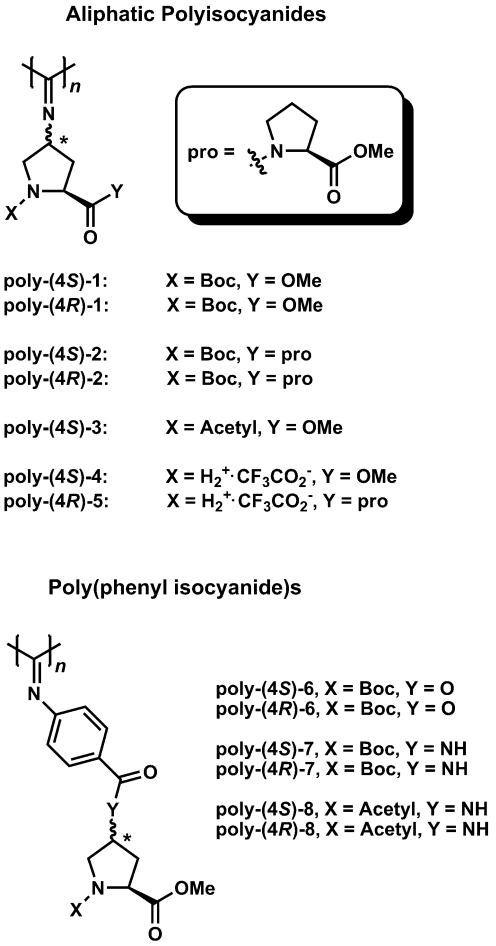


Figure 1. Chemical structures of the proline-based polyisocyanides discussed herein. Boc = *tert*-butoxycarbonyl. Asterisks (*) donate chiral centers.

Abstract in Chinese:

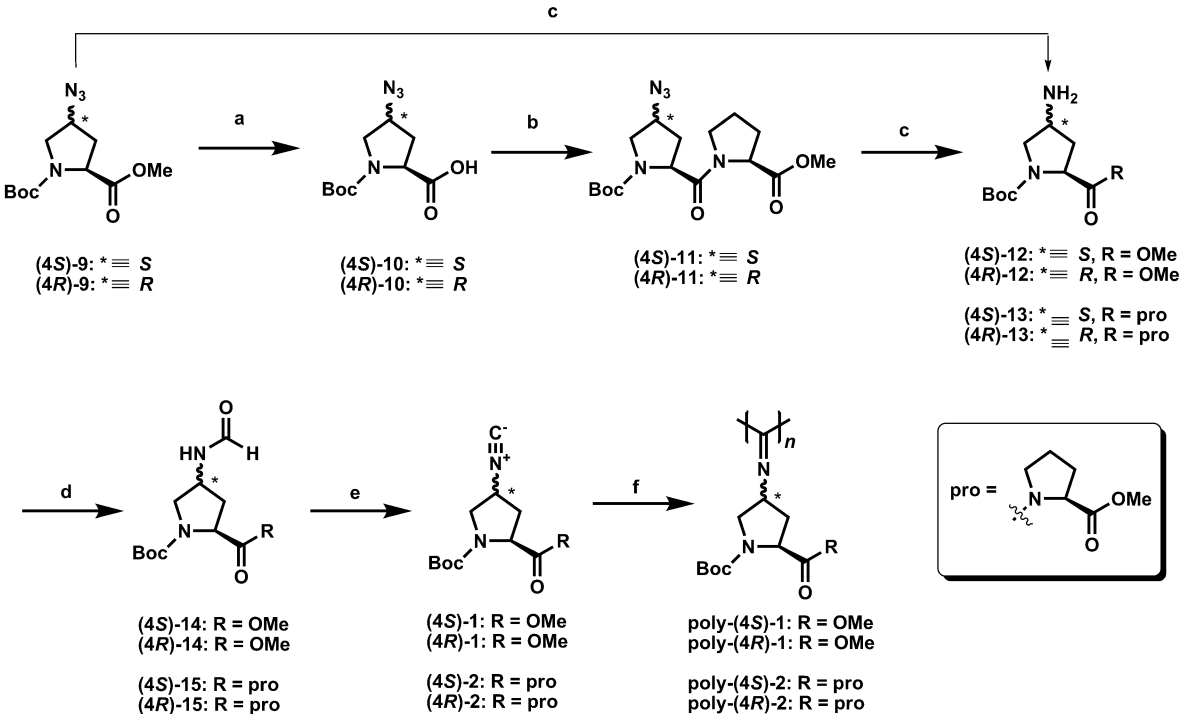
螺旋聚合物的结构简单性及构象稳定性将有利于拓展其在手性支撑材料和不对称催化合成等领域的广泛应用。本文报道带有不同脯氨酸侧基的脂肪族及芳香族聚异氰的合成及其螺旋结构分析。重点考察了手性侧基氨基端和羧基端的空阻效应、4-位手性中心的构型，以及不同溶剂极性与溶液温度等对聚合物主链螺旋构象的形成和稳定性的影响。将手性脯氨酸侧基通过酯键或酰胺键方式键联于芳香族聚合物主链，研究了侧链基元之间氢键作用对主链螺旋构象的增强与稳定化作用。发现脯氨酸五元手性环结构赋予了足够位阻及手性诱导效应，即使在没有强氢键的作用下，也可以促使聚异氰呈现稳定的螺旋构象，且其螺旋构象的手性可以通过选择脯氨酸 4 位上的手性中心构型得以控制。这种高螺旋稳定性说明五元环的脯氨酸基元赋予了聚异氰主链以高刚性特征。相信这类化学结构简单、构象稳定的螺旋聚合物在不对称催化合成方面具有重要应用前景。

ants on stabilizing the helical conformation of the resulting aromatic polymers were investigated. The chirality of the polyisocyanides can be amplified and stabilized by an individual small proline pendant, which is a rigid five-membered ring.

Results and Discussion

Synthesis of the Aliphatic Polyisocyanides

The synthesis of aliphatic isocyanide monomers (4*S*)-**1** and (4*R*)-**1**, which carry a single proline moiety, started from 4-azidoprolines with either *S* or *R* configuration at the 4-position. To examine the steric effects from the chiral substituents at the 2-position of proline on the chiroptical properties of the resulting polymers, monomers (4*S*)-**2** and (4*R*)-**2**, which carry proline dipeptides, were prepared. To investigate the steric effects of the substituent at the 1-position of the proline moiety, acetylated isocyanide (4*S*)-**3** was also prepared for comparison with the Boc-protected compounds. Detailed synthetic procedures for monomers **1** and **2** are outlined in Scheme 1. Saponification of **9** with LiOH yielded acid **10**. Amidation of acid **10** with proline methyl ester afforded dipeptide **11** by using a typical peptide coupling method in the presence of EDC and HOBt.[21] Reduction of azides **9** and **11** with triphenylphosphine[22] gave the corresponding 4-aminoproline derivatives **12** and **13**, which were treated with ethyl formate to give the *N*-formylprolines **14** and **15**, respectively. Dehydration of the formamides with triphosgene in dry CH_2Cl_2 gave rise to the corresponding isocyanide monomers **1** and **2** in high yields. A similar methodology was applied for the synthesis of (4*S*)-**3** (see Scheme S1 in the Supporting Information). These new monomers were characterized by NMR spectroscopy and high-resolution mass spectrometry (HRMS). Polymerization was readily conducted by using the achiral catalyst $NiCl_2{\cdot}6H_2O$ in CH_2Cl_2 or THF at room temperature. Polymerizations proceeded homogeneously and afforded the polyisocyanides poly-**1**, poly-**2**, and poly-(4*S*)-**3** with moderate to high molecular weights. The polymerization results are summarized in Table 1 (entries 1 to 7). Generally speaking, polyisocyanides of higher molecular weights can be achieved with a higher molar ratio of monomer to initiator (Table 1, entries 1–3), but the large pendants in the monomers will contribute significantly to steric hindrance, which clearly reduces the molar masses of the resulting polymers (Table 1, entries 5 and 6). Contrary to polymers prepared in CH_2Cl_2, those obtained from a more polar solvent, THF, have much higher molecular weights. All polymers have different solubility in conventional solvents. Boc-protected polymers poly-(4*S*)-**1**, poly-(4*R*)-**1**, poly-(4*S*)-**2**, and poly-(4*R*)-**2** show good solubility in THF or CH_2Cl_2, but their solubility is much worse in methanol. Polymers with high molar masses are no longer soluble in methanol. Acetylated polymer poly-(4*S*)-**3** is soluble in CH_2Cl_2 or methanol, but sparingly so in THF. After deprotection with trifluoroacetic acid (TFA),[22] the positive-



Scheme 1. Synthesis and polymerization of aliphatic isocyanides. Reagents and conditions: a) **9**, LiOH·H_2O, H_2O/MeOH, 0 °C, 2 h (100 %); b) **10**, H-Pro-OMe·HCl, DIPEA, EDC, HOBt, CH_2Cl_2, −15 °C, 5 h (72–77 %); c) **9** or **11**, PPh_3, THF/H_2O, 50 °C, 2 h (85–96 %); d) **12** or **13**, ethyl formate, sodium formate, 50 °C, 5 h (87–90 %); e) **14** or **15**, TEA, triphosgene, CH_2Cl_2, −10 °C to RT, 5 h (81–84 %); f) monomer **1** or **2**, $NiCl_2{\cdot}6H_2O$ (10 wt % in MeOH), CH_2Cl_2 or THF, 25 °C (47–82 %). DIPEA = diisopropylethylamine, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxy-1H-benzotriazole, THF = tetrahydrofuran, TEA = triethylamine.

Table 1. Polymerization of the isocyanide monomers with achiral catalyst $NiCl_2 \cdot 6H_2O$.[a]

Entry	Monomer	Polymerization conditions $[M]_0/[I]_0$	Time [h]	Solvent	Yield [%]	GPC results[b] M_n ($\times 10^{-3}$)	PDI
1	(4*S*)-**1**	50:1	24	CH_2Cl_2	70	4.6	1.31
2	(4*S*)-**1**	100:1	24	CH_2Cl_2	82	10.5	1.48
3	(4*S*)-**1**	200:1	48	THF	62	43.9	1.10
4	(4*R*)-**1**	100:1	24	CH_2Cl_2	70	7.4	1.13
5	(4*S*)-**2**	100:1	72	CH_2Cl_2	47	2.2	1.12
6	(4*R*)-**2**	100:1	72	CH_2Cl_2	64	2.1	1.07
7	(4*S*)-**3**	200:1	24	THF	78	49.6	1.05
8	(4*S*)-**6**	100:1	72	THF	55	131.4	1.26
9	(4*R*)-**6**	100:1	48	THF	48	144.7	2.21
10	(4*S*)-**7**	80:1	48	THF	62	48.0	1.63
11	(4*R*)-**7**	100:1	48	THF	55	36.6	1.44
12	(4*S*)-**8**	200:1	72	THF	60	45.3	1.45
13	(4*R*)-**8**	200:1	48	THF	46	39.5	1.35

[a] General polymerization condition: nitrogen atmosphere at room temperature (25 °C). $[M]_o/[I]_o$ represents the initial molar ratio of monomer to initiator. $[M]_o$ is in the range of 0.66–1.00 mol L^{-1}. [b] GPC measurements were performed with *N*,*N*-dimethylformamide (DMF) as the eluent containing 0.10 wt % LiBr at 45 °C. M_n = number-average molecular weight. PDI = polydispersion index.

ly charged polyisocyanides poly-(4*S*)-**4** and poly-(4*R*)-**5** are soluble in water.

Chiroptical Properties of Aliphatic Polyisocyanides

Because these polyisocyanides were prepared from optically pure isocyanide monomers, a single-handed helix conformation for the resulting polymers was expected, and their chiroptical properties were thus characterized with circular dichroism (CD) spectroscopy. The CD spectra of the polyisocyanides show Cotton effects in the range from 240 to 380 nm (Figure 2), which are ascribed to n–π* transitions of the C–N chromophores.[23] For comparison, CD spectra from corresponding monomers were recorded (Figure S1 in the Supporting Information), and no clear Cotton effects were observed. Therefore, the Cotton effects suggest that these polymers all contain an excess of one helical sense. As expected, polymers with higher molar masses show stronger Cotton effects (compare the curves of poly-(4*S*)-**1a** (entry 1 in Table 1), poly-(4*S*)-**1b** (entry 2 in Table 1) and poly-(4*S*)-**1c** (entry 3 in Table 1) in Figure 2a). This molecular weight dependence of the Cotton effect is consistent with previous results.[13b]

First, the effect of the absolute configuration at the 4-position of the proline moiety on the chiroptical properties of poly-1 are discussed. Poly-(4*S*)-**1** and poly-(4*R*)-**1** have *S*- or *R*-configured chiral centers at the 4-position of the proline moiety, respectively. For the former, the CD spectrum in Figure 2a displays a negative sign at the first Cotton effect with an intensity value ($\Delta\varepsilon_{1st}$) of about −1.0, whereas, for the latter, the CD spectrum (Figure 2a) shows the opposite sign for the first Cotton effect with an intensity value ($\Delta\varepsilon_{1st}$) of about +1.0. The opposite Cotton effect sign is indicative of inversion of the helical conformation of the polymer backbones. According to Tinoco[24] and DeVoe,[25] polyisocyanides adopt right-handed helices if the couplets are Z shaped (negative for $\Delta\varepsilon_{1st}$), whereas a left-handed helical conformation would be expected in the case of S-shaped couplets (positive for $\Delta\varepsilon_{1st}$).[23b,26,27] Therefore, the configuration at the 4-position of the proline determines the handedness of the helical conformations of the polyisocyanides. The *S* configuration at the 4-position of proline leads to the formation of polymers with *P* helical structure, whereas the *R*-configured chiral center results in the formation of polymers with the *M* helical conformation.

Second, to understand how steric hindrance from the proline pendants contributes to control of the helical conformation of the resulting polymers, poly-**2** and poly-(4*S*)-**3** were prepared (Scheme S1 in the Supporting Information). Poly-**2** carries a proline-based dipeptide with either *S*- or *R*-configured chiral centers at the 4-position of the first proline moiety, resulting in polymers poly-(4*S*)-**2** and poly-(4*R*)-**2**, respectively. This allows us to check the effect of the bulkiness arising from substitution at the 2-position on the chiroptical properties of the polymers. Poly-(4*S*)-**3** carries a single acetylated proline moiety with an *S*-configured chiral center at the 4-position and allows an examination of how the bulkiness at the 1-position of the proline moiety affects the chiroptical properties of the polymer. The CD spectra of these polymers are shown in Figure 2b. Disregarding the *S*- or *R*-configured chiral centers at the 4-position, poly-**2** undergoes a small bathochromic shift relative to poly-**1**, which indicates a tighter helical conformation.[28] Surprisingly, increasing the steric hindrance by increasing the pendant size did not lead to a clear enhancement of the Cotton effects. On the contrary, the intensities of the first Cotton effects of poly-**2** slightly decreased relative to those of poly-**1**, most probably as a result of the lower molar masses of the polymers. Once the Boc protecting group (for poly-**1**) was changed to an acetyl one (for poly-(4*S*)-**3**), the bulkiness of pendants along the polymer backbone reduced owing to a decrease in the size of the acetyl group when compared with that of the Boc group. From the CD spectrum of poly-(4*S*)-**3**, the first Cotton effect shows a similar shape to those of poly-**1**, but with slightly reduced intensities. The effect of the bulkiness of the Boc group on the chiroptical properties was also investigated by deprotection of poly-(4*S*)-**1c** and poly-(4*R*)-**2** with TFA to yield the corresponding deprotected, charged polymers poly-(4*S*)-**4** and poly-(4*R*)-**5**, respectively. As shown by the CD spectra in Figure 2b, both deprotected polymers had significantly decreased Cotton effects at around 294 nm. Similar results were obtained for CD spectra in THF (data not shown). The weakened Cotton effect indicates that deprotected polymers hold less defined helical structures,

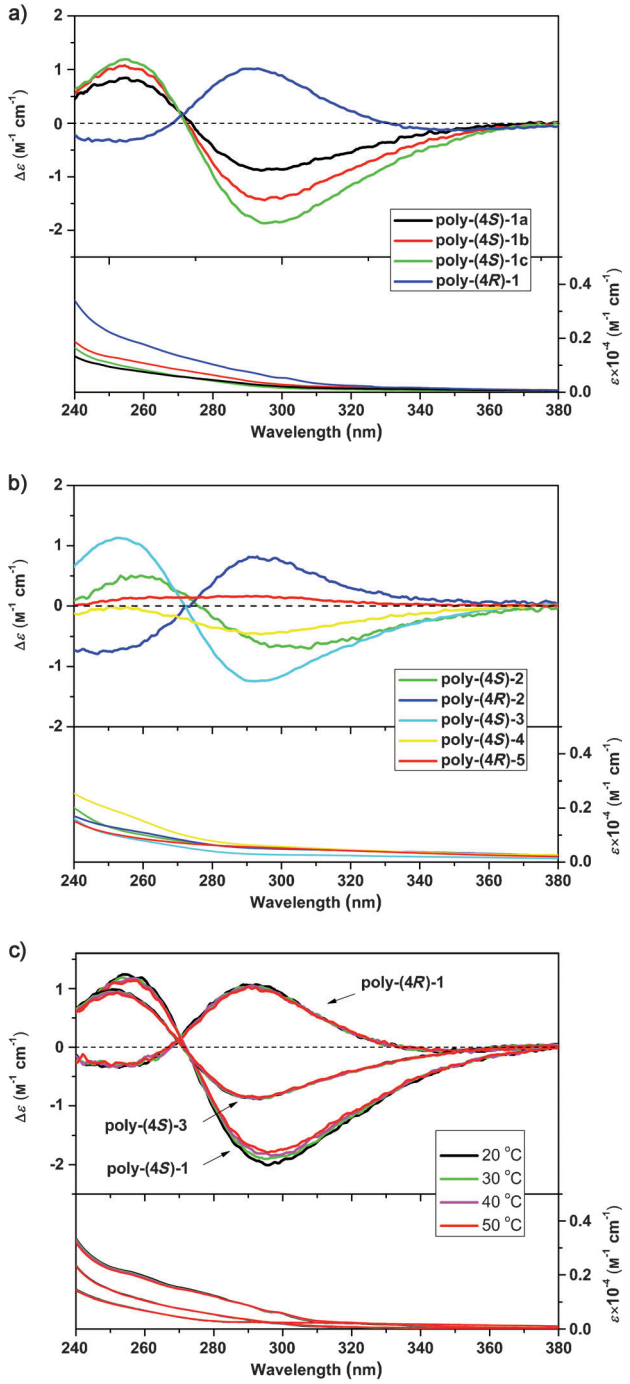


Figure 2. CD and UV spectra of a) poly-**1** measured in THF at 25 °C; b) poly-**2** and poly-(4*S*)-**3** in CH_2Cl_2, poly-(4*S*)-**4** and poly-(4*R*)-**5** in water at 25 °C; and c) CD spectra of poly-**1** in THF and poly-(4*S*)-**3** in methanol at various temperatures. $c = 0.05$ wt %.

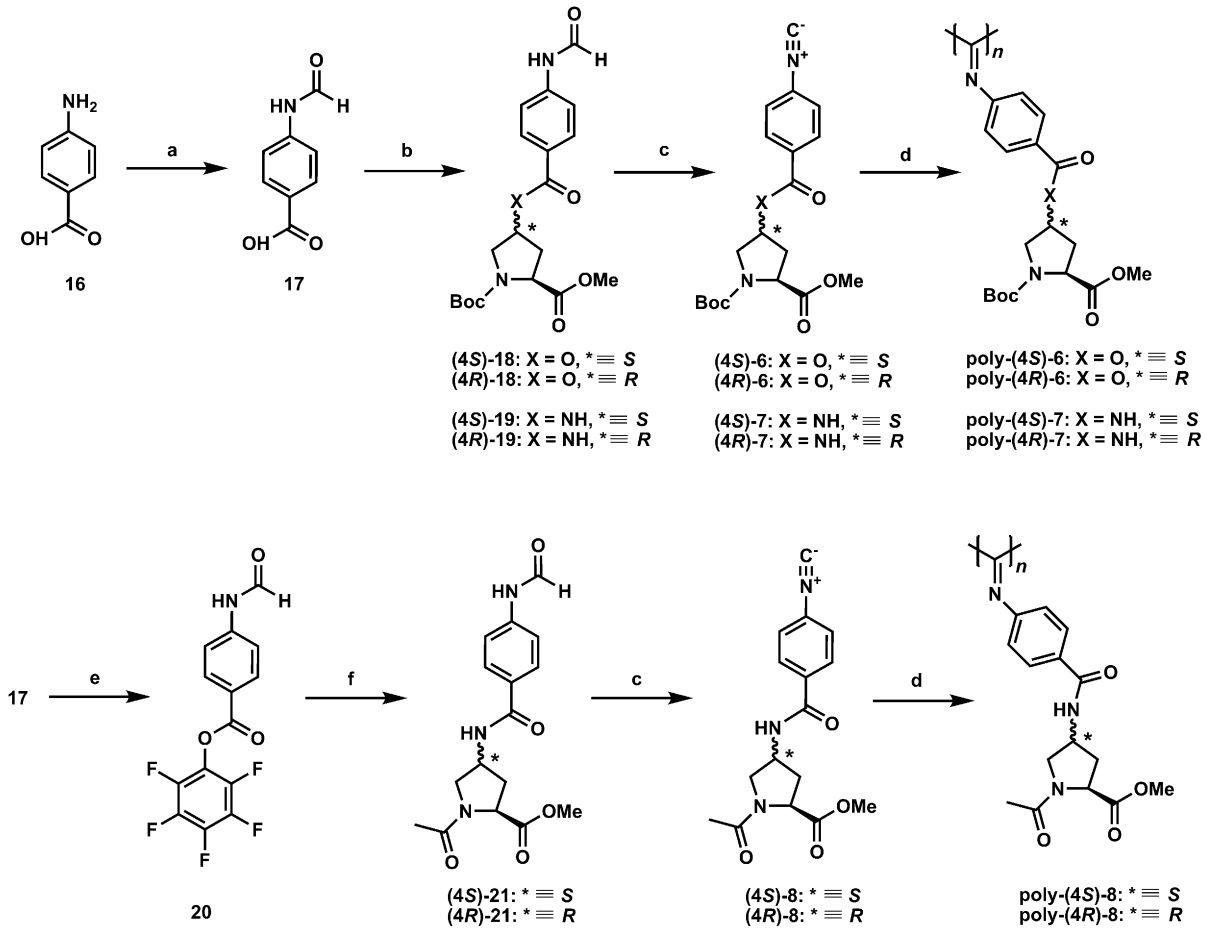
which might be caused by reduced steric hindrance together with repulsions between the positive charges.[29]

Third, the thermal stability of the helical conformation of these chiral polymers was examined at various temperatures (20–50 °C); the CD spectra of poly-**1** and poly-(4*S*)-**3** are shown in Figure 2c and negligible CD signal changes are observed, even at 50 °C. Thus, the helical conformations of all polymers examined are stable within the measured temperature range. The Cotton effects of these polyisocyanides are also similar to each other in different solvents. These results suggest that these chiral polymers possess helical conformations that are stable to temperature and solvent polarity. This high stability could be attributed to sufficient steric hindrance from the proline pendants, which makes the main chain rigid enough to prevent conformation switching, even though there is an absence of strong intramolecular hydrogen bonding.

Synthesis and Secondary Structures of Aromatic Poly(phenyl isocyanide)s

From the results described above, it is clear that aliphatic polyisocyanides carrying a monoproline moiety can adopt stable helical conformations, and the handedness is mainly dependent on the configuration at the 4-position of the proline moiety. Motivated by these findings, we set out to examine the structural effects on the chiroptical properties of poly(phenyl isocyanide)s with these proline-based pendants. It is clear in poly(phenyl isocyanide)s that the chiral pendants are a benzene unit away from the isocyanide backbone, and thus, should show less steric hindrance effects for the same pendants when compared to the situation in aliphatic polyisocyanides. Therefore, poly(phenyl isocyanide)s with three types of proline-based pendants were prepared to check whether structural effects on the chiroptical properties of the aliphatic polyisocyanides can be inherited. For this purpose, compounds (4*S*)-**6** and (4*R*)-**6**, with proline pendants joined through an ester linkage, and (4*S*)-**7** and (4*R*)-**7**, with proline pendants joined through an amide linkage, were designed and synthesized. The chiroptical properties of the corresponding polymers were investigated and compared. To examine the effects of steric hindrance at the 1-position of proline moiety on the optical properties of the corresponding polymers, acetylated monomers (4*S*)-**8** and (4*R*)-**8** were also designed. The synthetic procedures for these monomers are outlined in Scheme 2, and their polymerization results are summarized in Table 1 (entries 8–13). With THF as the polymerization solvent, polymers of high molecular weights were obtained.

First, the secondary structures of poly-(4*S*)-**6** were characterized by CD spectroscopy, in which the proline pendant was connected to the main chain through an ester linkage. The CD spectra in THF at various temperatures are shown in Figure 3a. Interestingly, the positive first Cotton effect at around $\lambda = 358$ nm ($\Delta\varepsilon_{1st} = +2.84$) reveals that the poly(phenyl isocyanide) also adopts a preferred single-handed helix conformation, even with less steric hindrance and in the absence of strong hydrogen bonding. CD spectra at elevated temperatures indicate that this conformation has moderate thermal stability. The CD spectra of poly-(4*S*)-**6** in solvents with different polarities were also recorded (Figure 3b). The strongest first Cotton effect in THF was observed; this showed a clear dependence of the chiroptical properties on solvent polarity. To examine whether the con-



Scheme 2. Synthesis and polymerization of phenyl isocyanides. Reagents and conditions: a) **16**, ethyl formate, 50 °C, reflux, 24 h (93 %); b) for X = O: **17**, Boc-Hyp-OMe, DEAD, PPh_3, THF, 0–5 °C, 12 h (57–62 %); for X = NH: **12**, **17**, DIPEA, PyBOP, HOBt, CH_2Cl_2, −15 °C, 5 h (85 %); c) **18**, **19**, or **21**, TEA, triphosgene, CH_2Cl_2, −10 °C to RT, 5 h (79–86 %); d) monomer **6**, **7**, or **8**, $NiCl_2{\cdot}6H_2O$ (1 wt % in MeOH), THF, 25 °C, 48–72 h (50–80 %); e) **17**, pentafluorophenol, DMF, EDC, overnight (70 %); f) **20**, **24**, DMF, TEA, RT, 12 h (65–87 %). DEAD = diethyl azodicarboxylate, PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, Boc-Hyp-OMe = *N*-Boc-*trans* (or *cis*)-4-hydroxy-L-proline methyl ester.

figuration at the 4-position of the proline pendant influences the handedness of the preferred helical conformation, poly-(4*R*)-**6** was prepared. Surprisingly, the sign of the first Cotton effect of this polymer was the same as that of poly-(4*S*)-**6** (Figure 3c). This is in contrast to the situation for aliphatic polyisocyanides, for which polymers adopt a helical conformation with inversed handedness upon changing the configuration at the 4-position from *S* to *R*. One possible reason for this contradiction could be due to free rotation of the ester linkages in poly-(4*S*)-**6** and poly-(4*R*)-**6**, which dampen the configuration effect of the 4-position of the proline moiety.[30]

To examine how hydrogen bonding plays a rule in controlling the helical conformation in such aromatic polymers, poly-(4*S*)-**7** and poly-(4*R*)-**7** were synthesized. The CD spectra recorded in THF are shown in Figure 3c. Interestingly, the first Cotton effect of poly-(4*S*)-**7** is much stronger (λ = 362 nm, $\Delta\varepsilon_{1st} = +4.87$) than those from counterparts with ester linkages. The signs of the first Cotton effects are inverted for poly-(4*S*)-**7** and poly-(4*R*)-**7**, which suggests that the amide linkage between the proline pendant and isocyanide backbone contributes a significant barrier to pendant group rotation.[30] The enhanced Cotton effects should be partially achieved by strong hydrogen bonding within the pendant groups. A clear contribution from strong hydrogen bonding within these two polymers is also observed CD spectra recorded at various temperatures in protic solvent methanol (Figure 3d). Within the measured temperature range, the intensities of the first Cotton effects show almost no deviations, suggesting the high thermal stability of their helical conformations. Further work was conducted to assess the effects of steric hindrance. By substituting the Boc protecting group with an acetylated one, poly-(4*S*)-**8** and poly-(4*R*)-**8** with less hindered pendants were synthesized. Based on the CD spectra (Figure 3e), both polymers inherit from their Boc-protected counterparts a preference to adopt a single-handed helical conformation with inverted signs. Surprisingly, the intensities of the first Cotton effects (λ = 364 nm, $\Delta\varepsilon_{1st} = +8.50$) are doubled compared with those of the Boc-protected polymers; this suggests the existence of a subtle balance between steric effects and optical properties. The positive $\Delta\varepsilon_{1st}$ values consistently gradually de-

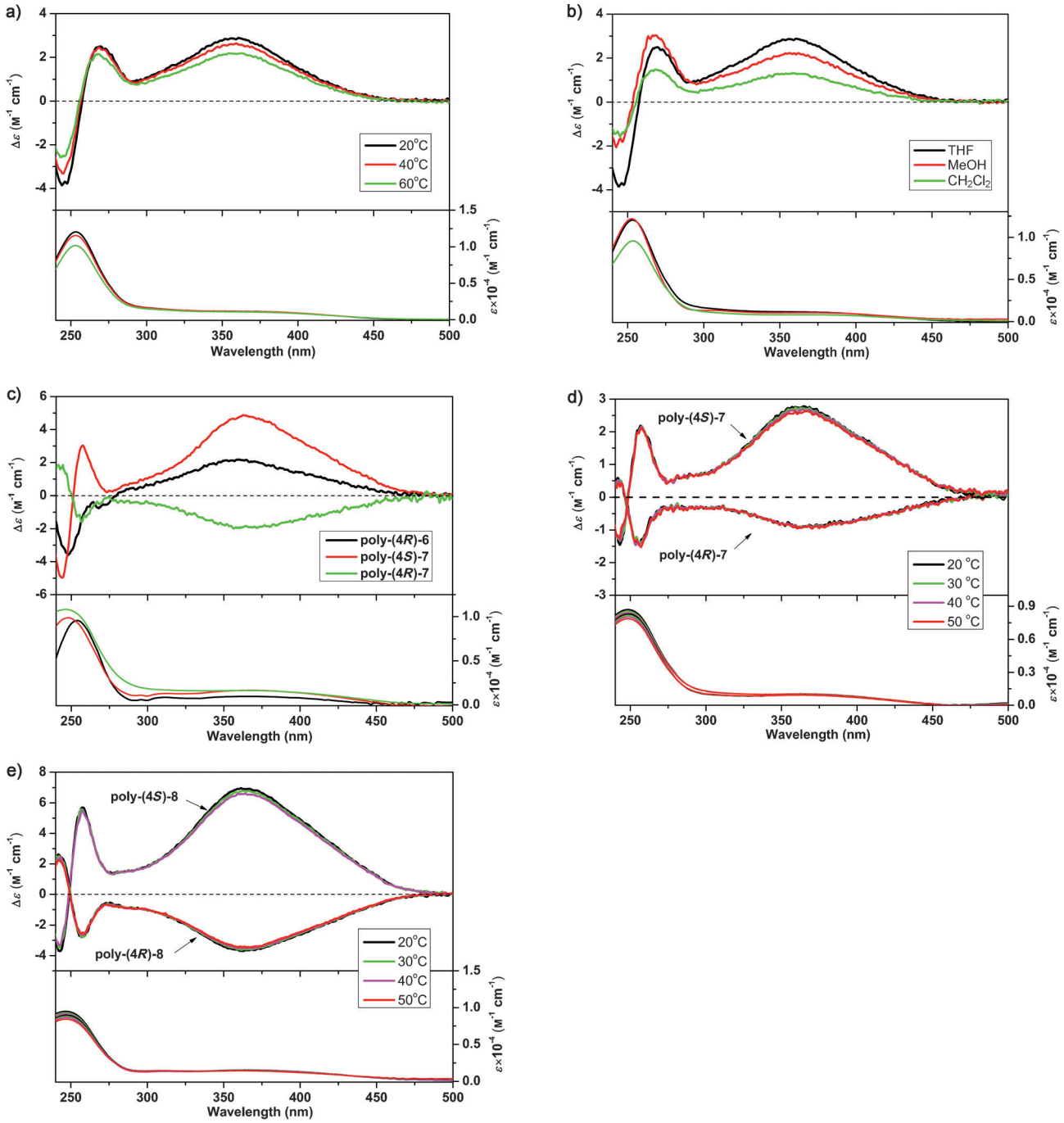


Figure 3. CD and UV spectra of a) poly-(4*S*)-**6** in THF at different temperatures; b) poly-(4*S*)-**6** in different polarity solvents at 25 °C; c) poly-(4*R*)-**6**, poly-(4*S*)-**7**, and poly-(4*S*)-**7** in THF at 25 °C; d) poly-(4*S*)-**6** and poly-(4*R*)-**6** in methanol at 25 °C; and e) poly-(4*S*)-**8** and poly-(4*R*)-**8** in methanol at different temperatures. $c = 0.05$ wt %.

creased from +8.50 to +6.84 when the solvent changed from less polar CH_2Cl_2 to polar MeOH. Furthermore, these helical conformations are stable over the temperature range of 20–50 °C, as shown in Figure 3e. These results are in contradiction to our initial assumption. By comparing these results with those for the aliphatic polyisocyanides, aromatic polyisocyanides carrying the same pendant groups should have less steric hindrance, leading to the formation of less ordered helical conformations with impaired thermal stabilities. We speculate that these contradictions mainly come from strong hydrogen bonding between the pendant groups along the polymer backbone, which should have been enhanced with reduced steric hindrance at the 1-position of the proline moiety.[31] Enhanced interactions leave the main chain more intact to prevent the conformation from switching, and thus, affording chiral polymers with stable helical conformations.

Conclusion

We have prepared a series of novel aliphatic and aromatic polyisocyanides with various mono- and diproline derivatives as pendant groups. The effects of the bulkiness of the pendant, the configuration of the chiral center, solvent polarity, and solution temperature on the helical conformation of these polyisocyanides were evaluated by CD spectroscopy and demonstrated that the chiral polymers with stable helical conformations could be realized by small, rigid five-membered proline pendants, even in the absence of strong hydrogen bonds. The handedness of the helices could be mediated by the configuration at the 4-position of the proline moieties. Steric effects from the five-membered ring in the chiral substituents were proposed to be the most important factor to induce and stabilize the helical conformation for these polyisocyanides. Aromatic representatives with proline pendants attached through ester or amide linkages were prepared to confirm this conjecture. Hydrogen bonds from the amide linkages among the pendants are important in the less bulky cases to guarantee the rigidity of polymer backbone, and thus, enhance and stabilize the helical conformation. This work provides a novel perspective for controlling the helical conformation of polyisocyanides. Based on their simplified chemical structures and enhanced stable helical conformation, these chiral polyisocyanides with proline pendants may find promising applications in chiral materials and asymmetrical catalysis.

Experimental Section

Materials

Compounds (4*S*)-**9**,[22] (4*R*)-**9**,[22] (4*S*)-**10**,[22] (4*R*)-**10**,[22] (4*S*)-**12**,[20] and (4*R*)-**12**[20] were prepared according to previous reports. All other chemicals were purchased with purities higher than 98% and used without further purification unless otherwise specified. $NiCl_2{\cdot}6H_2O$ has a purity of over 99.9999%. CH_2Cl_2 was dried over CaH_2. THF was predried over sodium and then heated at reflux over lithium aluminum hydride before use. Analytical TLC was performed by using TLC plates precoated with silica gel 60 G/UV254, 0.25 mm. Separation on the plates was visualized by treatment with a solution of ninhydrin in ethanol (0.3 wt%) and subsequent heating at around 200 °C. Silica gel 60M (300–400 mesh) was used as the stationary phase for column chromatography. All samples were dried thoroughly under vacuum prior to analytical measurements to remove strongly adhering solvent molecules.

Instrumentation and Measurements

^{1}H NMR spectra were recorded on a Bruker AV500 (500 MHz) spectrometer at room temperature with $CDCl_3$ as the solvent (unless noted otherwise). All chemical shifts were reported in ppm relative to tetramethylsilane. Gel permeation chromatography (GPC) measurements were carried out on a Waters GPC e2695 instrument with a three-column set (Styragel HR3+HR4+HR5) equipped with a refractive index detector (Waters 2414) and DMF (containing 1 mg mL^{-1} LiBr) as the eluent at 45 °C. The calibration was performed with poly(methyl methacrylate) standards in the range of M_p=2580–981 000 (Polymer Standards Service USA, Inc.). High-resolution MALDI-TOF-MS analyses were performed on IonSpec Ultra instruments. CD measurements were performed on a JASCOJ-815 spectropolarimeter (continuous scanning mode; scanning speed: 50 nm min^{-1}; data pitch: 1 nm; response: 1 s; band width: 2.0 nm). A thermally controlled quartz cell with a path length of 1 mm was used. CD data are given as mean molar ellipticities based on repeating units.

General Procedure for Formylation (A)

Sodium formate (18.37 mmol) and the amino compound (16.14 mmol) were dissolved in ethyl formate (50 mL). The mixture was heated to reflux for 3 h. After the precipitate was filtered out and washed with CH_2Cl_2, the combined filtrate was concentrated in vacuo and the residue was purified by column chromatography with MeOH/CH_2Cl_2 (1/20, v/v) to afford the formamide compounds as colorless oils or solids.

General Procedure for the Dehydration of Formamide with Triphosgene (B)

Triphosgene (2.19 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of TEA (10.87 mmol) and the formamide (3.67 mmol) in dry CH_2Cl_2 (80 mL) over 30 min at −10 °C. The mixture was allowed to warm to 0 °C before the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and then the solution was stirred vigorously for 10 min. After washing successively with brine, the organic phase was collected and dried over $MgSO_4$. Purification by column chromatography with ethyl acetate/hexane (1/5, v/v) afforded the monomer as a yellow oil, which was stored under 0 °C before use.

General Procedure for Amide Coupling (C)

The deprotected compound (36.23 mmol) and acid (30.05 mmol) were dissolved in dry CH_2Cl_2 (80 mL) at room temperature. After the solution was cooled to −15 °C, TEA (89.93 mmol), HOBt (36.02 mmol), and EDC (35.99 mmol) or PyBOP (35.99 mmol) were added successively under N_2. The mixture was kept at that temperature for 2 h, then for 14 h at room temperature. It was washed successively with $NaHCO_3$ and brine, and all of the aqueous phases were extracted with CH_2Cl_2 three times. The combined organic phases were dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo. Purification by column chromatography with ethyl acetate/hexane (1:1 then 2:1, v/v) yielded the title compounds as colorless solids.

General Procedure for the Mitsunobu Reaction (D)

DEAD (40% in toluene, 11.02 mmol) was added dropwise to a mixture of hydroxyproline (8.19 mmol), **17** (9.08 mmol), and PPh_3 (11.82 mmol) in dry THF (80 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and then at room temperature for 12 h before the solvent was evaporated in vacuo. Purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) afforded the title compounds as white solids.

General Procedure for Polymerization (E)

Polymerization of the monomer was carried out in organic solvent (CH_2Cl_2 or THF) with $NiCl_2{\cdot}6H_2O$ as the catalyst at room temperature. A typical procedure was as follows: $NiCl_2{\cdot}6H_2O$ in MeOH (10 wt% or 1 wt%) was added to a solution of monomer in organic solvent. The brown solution was stirred for 24–72 h at room temperature and then purified by column chromatography with CH_2Cl_2 as the eluent to afford the polymer as a yellow solid.

*Synthesis of (4S)-**11***

According to general procedure C, from Pro-OMe·HCl (6.00 g, 36.23 mmol), (4*S*)-**10** (7.70 g, 30.05 mmol), TEA (9.10 g, 89.93 mmol), HOBt (4.87 g, 36.02 mmol), and EDC (6.90 g, 35.99 mmol), (4*S*)-**11** was afforded as a colorless solid (7.98 g, 72%). ^{1}H NMR: δ=1.40 and 1.46 (2×s, 9H; H-Boc), 1.93–2.27 (m, 5H; CH_2), 2.58–2.64 (m, 1H; CH_2), 3.37–3.43 (m, 1H; CH_2), 3.55–3.91 (m, 6H; CH_2, CH_3), 4.02–4.11 (m, 1H; CH), 4.41–4.64 ppm (m, 2H; CH).

*Synthesis of (4R)-**11***

According to general procedure C, from Pro-OMe·HCl (6.00 g, 36.23 mmol), (4*R*)-**10** (7.70 g, 30.05 mmol), TEA (9.10 g, 89.93 mmol), HOBt (4.87 g, 36.02 mmol), and EDC (6.90 g, 36.10 mmol) in dry CH_2Cl_2 (80 mL), (4*R*)-**11** was yielded as a colorless solid (8.47 g, 77%). ^{1}H NMR:

δ = 1.41 and 1.46 (2×s, 9H; H-Boc), 1.93–2.35 (m, 6H; CH_2), 3.46–3.91 (m, 7H; CH_2, CH_3), 4.24–4.33 (m, 1H; CH), 4.50–4.67 ppm (m, 2H; CH).

*Synthesis of (4S)-**13***

A solution of (4*S*)-**11** (1.00 g, 2.72 mmol) and PPh_3 (1.07 g, 4.08 mmol) in THF (50 mL) and water (5 mL) was stirred at 50 °C for 4 h. The solvent was evaporated and the residue was purified by column chromatography with MeOH/CH_2Cl_2 (1/20, v/v) to afford (4S)-**13** as a colorless oil (0.79 g, 85 %). ^{1}H NMR: δ = 1.40 and 1.46 (2×s, 9H; H-Boc), 1.88–2.27 (m, 5H; CH_2), 2.43–2.52 (m, 1H; CH_2), 3.41–3.47 (m, 1H; CH_2), 3.53–3.85 (m, 7H; CH_2, CH_3), 4.41–4.64 ppm (m, 2H; CH).

*Synthesis of (4R)-**13***

A solution of (4*R*)-**11** (1.00 g, 2.72 mmol) and PPh_3 (1.07 g, 4.08 mmol) in THF (50 mL) and water (5 mL) was stirred at 50 °C for 4 h. The solvent was evaporated and the residue was purified by silica chromatography with MeOH/CH_2Cl_2 (1/20, v/v) to afford (4*R*)-**13** as a colorless oil (0.89 g, 96 %). ^{1}H NMR: δ = 1.40 and 1.45 (2×s, 9H; H-Boc), 1.92–2.25 (m, 6H; CH_2), 3.08–3.28 (m, 1H; CH_2), 3.56–3.87 (m, 7H; CH, CH_2, CH_3), 4.52–4.64 ppm (m, 2H; CH).

*Synthesis of (4S)-**14***

According to general procedure A, from compound (4*S*)-**12** (1.50 g, 6.14 mmol) and sodium formate (1.58 g, 18.37 mmol) in ethyl formate (50 mL), (4*S*)-**14** was afforded as a colorless solid (1.50 g, 90 %). ^{1}H NMR: δ = 1.44 and 1.48 (2×s, 9H; H-Boc), 1.92–2.01 (m, 1H; CH_2), 2.43–2.57 (m, 1H; CH_2), 3.49–3.67 (m, 2H; CH_2), 3.79 and 3.81 (2×s, 3H; CH_3), 4.37 (d, J = 9.0 Hz, 1H; CH), 4.78 (s, 1H; CH), 6.75–6.99 (m, 1H; NH), 8.11 ppm (s, 1H; CHO).

*Synthesis of (4R)-**14***

According to general procedure A, from (4*R*)-**12** (1.50 g, 6.14 mmol) and sodium formate (1.58 g, 18.37 mmol) in ethyl formate (50 mL), (4*R*)-**14** was afforded as a colorless oil (1.51 g, 90 %). ^{1}H NMR: δ = 1.43 and 1.47 (2×s, 9H; H-Boc), 2.21–2.38 (m, 2H; CH_2), 3.31–3.47 (m, 1H; CH_2), 3.70–3.93 (m, 4H; CH_2, CH_3), 4.24–4.45 (m, 1H; CH), 4.61 (s, 1H; CH), 6.02–6.40 (m, 1H; NH), 8.10–8.18 ppm (m, 1H; HCO).

*Synthesis of (4S)-**15***

According to general procedure A, from compound (4*S*)-**13** (0.80 g, 2.34 mmol) and ethyl formate (40 mL), (4*S*)-**15** was afforded as a colorless solid (0.77 g, 89 %). ^{1}H NMR: δ = 1.41 and 1.45 (2×s, 9H; H-Boc), 1.96–2.31 (m, 5H; CH_2), 2.40–2.52 (m, 1H; CH), 3.52–3.94 (m, 7H; CH_2, CH_3), 4.49–4.63 (m, 2H; CH), 4.78–4.85 (m, 1H; CH), 7.70 (dd, J = 9.3, 9.2 Hz, 1H; NH), 8.02–8.08 ppm (m, 1H; HCO).

*Synthesis of (4R)-**15***

According to general procedure A, from (4*R*)-**13** (0.80 g, 2.34 mmol) and sodium formate dihydrate (0.73 g, 7.02 mmol) in ethyl formate (40 mL), (4*R*)-**15** was afforded as a colorless solid (0.75 g, 87 %). ^{1}H NMR: δ = 1.40 and 1.45 (2×s, 9H; H-Boc), 1.92–2.44 (m, 6H; CH_2), 3.17–3.58 (m, 7H; CH_2, CH_3), 4.45–4.68 (m, 3H; CH_2, CH), 5.88–6.28 (m, 1H; NH), 8.05–8.18 ppm (m, 1H; HCO).

*Synthesis of (4S)-**1***

According to general procedure B, from (4*S*)-**14** (1.00 g, 3.67 mmol), TEA (1.10 g, 10.87 mmol), and triphosgene (0.65 g, 2.19 mmol), (4*S*)-**1** was afforded as thick yellowish needles (0.78 g, 84 %). ^{1}H NMR: δ = 1.44 and 1.50 (2×s, 9H; H-Boc), 2.34–2.43 (m, 1H; CH_2), 2.56–2.69 (m, 1H; CH_2), 3.64–3.76 (m, 1H; CH_2), 3.80 (s, 3H; CH_3), 3.83–3.96 (m, 1H; CH_2), 4.11–4.19 (m, 1H; CH), 4.33–4.40 (m, 1/2H; CH), 4.43–4.50 ppm (m, 1/2H; CH); HRMS (ESI): m/z calcd for $C_{12}H_{19}N_2O_4$ $[M+H]^+$: 255.1345; found: 255.1343.

*Synthesis of (4R)-**1***

According to general procedure B, from (4*R*)-**14** (1.00 g, 3.67 mmol), triphosgene (0.65 g, 2.19 mmol), and TEA (1.10 g, 10.87 mmol) in CH_2Cl_2 (60 mL) under an N_2 atmosphere, (4*R*)-**1** was afforded as thick yellowish needles (0.77 g, 83 %). ^{1}H NMR: δ = 1.44 and 1.49 (2×s, 9H; H-Boc), 2.25–2.35 (m, 1H; CH_2), 2.47–2.62 (m, 1H; CH_2), 3.66–3.84 (m, 5H; CH_3, CH_2), 4.20–4.29 (m, 1H; CH), 4.43–4.56 ppm (m, 1H; CH); HRMS (ESI): m/z calcd for $C_{12}H_{19}N_2O_4$ $[M+H]^+$: 255.1345; found: 277.1155.

*Synthesis of (4S)-**2***

According to general procedure B, from (4*S*)-**15** (0.60 g, 1.62 mmol), TEA (0.50 g, 4.94 mmol), and triphosgene (0.29 g, 0.98 mmol) in CH_2Cl_2 (40 mL) under an N_2 atmosphere, (4*S*)-**2** was afforded as thick yellowish needles (0.46 g, 81 %). ^{1}H NMR: δ = 1.40 and 1.46 (2×s, 9H; H-Boc), 1.95–2.32 (m, 5H; CH_2), 2.74–2.83 (m, 1H; CH_2), 3.54–3.83 (m, 6H; CH, CH_2, CH_3), 4.02–4.13 (m, 2H; CH_2), 4.38–4.66 ppm (m, 2H; CH); HRMS (ESI): m/z calcd for $C_{17}H_{26}N_3O_5$ $[M+H]^+$: 352.1872; found: 352.1874.

*Synthesis of (4R)-**2***

According to general procedure B, from (4*R*)-**15** (0.50 g, 1.35 mmol), triphosgene (0.24 g, 0.81 mmol), TEA (0.55 g, 5.44 mmol), and CH_2Cl_2 (45 mL) under an N_2 atmosphere, (4*R*)-**2** was afforded as thick yellowish needles (0.39 g, 82 %). ^{1}H NMR: δ = 1.42 and 1.47 (2×s, 9H; H-Boc), 1.93–2.56 (m, 6H; CH_2), 3.58–3.72 (m, 2H; CH_2), 3.72–3.77 (m, 3H; CH_3), 3.77–3.93 (m, 2H; CH_2), 4.28–4.41 (m, 1H; CH), 4.53–4.74 ppm (m, 2H; CH); HRMS (ESI): m/z calcd for $C_{17}H_{26}N_3O_5$ $[M+H]^+$: 352.1872; found: 352.1860.

*Synthesis of **17***

A solution of 4-aminobenzoic acid (3.00 g, 21.88 mmol) in ethyl formate (50 mL) was heated to reflux for 24 h. Then the precipitate was filtered and washed thoroughly with CH_2Cl_2 to afford product **17** as a white solid (3.35 g, 93 %). ^{1}H NMR ([D_6]DMSO): δ = 7.69 and 7.71 (2×s, 2H; Ph-H), 7.90 and 7.92 (2×s, 2H; Ph-H), 8.31–8.36 (m, 1H; CHO), 10.53 (s, 1H; NH), 12.81 ppm (br, 1H; COOH).

*Synthesis of (4S)-**18***

According to general procedure D, from DEAD (40 % in toluene, 4.80 g, 11.02 mmol), (4*R*)-hydroxyproline (2.01 g, 8.19 mmol), **17** (1.50 g, 9.08 mmol), and PPh_3 (3.10 g, 11.82 mmol), (4*S*)-**18** was afforded as a white solid (1.84 g, 57 %). ^{1}H NMR: δ = 1.46 and 1.50 (2×s, 9H; H-Boc), 2.37–2.63 (m, 2H; CH_2), 3.66–3.87 (m, 5H; CH_3, CH_2), 4.46–4.64 (m, 1H; CH), 5.54 (s, 1H; CH), 7.11–7.16 (m, 1H; NH), 7.61–8.18 (m, 4H; Ph-H), 8.44–8.92 ppm (m, 1H; CHO).

*Synthesis of (4R)-**18***

According to general procedure D, from DEAD (40 % in toluene, 4.80 g, 11.02 mmol), (4*S*)-hydroxyproline (2.00 g, 8.19 mmol), **17** (1.50 g, 9.08 mmol), and PPh_3 (3.10 g, 11.82 mmol), (4*R*)-**18** was afforded as a white solid (2.00 g, 62 %). This compound was roughly purified by column chromatography and used directly in subsequent syntheses.

*Synthesis of (4S)-**19***

According to general procedure C, from compound (4*S*)-**12** (1.00 g, 4.09 mmol), HOBt (0.68 g, 5.03 mmol), DIPEA (1.93 g, 14.93 mmol), PyBOP (2.60 g, 5.00 mmol), and **17** (0.82 g, 4.97 mmol) in dry DMF (5 mL) and CH_2Cl_2 (50 mL), the residue was purified by silica chromatography with ethyl acetate/hexane (from 1/1 to 2/1, v/v) to afford (4*S*)-**19** as a white foam (1.36 g, 85 %). ^{1}H NMR: δ = 1.46 and 1.48 (2×s, 9H; H-Boc), 2.03–2.14 (m, 1H; CH_2), 2.48–2.61 (m, 1H; CH_2), 3.60–3.86 (m, 5H; CH_2, CH_3), 4.33–4.48 (m, 1H; CH), 4.87–4.95 (m, 1H; CH), 7.13–7.20 (m, 1H; NH), 7.48–7.91 (m, 5H; NH, Ph-H), 8.42–8.86 ppm (m, 1H; CHO).

*Synthesis of (4R)-**19***

According to general procedure C, from (4*R*)-**12** (1.00 g, 4.09 mmol), HOBt (0.68 g, 5.03 mmol), DIPEA (1.93 g, 14.93 mmol), PyBOP (2.60 g,

5.00 mmol), and **17** (0.82 g, 4.97 mmol) in dry DMF (5 mL) and CH_2Cl_2 (50 mL), the residue was roughly purified by silica chromatography with ethyl acetate/hexane (from 1/1 to 2/1, v/v) and used directly for subsequent syntheses.

*Synthesis of (4S)-**6***

According to general procedure B, from (4*S*)-**18** (0.60 g, 1.53 mmol), triphosgene (0.39 g, 1.31 mmol), and TEA (1.00 g, 9.88 mmol) in CH_2Cl_2 (60 mL) under an N_2 atmosphere, (4*S*)-**6** was afforded as thick yellowish needles (0.47 g, 82%). ^{1}H NMR: δ = 1.46 and 1.50 (2×s, 9H; H-Boc), 2.42–2.64 (m, 2H; CH_2), 3.69 and 3.70 (2×s, 3H; CH_3), 3.71–3.86 (m, 2H; CH_2), 4.49 (dd, J = 1.4, 8.5 Hz, 1/2H; CH), 4.62 (dd, J = 1.2, 9.3 Hz, 1/2H; CH), 5.52–5.62 (m, 1H; CH), 7.46 (d, J = 8.3 Hz, 2H; Ph-H), 8.04 ppm (d, J = 8.1 Hz, 2H; Ph-H).

*Synthesis of (4R)-**6***

According to general procedure B, from (4*R*)-**18** (0.60 g, 1.53 mmol), TEA (1.00 g, 9.88 mmol), and triphosgene (0.35 g, 1.18 mmol) in CH_2Cl_2 under an N_2 atmosphere, (4*R*)-**6** was afforded as thick yellowish needles (0.48 g, 84%). ^{1}H NMR: δ = 1.45 and 1.48 (2×s, 9H; H-Boc), 2.30–2.40 (m, 1H; CH_2), 2.49–2.60 (m, 1H; CH_2), 3.66–3.90 (m, 5H; CH_2, CH_3), 4.40–4.57 (m, 1H; CH), 5.52–5.57 (m, 1H; CH), 7.48 (d, J = 8.2 Hz, 2H; Ph-H), 8.07 ppm (d, J = 8.3 Hz, 2H; Ph-H).

*Synthesis of (4S)-**7***

According to general procedure B, from (4*S*)-**19** (0.60 g, 1.53 mmol), TEA (1.00 g, 9.88 mmol), and triphosgene (0.39 g, 1.31 mmol) in CH_2Cl_2 under an N_2 atmosphere, (4*S*)-**7** was afforded thick yellowish needles (0.45 g, 79%). ^{1}H NMR: δ = 1.46 and 1.48 (2×s, 9H; H-Boc), 2.02–2.12 (m, 1H; CH_2), 2.49–2.61 (m, 1H; CH_2), 3.60–3.86 (m, 5H; CH_2, CH_3), 4.33–4.48 (m, 1H; CH), 4.87–4.95 (m, 1H; CH), 7.48 (d, J = 8.3 Hz, 2H; Ph-H), 7.77–8.04 ppm (m, 3H; Ph-H, NH); HRMS (ESI): *m/z* calcd for $C_{19}H_{24}N_3O_5$ $[M+H]^+$: 374.1716; found: 374.1710.

*Synthesis of (4R)-**7***

According to general procedure B, from (4*R*)-**19** (0.60 g, 1.53 mmol), TEA (1.00 g, 9.88 mmol), and triphosgene (0.39 g, 1.31 mmol) in CH_2Cl_2 under an N_2 atmosphere, (4*R*)-**7** was afforded as thick yellowish needles (0.49 g, 86%). ^{1}H NMR: δ = 1.43 and 1.47 (2×s, 9H; H-Boc), 2.26–2.49 (m, 2H; CH_2), 3.35–3.96 (m, 5H; CH_2, CH_3), 4.29–4.52 (m, 1H; CH), 4.66–4.81 (m, 1H; CH), 6.40–6.85 (m, 1H; CH), 7.46 (d, J = 8.3 Hz, 2H; Ph-H), 7.80–7.91 ppm (m, 2H; Ph-H); HRMS (ESI): *m/z* calcd for $C_{19}H_{24}N_3O_5$ $[M+H]^+$: 374.1716; found: 374.1720.

*Synthesis of **20***

Acid **17** (2.00 g, 12.11 mmol) and pentafluorophenol (2.60 g, 14.13 mmol) were dissolved in DMF (100 mL) and stirred for 10 min before EDC (2.78 g, 14.50 mmol) was then added. After stirring for 18 h and evaporation of the solvents in vacuo, the reaction mixture was dissolved in ethyl ethanoate and washed with a saturated aqueous solution of NH_4Cl. After the organic phase had been dried over $MgSO_4$, evaporation of the solvents in vacuum yielded **20** as a white solid (2.81 g, 70%). ^{1}H NMR ([D$_6$]DMSO): δ = 7.84 and 7.86 (2×s, 2H; Ph-H), 8.15 and 8.16 (2×s, 2H; Ph-H), 8.38–8.43 (m, 1H; CHO), 10.77 ppm (s, 1H; NH).

*Synthesis of (4S)-**21***

A solution of (4*S*)-**24** (see the Supporting Information, 0.47 g, 2.52 mmol) and DIPEA (1.30 g, 10.06 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to a solution of **20** (1.00 g, 3.02 mmol) in dry DMF (10 mL) at room temperature. After the reaction mixture had been stirred overnight, it was washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic phase was dried with $MgSO_4$. Purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) as the eluent afforded (4*S*)-**21** as colorless crystals (0.55 g, 65%).^{1}H NMR: δ = 2.07–2.16 (m, 4H; CH_3, CH_2), 2.51–2.60 (m, 1H; CH_2), 3.76–3.88 (m, 5H; CH_3, CH_2), 4.54–4.59 (m, 1H; CH), 4.98–5.05 (m, 1H; CH), 7.12–7.21 (m, 1H; NH), 7.62–8.01 (m, 5H; NH, Ph-H), 8.41–8.87 ppm (m, 1H; CHO).

*Synthesis of (4R)-**21***

A solution of (4*R*)-**24** (see the Supporting Information, 0.56 g, 3.01 mmol) and DIPEA (1.30 g, 10.06 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to a solution of **20** (1.20 g, 3.62 mmol) in dry DMF (10 mL) at room temperature. After the reaction mixture had been stirred overnight, it was washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic phase was dried with $MgSO_4$. Purification by column chromatography with CH_2Cl_2/MeOH (20/1, v/v) as the eluent afforded (4*R*)-**21** as colorless crystals (0.87 g, 87%).^{1}H NMR ([D$_6$]DMSO): δ = 2.02–2.16 (m, 4H; CH_2, CH_3), 2.26–2.39 (m, 1H; CH_2), 3.38–3.49 (m, 2H; CH_2), 3.64 (s, 3H; CH_3), 4.42–4.61 (m, 2H; CH), 7.62–7.68 (m, 2H; Ph-H), 7.76–7.83 (m, 2H; Ph-H), 8.41–8.53 (m, 1H; CHO), 10.18 ppm (s, 1H; NH).

*Synthesis of (4S)-**8***

According to general procedure B, from (4*S*)-**21** (0.42 g, 1.26 mmol), TEA (0.78 g, 7.71 mmol), and triphosgene (0.31 g, 1.04 mmol) in CH_2Cl_2 (50 mL) under an N_2 atmosphere, (4*S*)-**8** was afforded as thick yellowish needles (0.33 g, 83%). ^{1}H NMR: δ = 2.03–2.11 (m, 4H; CH_3, CH_2), 2.51–2.59 (m, 1H; CH_2), 3.70–3.87 (m, 5H; CH_3, CH_2), 4.50–4.59 (m, 1H; CH), 4.98–5.04 (m, 1H; CH), 7.46–7.51 (m, 2H; Ph-H), 7.89–7.94 (m, 2H; Ph-H), 8.03–8.16 ppm (m, 1H; NH).

*Synthesis of (4R)-**8***

According to general procedure B, from (4*R*)-**21** (0.40 g, 1.20 mmol), TEA (0.75 g, 7.41 mmol), and triphosgene (0.27 g, 0.91 mmol) in CH_2Cl_2 (50 mL) under an N_2 atmosphere, (4*R*)-**8** was afforded as thick yellowish needles (0.30 g, 79%). This monomer was used directly for polymerization.

*Synthesis of Poly-(4S)-**1***

According to general procedure E, $NiCl_2{\cdot}6H_2O$ (9.30 mg, 10 wt% in MeOH, 3.91×10^{-3} mmol) was added to (4*S*)-**1** (0.10 g, 0.39 mmol) in CH_2Cl_2 (0.6 mL) or THF (0.4 mL) under an N_2 atmosphere at room temperature for 24 h. Purification by column chromatography with MeOH/CH_2Cl_2 (from 1/20 to 1/10,v/v) as the eluent afforded poly-(4*S*)-**1** as a brown solid (82 mg, 82%). ^{1}H NMR: δ = 1.05–2.09 (br, 11H; H-Boc, CH_2), 3.33–4.04 (br, 5H; CH_3, CH_2), 4.04–5.50 ppm (br, 2H; CH, CH).

*Synthesis of Poly-(4R)-**1***

According to general procedure E, from monomer (4*R*)-**1** (0.10 g, 0.39 mmol) and $NiCl_2{\cdot}6H_2O$ (9.30 mg, 10 wt% in MeOH, 3.91×10^{-3} mmol) in CH_2Cl_2 (0.6 mL), poly-(4*R*)-**1** was afforded as a brown solid (70 mg, 70%). ^{1}H NMR: δ = 1.15–1.65 (br, 9H; H-Boc), 1.75–2.70 (br, 2H; CH_2), 2.81–4.06 (br, 5H; CH_3, CH_2), 4.07–4.85 ppm (br, 2H; CH).

*Synthesis of Poly-(4S)-**2***

According to general procedure E, from (4*S*)-**2** (100 mg, 0.28 mmol) and $NiCl_2{\cdot}6H_2O$ (6.70 mg, 2.82×10^{-3} mmol, 10 wt% in MeOH) in CH_2Cl_2 (0.6 mL), poly-(4*S*)-**2** was afforded as a brown solid (47 mg, 47%). ^{1}H NMR: δ = 0.95–1.65 (br, 9H; H-Boc), 1.65–2.89 (br, 6H; CH_2), 2.89–4.17 (br, 7H; CH_3, CH_2), 4.07–5.57 ppm (br, 3H; CH).

*Synthesis of Poly-(4R)-**2***

According to general procedure E, from (4*R*)-**2** (100 mg, 0.28 mmol) and $NiCl_2{\cdot}6H_2O$ (6.70 mg, 2.82×10^{-3} mmol, 10 wt% in MeOH) in CH_2Cl_2 (0.6 mL), poly-(4*R*)-**2** was afforded as a brown solid (64 mg, 64%). ^{1}H NMR: δ = 1.07–1.67 (br, 9H; H-Boc), 1.67–2.53 (br, 5H; CH_2), 2.53–2.96 (br, 1H; CH_2), 3.05–4.17 (br, 7H; CH_3, CH_2), 4.17–5.13 ppm (br, 3H; CH).

*Synthesis of Poly-(4S)-**6***

According to general procedure E, from (4*S*)-**6** (100 mg, 0.26 mmol) and $NiCl_2{\cdot}6H_2O$ (64 mg, 2.69×10^{-3} mmol, 1 wt% in MeOH) in THF (0.2 mL), poly-(4*S*)-**6** was afforded as brown solid (55 mg, 55%). ^{1}H NMR: δ = 0.94–1.77 (br, 9H; H-Boc), 1.79–2.91 (br, 2H; CH_2), 3.00–

4.10 (br, 4H; CH_3, CH_2), 4.18–4.72 (br, 1H; CH_2), 4.72–6.28 (br, 2H; CH), 6.28–8.35 ppm (br, 2H; Ph-H).

*Synthesis of Poly-(4R)-**6***

According to general procedure E, from (4*R*)-**6** (100 mg, 0.26 mmol) and $NiCl_2{\cdot}6H_2O$ (64 mg, 2.69×10^{-3} mmol, 1 wt% in MeOH) in THF (0.2 mL), poly-(4*R*)-**6** was afforded as a brown solid (48 mg, 48%). ^{1}H NMR: $\delta=1.03$–1.70 (br, 9H; H-Boc), 1.86–2.91 (br, 2H; CH_2), 3.05–4.71 (br, 5H; CH_3, CH_2), 4.71–6.30 (br, 2H; CH), 6.28–8.09 ppm (br, 2H; Ph-H).

*Synthesis of Poly-(4S)-**7***

According to general procedure E, from (4*S*)-**7** (100 mg, 0.26 mmol) and $NiCl_2{\cdot}6H_2O$ (77 mg, 3.24×10^{-3} mmol, 1 wt% in MeOH) in THF (0.2 mL), poly-(4*S*)-**7** was afforded as a brown solid (62 mg, 62%). ^{1}H NMR: $\delta=1.27$–1.57 (br, 9H; H-Boc), 1.66–2.96 (br, 2H; CH_2), 2.99–4.10 (br, 5H; CH_3, CH_2), 4.12–6.06 (br, 2H; CH), 6.08–9.27 ppm (br, 4H; Ph-H, NH).

*Synthesis of Poly-(4R)-**7***

According to general procedure E, from (4*R*)-**7** (100 mg, 0.26 mmol) and $NiCl_2{\cdot}6H_2O$ (64 mg, 2.69×10^{-3} mmol, 1 wt% in MeOH) in THF (0.2 mL), poly-(4*R*)-**7** was afforded as a brown solid (55 mg, 55%). ^{1}H NMR: $\delta=0.99$–1.78 (br, 9H; H-Boc), 1.92–2.99 (br, 2H; CH_2), 2.99–5.06 (br, 5H; CH_3, CH_2), 5.06–7.66 (br, 2H; CH), 7.78–9.20 ppm (br, 1H; Ph-H).

*Synthesis of Poly-(4S)-**8***

According to general procedure E, from (4*S*)-**8** (100 mg, 0.31 mmol) and $NiCl_2{\cdot}6H_2O$ (38 mg, 1.60×10^{-3} mmol, 1 wt% in MeOH) in THF (0.2 mL), poly-(4*S*)-**8** was afforded as a brown solid (60 mg, 60%). ^{1}H NMR (CD_3OD): $\delta=1.69$–3.07 (br, 5H; CH_3, CH_2), 3.41–4.16 (br, 5H; CH_3, CH_2), 4.62–6.20 (br, 3H; CH, NH), 6.26–7.29 ppm (br, 2H; Ph-H).

*Synthesis of Poly-(4R)-**8***

According to general procedure E, from (4*R*)-**8** (100 mg, 0.31 mmol) and $NiCl_2{\cdot}6H_2O$ (38 mg, 1.60×10^{-3} mmol, 1 wt% in MeOH) in THF (0.2 mL), poly-(4*R*)-**8** was afforded as a brown solid (46 mg, 46%). ^{1}H NMR (CD_3OD): $\delta=1.73$–2.98 (br, 5H; CH_3, CH_2), 3.39–4.24 (br, 5H; CH_3, CH_2), 4.43–5.92 (br, 3H; CH, NH), 6.62–7.76 ppm (br, 2H; Ph-H).

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