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Synthesis of Optically Active Polyguanidines by Polyaddition Reaction of Biscarbodiimides with Chiral Diamines

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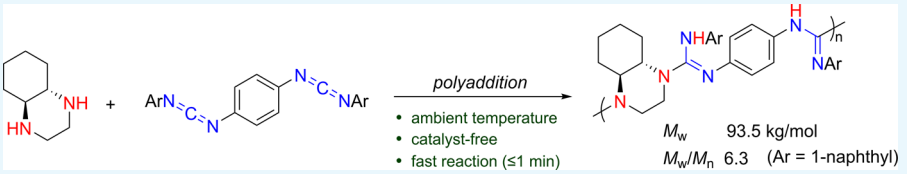

ABSTRACT: Herein, we present the first study on the polyaddition reaction of biscarbodiimides with chiral diamines, which focuses on a definite case using optically active *trans*-4a,8a-decahydroquinoxaline and 1,4-phenylenebis(arylcarbodiimide)s, which readily react with each other under ambient and catalyst-free conditions. The specific reactivity allows for facile access to not only the corresponding chiral polyguanidines under balanced stoichiometry but also their oligomeric analogues under imbalanced stoichiometry via a step-by-step procedure. Spectroscopic, chromatographic, and computational characterization of the novel molecular chains containing arrayed guanidines have revealed their structural, optical, and conformational properties as well as the mechanism of polymerization assisted by molecular association. Their potential use as asymmetric catalysts is also described.

INTRODUCTION

Formation of molecules by repeating nucleophilic addition of bifunctional nucleophiles with bifunctional electrophiles, namely, polyaddition, is one of the most basic concepts in polymer synthesis. Particular representatives are syntheses of polyurethanes and polyureas by means of diols/diamines as bifunctional nucleophiles and diisocyanates (OCN-R-NCO) as bifunctional electrophiles.[1,2] Despite their successful developments, the use of biscarbodiimides (R′NCN-R-NCNR′), nitrogen analogues of diisocyanates, as bifunctional electrophiles has been little studied. To our knowledge, the only relevant works have been those reported by Iwakura and Noguchi more than half a century ago, in which some diols, dithiols, and diamines have been adopted as bifunctional nucleophiles although they are all achiral.[3,4] Needless to say, their replacement to chiral bifunctional nucleophiles can give an opportunity of preparing optically active copolymers, which may be valuable to be studied at last due to growing interest and demand for (chir)optical properties of materials.

Herein, we present the first study on the polyaddition reaction of biscarbodiimides with chiral diamines for preparing a new type of optically active chiral polyguanidines.[5−12] The hydroamination of carbodiimides is one of the most common methods for access to guanidines that are versatile as ligands, catalysts, and other functional molecules including polymers.[13] Iwakura and Noguchi dealt with straight-chain achiral diamines including di/tri/tetra/hexa/hepta/nonamethylene diamines and biscarbodiimides including 1,3/1,4-phenylenebis(*tert*-butylcarbodiimide) and 1,4-phenylenebis(2,6-xylylcarbodiimide), introducing that the reactions proceeded stepwise in toluene under reflux to provide the corresponding polyguanidines having intrinsic viscosities up to 0.84 and molar masses up to 15,000 in high yields without apparent side reactions (Figure 1a).[3,4] At that time, the structural analysis and molar mass determination were based on only infrared (IR) spectroscopy and vapor pressure osmometry (VPO),

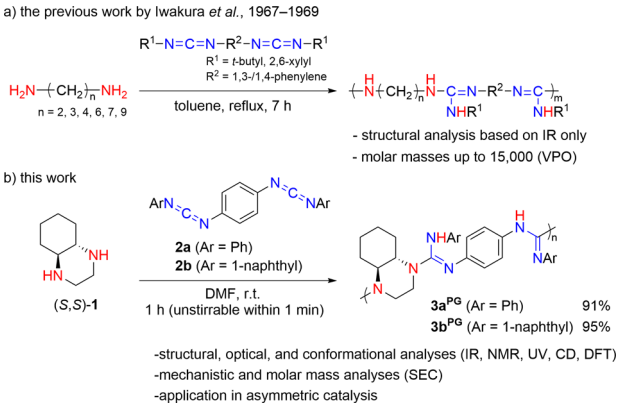

Figure 1. Polyaddition reaction of biscarbodiimides with diamines.

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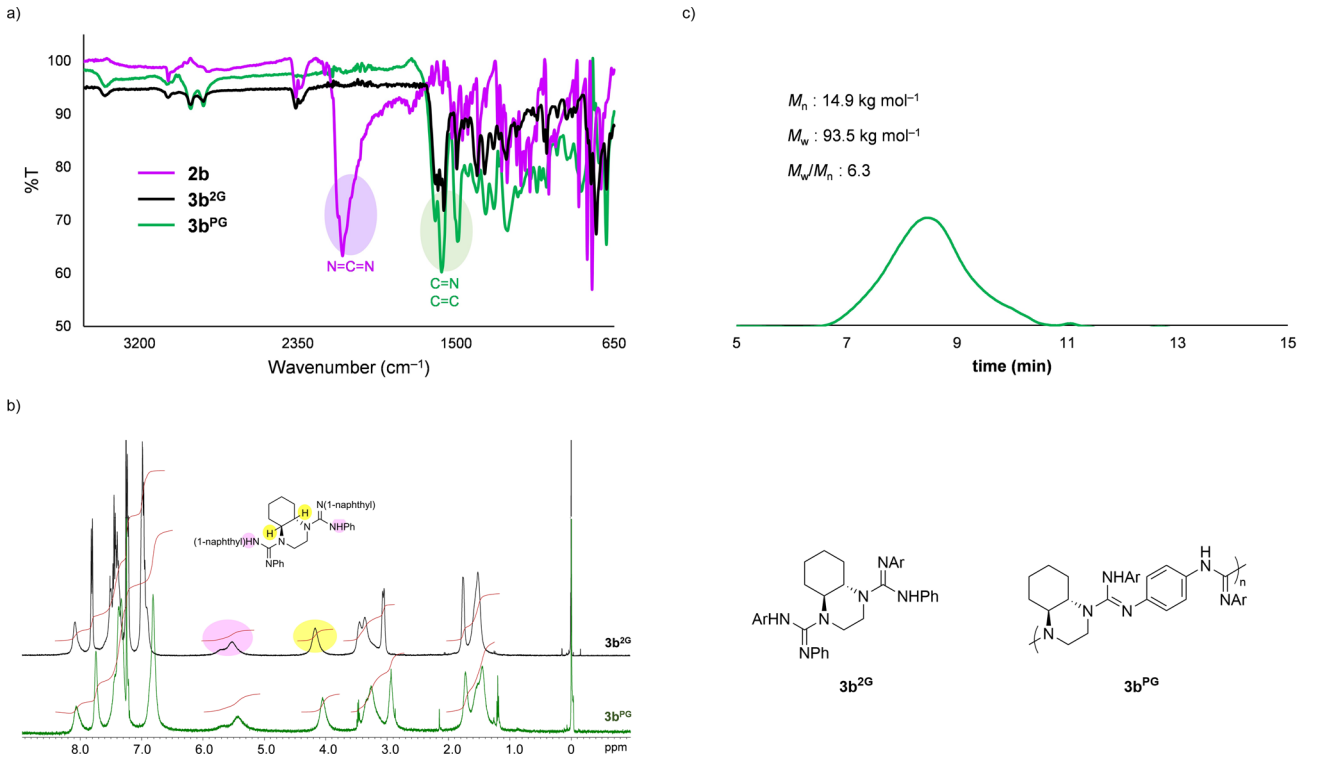

Figure 2. Characterization of $\mathbf{3b}^{PG}$ as compared to $\mathbf{3b}^{2G}$ (Ar = 1-naphthyl): (a) IR spectra of **2b**, $\mathbf{3b}^{2G}$, and $\mathbf{3b}^{PG}$, (b) ^{1}H NMR spectra for $\mathbf{3b}^{2G}$ (ca. 25 °C) and $\mathbf{3b}^{PG}$ (50 °C) in $CDCl_3$, (c) SEC chromatogram of $\mathbf{3b}^{PG}$ (eluent, THF with 5% NEt_3, polystyrene standard).

respectively. Thus, their seminal work prompted us to design the polyaddition reaction between aliphatic chiral diamines and biscarbodiimides containing aromatic residues with detailed product characterization by means of current theoretical as well as experimental standards, such as density functional theory (DFT) calculation, nuclear magnetic resonance (NMR) spectroscopy, and size-exclusion chromatography (Figure 1b). In particular, we focused on (4a*S*,8a*S*)-decahydroquinoxaline,[14] (*S*,*S*)-**1**, as a chiral diamine comonomer because it was expected (a) to be highly reactive that allows for the desired polyaddition under mild conditions, (b) structurally not to involve the formation of cyclic oligomers/polymers, which renders the polymerization system to be simpler and more predictable, and (c) to provide an effective chiral environment for application such as asymmetric catalysis.

RESULTS AND DISCUSSION

In the light of the previous report that guanidine formations by the addition of cyclic secondary amines, such as piperidine and piperazine, to *N*,*N*′-diaryl substituted monocarbodiimides occurred smoothly under catalyst-free conditions,[15] we started our investigations by exploring the reaction of (*S*,*S*)-**1** with an equimolar amount of 1,4-phenylenebis(phenylcarbodiimide) (**2a**) in *N*,*N*-dimethylformamide (DMF) at ambient temperature (Figure 1b). Interestingly, the reaction mixture became highly viscous like a gel and unstirrable within a minute, implying that some reactions took place extremely fast, which was in sharp contrast to any case with chiral primary diamines such as *trans*-1,2-cyclohexanediamine, *trans*-1,2-diphenyl-1,2-ethanediamine, and 1,1′-binaphthyl-2,2′-diamine instead of **1** under identical conditions. The resulting solid obtained by washing with methanol after leaving for 1 h while agitation was no longer possible and drying in *vacuo* was characterized by IR spectroscopy, which suggested that the desired polymerization proceeded to afford chiral polyguanidine $\mathbf{3a}^{PG}$ in 91% yield since absorption peaks reasonable for guanidine were observed without any bands around 2100 cm^{-1} distinctive for carbodiimide. However, $\mathbf{3a}^{PG}$ was hardly soluble in common organic solvents and therefore hard to be characterized in solution (see Supporting Information, Tables S1 and S2). Fortunately, the use of 1,4-phenylenebis(1-naphthylcarbodiimide) (**2b**) instead of **2a** resulted in a similar reaction behavior (Figure 1b) and IR spectrum (Figure 2a), and the corresponding chiral polyguanidine $\mathbf{3b}^{PG}$ obtained in 95% yield was soluble in a few solvents including chloroform ($CHCl_3$) under dryer heating. For comparison, its monomeric analogue $\mathbf{3b}^{2G}$ (2G stands for two guanidino groups) was prepared (Figure 2). Note that the tautomerism of guanidino groups in the given structure of $\mathbf{3b}^{2G}$ was estimated by DFT calculations (see Supporting Information, chapter II-2). The IR (Figure 2a) and ^{1}H NMR spectra ($CDCl_3$, Figure 2b) for $\mathbf{3b}^{2G}$ and $\mathbf{3b}^{PG}$ indicated their high-level spectral similarity, which convinced us that the present polyaddition reaction took place without serious side reactions.[4] The number-average molar mass (M_n), weight-average molar mass (M_w), and dispersity (M_w/M_n) of $\mathbf{3b}^{PG}$ were estimated by SEC using polystyrene standards eluting with tetrahydrofuran (THF) containing 5% triethylamine to be 14.9 kg mol^{-1}, 93.5 kg mol^{-1}, and 6.3, respectively (Figure 2c). These values may be valid albeit with some over-/underestimation due to an affinity of polyguanidines for SEC columns.[5]

The large dispersity of $\mathbf{3b}^{PG}$ rather deviates from its theoretical value based on the classical theory of stepwise polymerization, implying that all molecules are not equally reactive independent of molar mass.[16,17] Such a situation in the present system might come from the reactivity of the

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carbodiimide group affectable via the resonance effect on a benzene ring. We thus carried out DFT calculations (B3LYP/6-31G*, Figure 3) to estimate the reactivity of **2b** and its

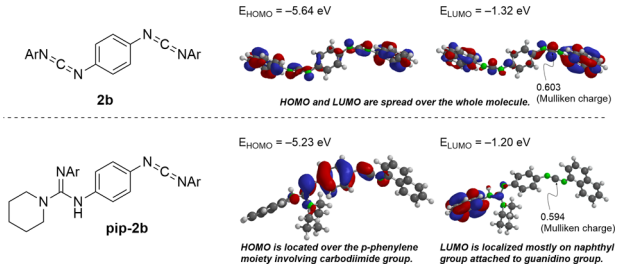

Figure 3. Frontier molecular orbitals and electronic properties of **2b** and **pip-2b** estimated by DFT calculations (Ar = 1-naphthyl).

mono-piperidine adduct, **pip-2b**. The computations show that **2b** has a lower LUMO level (−1.32 eV) and a higher Mulliken charge value (0.603) compared to those in **pip-2b** (−1.20 eV, 0.594), in which the carbodiimide group of **pip-2b** is even not involved in the corresponding LUMO localized mostly on the naphthyl group, suggesting that **2b** could be more electrophilic than **pip-2b**. In fact, it was experimentally shown that **2b** could be approximately 7-fold more reactive than **1-2b** (see Supporting Information, chapter III). However, this kind of reactivity trend is not unusual[18] and does not explain the polyaddition behavior that proceeds very fast to afford $\mathbf{3b}^{PG}$ with the large dispersity (Figures 1b and 2c). We thus paid attention to not only the LUMO in **pip-2b** but also its HOMO located over the *p*-phenylene moiety and the fact that their energy gap (4.03 eV) is narrower than that of **2b** (4.32 eV), which led us to anticipate intermolecular associations that become stronger as the chain length increases to offer a situation where longer chains are more likely reactive (propagative).

To verify this hypothesis, we conducted a step-by-step chain-elongation experiment as follows. First, **1-2b-1** (containing ca. 7 mol % of $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_2$) was prepared by reacting **2b** with 3 equivalents of (*S*,*S*)-**1** in CH_2Cl_2 at room temperature followed by the removal of water-soluble unreacted (*S*,*S*)-**1** through extraction (Figure 4a, 1st elongation). Subsequently, the **1-2b-1** was treated with 0.5 equivalents of **2b** under similar conditions, which afforded a mixture containing only molecular chains represented by $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_n$ after removal of the solvent (Figure 4a, 2nd elongation, the value of *n* was determined to be 3 on average by ^{1}H NMR spectroscopy). Likewise, the $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_n$ was further extended to $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_{2n+1}$ by treating with a half molar of **2b** under the same conditions (Figure 4a, 3rd elongation, the value of $2n + 1$ was determined to be 7 on average by ^{1}H NMR spectroscopy). Note that all these reaction systems were homogeneous. No reaction took place when $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_7$ was mixed with 3 equivalents of (*S*,*S*)-**1** in $CDCl_3$ at room temperature, indicating that no backward reactions are involved under ambient conditions and all the above elongations are kinetically controlled (see Supporting Information, chapter V). Finally, the **1-2b-1**, $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_3$, and $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_7$ containing an amino group at both ends were quantitatively end-capped by reacting with 1-naphthylphenylcarbodiimide to derive into the corresponding oligoguanidines $\mathbf{3b}^{4G}$, $\mathbf{3b}^{8G}$, and $\mathbf{3b}^{16G}$, respectively (Figure 4a, 4G/8G/16G stands for 4/8/16 guanidino groups on average), which were analyzed by SEC under the conditions that were used for $\mathbf{3b}^{PG}$. Not surprisingly, the SEC profile of $\mathbf{3b}^{4G}$ (the theoretical molar mass, M^{theo}, is 1180 g mol^{-1}) formed via the 1st elongation was relatively sharp and unimodal, which was detected with a M_n of 0.66 kg mol^{-1}, a M_w of 0.82 kg mol^{-1}, and the dispersity of 1.2 (Figure 4c, purple). By contrast, the SEC signal for $\mathbf{3b}^{8G}$ was multimodal having three characteristic peaks that could be attributed to $\mathbf{3b}^{12G,8G,4G}$ derived from $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_5$, $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_3$, and **1-2b-1** in ascending order of elution time (Figure 4c,

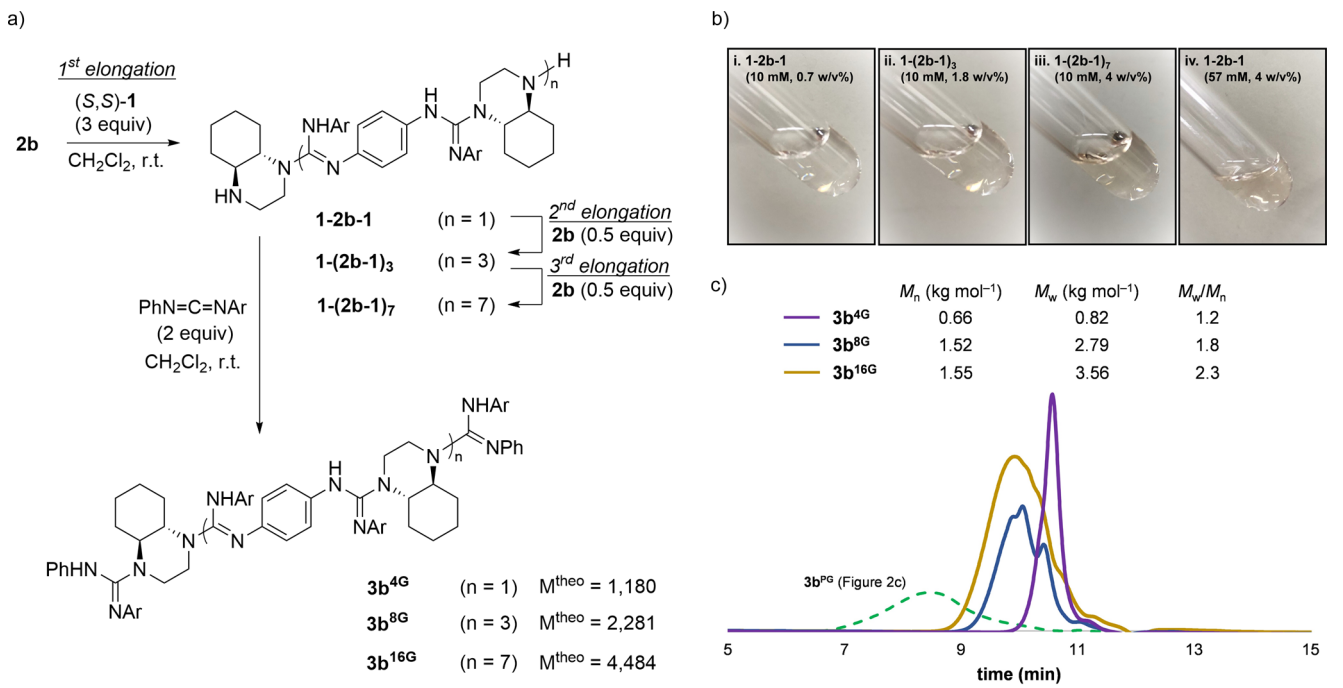

Figure 4. Step-by-step chain-elongation experiment (Ar = 1-naphthyl): (a) synthetic scheme; (b) photographs of **1-2b-1**, $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_3$, and $\mathbf{1}\text{-}(\mathbf{2b}\text{-}\mathbf{1})_7$ in CH_2Cl_2 at a defined concentration; (c) SEC chromatograms of $\mathbf{3b}^{4G}$, $\mathbf{3b}^{8G}$, and $\mathbf{3b}^{16G}$ (eluent, THF with 5% NEt_3, polystyrene standard).

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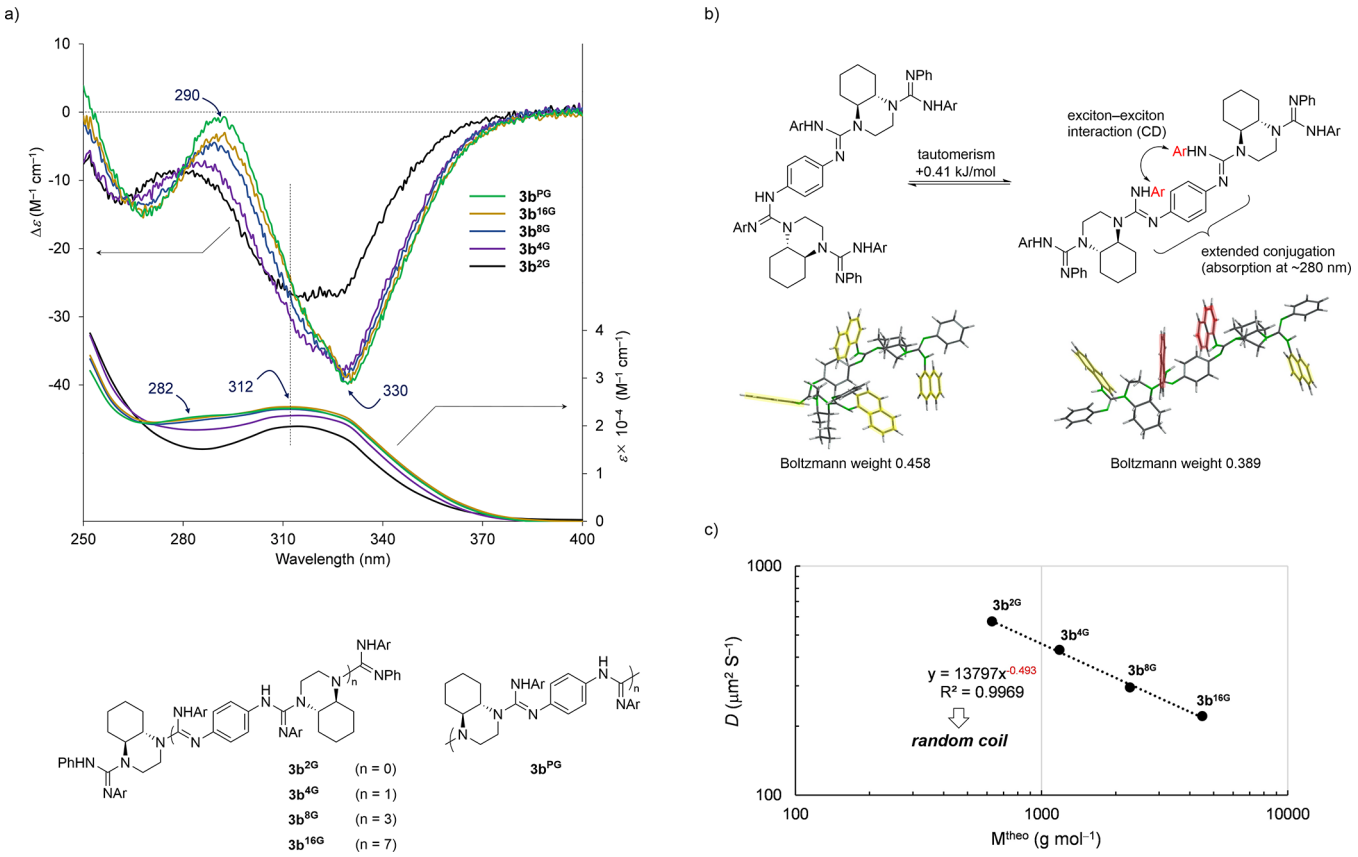

Figure 5. Optical and conformational aspects of $\mathbf{3b}^{PG}$ and its analogues (Ar = 1-naphthyl): (a) CD (25 °C) and absorption (ca. 25 °C) spectra of $\mathbf{3b}^{2G}$, $\mathbf{3b}^{4G}$, $\mathbf{3b}^{8G}$, $\mathbf{3b}^{16G}$, and $\mathbf{3b}^{PG}$ in $CHCl_3$ (0.02 M), (b) tautomeric and conformational preference of $\mathbf{3b}^{4G}$ estimated by molecular mechanics calculations, (c) correlation between molar mass (M^{theo}) and self-diffusion coefficient (D) determined by DOSY.

blue), implying that the 2nd elongation was no longer dominated by the electronically controlled reactivity that should result in preferential consumption of **1**-**2b**-**1** to form **1**-$(\mathbf{2b}\text{-}\mathbf{1})_3$ much more selectively than **1**-$(\mathbf{2b}\text{-}\mathbf{1})_5$. The turned reactivity was arguably taken over the third elongation since $\mathbf{3b}^{16G}$ appeared as an even broader distribution in SEC (Figure 4c, ocher). It should be noted that the reaction mixture of the first elongation was nearly colorless (Figure 4b-i), while those of the second (Figure 4b-ii) and third (Figure 4b-iii) elongations were apparently colored and the latter was more intense. The first elongation was much less colored even at a higher concentration (Figure 4b-iv). These results support the computational prediction that intermolecular associations, possibly driven by $\pi-\pi$/n$-\pi^*$ interactions between one main chain and the other side chain (see Supporting Information, chapter VI), can be involved in the present polyaddition to provide $\mathbf{3b}^{PG}$ with the large dispersity.

With not only $\mathbf{3b}^{2G}$ but also $\mathbf{3b}^{4G}$, $\mathbf{3b}^{8G}$, and $\mathbf{3b}^{16G}$ in hand, the spectroscopic characterization of $\mathbf{3b}^{PG}$ was continued to explore its optical and conformational properties. In contrast to the above-mentioned IR and ^{1}H NMR studies, there was an arguable difference between $\mathbf{3b}^{2G}$ and $\mathbf{3b}^{PG}$ in their ultraviolet (UV) spectra; an absorption band with a peak at 312 nm assignable to $\pi-\pi^*$ transition of the naphthyl ring was shared by both cases, whereas the peak for $\mathbf{3b}^{PG}$ remained broad around 280 nm possibly due to the $\pi-\pi^*$ transition of the *p*-phenylene moiety in the main chain (Figure 5a, lower). A clearer difference was observed in their circular dichloism (CD) spectra; $\mathbf{3b}^{2G}$ showed a non-split negative Cotton effect with a line shape according to its UV absorption, while $\mathbf{3b}^{PG}$ showed a negative first Cotton effect at 330 nm and a positive second Cotton effect at 290 nm, namely, a split Cotton effect centered at 312 nm (Figure 5a, upper). Notably, the absorption maximum at 312 nm was common in $\mathbf{3b}^{4G/8G/16G}$ to become more apparent that there is another absorption at around 280 nm except $\mathbf{3b}^{2G}$. Such a chain-length dependence appeared more prominently in CD, making the process of growth in the split Cotton effect with increasing the average chain length so clear. The structural origin of these optical behaviors was explored by estimating the relative energies of 16 possible tautomers in $\mathbf{3b}^{4G}$ through molecular mechanics calculation, suggesting that two tautomers in $\mathbf{3b}^{4G}$ could be dominantly stable and one of them could have both a possibility of an extended conjugation system of the *p*-phenylene moiety and that of an exciton–exciton interaction between two internal naphthyl rings (Figure 5b). The computation also suggested that the corresponding molecular chains such as $\mathbf{3b}^{PG}$ could be rather flexible due to the fast tautomerism of guanidino groups. To make sure of the latter, diffusion-ordered NMR spectroscopy (DOSY) was utilized.[19] DOSY spectra of $\mathbf{3b}^{2G/4G/8G/16G}$ were recorded with a solute concentration of 1 w/v % in $CDCl_3$ at 35 °C, in which a 3 mm NMR tube was used to minimize convection in the tube and analyzed by the maximum entropy method.[20] The resulting self-diffusion coefficients (D, μm^2 S^{-1}) were found to be 573 ($\mathbf{3b}^{2G}$), 431 ($\mathbf{3b}^{4G}$), 295 ($\mathbf{3b}^{8G}$), and 221 ($\mathbf{3b}^{16G}$), respectively, which were well correlated with the corresponding M^{theo} in good accordance with the theory[21] that D is proportional to M

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to the power of ca. −0.5 under theta conditions for a random coil state (Figure 5c). Note that the most likely stable tautomerism of guanidino groups in $\mathbf{3b}^{\mathbf{4G}}$ on the calculation (Figure 5b) is adopted to give the structures of $\mathbf{3b}^{\mathbf{4G/8G/16G}}$ and $\mathbf{3b}^{\mathbf{PG}}$ in this article.

Finally, we explored the potential use of $\mathbf{3b}^{\mathbf{2G/4G/8G/16G}}$ and $\mathbf{3b}^{\mathbf{PG}}$ as a chiral Brønsted base organocatalyst.[22−25] The conjugate addition reaction between *trans*-*β*-nitrostyrene (**4**) and acetylacetone (**5**) was chosen as a test catalytic reaction. In the presence of 10 mol % of $\mathbf{3b}^{\mathbf{2G}}$, the reaction of **4** (0.5 M) with **5** (1.0 M) in CH_2Cl_2 at room temperature proceeded smoothly to give the corresponding adduct (*S*)-**6** after 1.5 and 24 h in 4 and 84% yields, respectively, with an enantioselectivity of 16% ee (Figure 6a). Interestingly, $\mathbf{3b}^{\mathbf{PG}}$

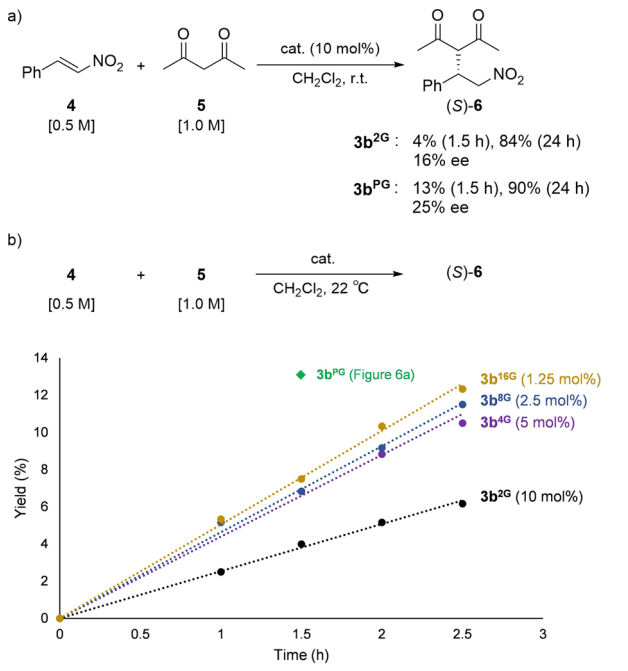

Figure 6. Catalytic conjugate addition reaction between **4** and **5**: (a) comparison of $\mathbf{3b}^{\mathbf{2G}}$ and $\mathbf{3b}^{\mathbf{PG}}$ with the same number of bisguanidine units, (b) comparison of $\mathbf{3b}^{\mathbf{2G}}$, $\mathbf{3b}^{\mathbf{4G}}$, $\mathbf{3b}^{\mathbf{8G}}$, and $\mathbf{3b}^{\mathbf{16G}}$ in the initial reaction stage.

exhibited a rather better catalytic performance in terms of both activity (13% yield in 1.5 h, 90% yield in 24 h) and stereoselectivity (25% ee) under identical conditions (Figure 6a). We therefore evaluated and compared catalytic activities of $\mathbf{3b}^{\mathbf{2G/4G/8G/16G}}$ in their initial reaction stage (Figure 6b), which indicated that the enhanced catalytic activity of $\mathbf{3b}^{\mathbf{PG}}$ could originate from the chain length. It should be noted that the stereoselectivity of $\mathbf{3b}^{\mathbf{4G}}$ (23% ee) was much higher than **1-2b-1** (7% ee) and comparable to $\mathbf{3b}^{\mathbf{PG}}$ (25% ee), indicating that the involvement of terminal amino groups in the catalysis of $\mathbf{3b}^{\mathbf{PG}}$ may be negligible, although the terminal structure of $\mathbf{3b}^{\mathbf{PG}}$ is unclear at this moment (see Supporting Information, chapter VII-4). Although mechanistic understanding is under investigation, not only an increased basicity of internal guanidino groups due to substituent resonance effect but also a substrate capturing by highly dense guanidino groups in the molecular chain may be of concern. Note that such enhancements in activity that clearly correlate with the size of oligomeric/polymeric catalysts are rare.[26] In addition, main chain functionalization of polymers through stepwise polymerizations has recently become a powerful tool for immobilizing chiral organocatalysts to polymers.[27,28] Though the above stereoinduction is yet immature, the present concept will offer a new tool for the development of polymeric chiral guanidine catalysts, rarely studied so far,[29,30] because of its design diversity as well as the ease of synthesis and characterization as demonstrated in this study.

CONCLUSIONS

In conclusion, we have introduced a new type of optically active polyguanidines, such as $\mathbf{3b}^{\mathbf{PG}}$ and its analogues $\mathbf{3b}^{\mathbf{2G/4G/8G/16G}}$, along with (a) their facile synthesis by the first polyaddition reaction between chiral diamines and biscarbodiimides, (b) their detailed characterization through spectroscopic, chromatographic, and computational analyses revealing not only their structural, optical, and conformational properties but also the molecular association-assisted polymerization mechanism, and (c) their tentative application in asymmetric catalysis. We believe that the study will provide a guide for designing and characterizing middle-sized and macrosized chiral guanidine molecules, which have been paid attention in synthetic chemistry, material sciences, chemical biology, and so on.

EXPERIMENTAL SECTION

General Information. Melting points were measured on an AS ONE ATM-01. NMR spectra were recorded using JEOL JNM-ECX-400S (^{1}H, 400 MHz and ^{13}C, 100 MHz) and JNM-ECA-500 W spectrometers (^{1}H, 500 MHz and ^{13}C, 125 MHz). Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. IR spectra were recorded on a JASCO IR-460 spectrometer with an ATR unit. Size exclusion chromatography (SEC) was performed on an analytical HPLC with a JASCO PU-2080 Plus HPLC pump and a JASCO RI-4035 detector using a TSK gel column [Tosoh Corp., SuperHM-M (150 × 6.5 mm, i.d)]. THF with 5% NEt_3 was used as a carrier solvent at a flow rate of 0.35 mL/min at 18 °C. A calibration curve was made to determine number-average molar mass (M_n), weight-average molar mass (M_w), and dispersity (M_w/M_n) values with polystyrene standards. UV spectra were recorded on a HITACHI U-3000 spectrophotometer. CD measurements were performed using a JASCO J-820 spectrometer. Optical rotations were measured with a JASCO P-2100 polarimeter with a 0.5 dm-long cell. Elemental analyses were carried out on a J-Science Lab JM10 micro corder. Mass spectra were obtained on a Bruker autoflex speed-TK MALDI-TOF mass spectrometer. HPLC analyses were performed on an analytical HPLC with a JACSO PU-4180 RHPLC Pump and a JASCO MD-4010 multiwavelength detector. DOSY measurements were performed using the JNM-ECA-500 W spectrometer equipped with a 5 mm FG/RO auto tune probe and bipolar pulse pairs stimulated echo (BPP-STE) as a pulse sequence, in which the echo signal intensity at the maximum pulse field gradient (PFG) was set to have an attenuation ratio of about 10 to 15% compared to that at minimum PFG. The resulting DOSY data were converted to binary files (.bin, .hdr) using Delta ver. 5 (JEOL), and their analyses by maximum entropy method were processed using NMRnotebook with DOSY module ver. 2.8 (NMR tec). Spartan'18 (Wavefunction, Inc.; Irvine, California, USA) was used for computational calculations. (4a*S*,8a*S*)-Decahydroquinoxaline, (*S*,*S*)-**1**, was prepared according to the literature

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procedure.[14] All other reagents were purchased from commercial supplies and used without purification.

Preparation of 1,4-Phenylenebis(phenylcarbodiimide) (2a). To a solution of phenyl isothiocyanate (2.63 g, 19.4 mmol) in a mixed solvent of EtOH (27 mL) and DMF (10 mL) was added 1,4-phenylenediamine (1.00 g, 9.3 mmol), and the mixture was stirred at room temperature where white solid started to precipitate in just a few minutes. After stirring the heterogeneous mixture overnight the precipitate was collected by filtration, which was washed with EtOH and then dried in *vacuo* to afford *N,N″*-1,4-phenylenebis(*N′*-phenylthiourea) as a colorless solid (3.40 g, 97%): M.p. 213 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6, 50 °C): δ = 7.13 (t, J = 7.5 Hz, 2H, ArH^{para}), 7.34 (t, J = 7.5 Hz, 4H, ArH^{meta}), 7.47 (brs, 4H, NH-C$_6H_4$-NH), 7.51 (d, J = 7.5 Hz, 4H, ArH^{ortho}), 9,65 (brs, 2H, NH), 9.66 ppm (brs, 2H, NH); ^{13}C NMR (125 MHz, DMSO-d_6, 50 °C): δ = 123.4, 123.6, 124.2, 128.2, 135.7, 139.3, 179.5 ppm; IR (ATR): ν = 3206 (N−H), 3033, 1523 (C═S), 1491, 1449, 1335, 1289, 1234, 1020, 931, 835, 758, 694, 686, 657 cm^{-1}; Elemental analysis: calculated for $C_{20}H_{18}N_4S_2$: C 63.46; H 4.79; N 14.80, found: C 63.45; H 4.79; N 14.84.

To a mixture of *N,N″*-1,4-phenylenebis(*N′*-phenylthiourea) (3.26 g, 8.6 mmol), 4-dimethylaminopyridine (0.42 g, 3.4 mmol), and triethylamine (7.2 mL, 52 mmol) in CH_2Cl_2 (86 mL) was added methanesulfonyl chloride (3.95 g, 35 mmol) at 0 °C, and the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with water (5 × 15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using CH_2Cl_2 followed by recrystallization (CH_2Cl_2/Hexane) to give **2a** as a light yellow solid (1.82 g, 68%): M.p. 64−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$, rt): δ = 7.13 (br, 4H, NH-C$_6H_4$-NH), 7.17−7.20 (m, 6H, ArH), 7.32−7.36 ppm (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt): δ = 124.4, 125.3, 125.8, 129.7, 135.2, 135.9, 138.3 ppm; IR (ATR): ν = 2094 (N═C═N), 1585, 1523, 1482, 1276, 1199, 1095, 1070, 1022, 1011, 996, 912, 834, 757, 713, 687 cm^{-1}; elemental analysis: calculated for $C_{20}H_{14}N_4$: C 77.40; H 4.55; N 18.05, found: C 77.48; H 4.65; N 17.99.

Preparation of 1,4-Phenylenebis(1-naphthylcarbodiimide) (2b). To a solution of 1-naphthyl isothiocyanate (2.19 g, 11.8 mmol) in DMF (12 mL) was added 1,4-phenylenediamine (0.59 g, 5.4 mmol), and the mixture was stirred at room temperature where white solid started to precipitate in just a few minutes. After stirring the heterogeneous mixture for 14 h, the precipitate was collected by filtration, which was washed with EtOH and CH_2Cl_2 and dried in *vacuo* to afford *N,N″*-1,4-phenylenebis(*N′*-1-naphthylthiourea) as a colorless solid (2.50 g, 97%): ^{1}H NMR (400 MHz, DMSO-d_6, 40 °C): δ = 7.49 (brs, 4H, ArH), 7.51−7.61 (m, 8H, ArH), 7.84−7.88 (m, 2H, ArH), 7.93−8.02 (m, 4H, ArH), 9.69 (s, 2H, NH), 9.77 ppm (s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 40 °C): δ = 123.0, 124.0, 125.2, 125.5, 125.9, 126.0, 126.6, 128.0, 129.9, 133.8, 135.0, 136.0, 181.2 ppm; IR (ATR): ν = 3318, 3174 (N−H), 3109, 2997, 1539 (C═S), 1497, 1297, 1219, 1202, 768, 677, 663 cm^{-1}; elemental analysis: calculated for $C_{28}H_{22}N_4S_2$: C 70.26; H 4.63; N 11.71, found: C 70.08; H 4.80; N 11.77.

To a mixture of *N,N″*-1,4-phenylenebis(*N′*-1-naphthylthiourea) (2.38 g, 5.0 mmol), 4-dimethylaminopyridine (0.26 g, 2.1 mmol), and trimethylamine (4.2 mL, 30 mmol) in CH_2Cl_2 (50 mL) was added methanesulfonyl chloride (2.28 g, 20 mmol) at 0 °C, and the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with water (5 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using CH_2Cl_2 followed by recrystallization (CH_2Cl_2) to give **2b** as a light yellow solid (0.91 g, 45%): M.p. 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ = 7.20 (brs, 4H, ArH), 7.37−7.46 (m, 4H, ArH), 7.50−7.59 (m, 4H, ArH), 7.70 (brd, J = 7.9 Hz, 2H, ArH), 7.83−7.87 (m, 2H, ArH), 8.27−8.32 ppm (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ = 121.2, 123.4, 125.4, 125.9, 126.0, 126.6, 126.8, 128.1, 128.8, 134.5, 134.6, 136.0 ppm; IR (ATR): ν = 2108 (N═C═N), 1519, 1500, 1464, 1438, 1379, 1276, 1254, 1225, 1173, 1151, 1129, 1103, 1000, 842, 797, 768, 720 cm^{-1}; elemental analysis: calculated for $C_{28}H_{18}N_4$: C 81.93; H 4.42; N 13.65, found: C 81.94; H 4.48; N 13.65.

Preparation of 1-naphthylphenylcarbodiimide. To a solution of phenyl isothiocyanate (3.08 g, 23 mmol) in EtOH (20 mL) was added 1-naphthylamine (2.87 g, 20 mmol), and the mixture was stirred at room temperature where white solid started to precipitate in just a few minutes. After stirring the heterogeneous mixture for 7.5 h, the precipitate was collected by filtration, which was washed with EtOH and then dried *in vacuo* to afford *N*-(1-naphthyl)-*N′*-phenylthiourea as a colorless solid (5.45 g, 98%): M.p. 197−199 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 40 °C): δ = 7.13 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.50−7.60 (m, 6H), 7.86 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 9.71 (s, 1H, NH), 9.79 ppm (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6, 40 °C): δ = 123.0, 123.9, 124.4, 125.2, 125.4, 125.9, 126.0, 126.5, 128.0, 128.2, 129.8, 133.8, 135.0, 139.5, 181.3 ppm; IR (ATR): ν = 3333, 3109 (N−H), 2954, 1591, 1533 (C═S), 1501, 1270, 1219, 781, 748, 694 cm^{-1}; elemental analysis: calculated for $C_{17}H_{14}N_2S$: C 73.35; H 5.07; N 10.06, found: C 73.21; H 5.21 ; N 10.01.

To a mixture of *N*-(1-naphthyl)-*N′*-phenylthiourea (5.00 g, 18 mmol), 4-dimethylaminopyridine (0.46 g, 3.8 mmol), and triethylamine (7.6 mL, 54 mmol) in CH_2Cl_2 (180 mL) was added methenesulfonyl chloride (4.11 g, 36 mmol) at 0 °C, and the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with water (5 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using CH_2Cl_2 followed by recrystallization (hexane) to give 1-naphthylphenylcarbodiimide as a light yellow solid (2.83 g, 64%): M.p. 62 °C; ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ = 7.18−7.26 (m, 2H, ArH), 7.32−7.45 (m, 4H, ArH), 7.50−7.58 (m, 2H, ArH), 7.67−7.72 (brd, J = 7.7 Hz, 1H, ArH), 7.83−7.88 (brd, J = 7.5 Hz, 1H, ArH), 8.28−8.35 ppm (brd, J = 8.2 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt): 121.1, 123.5, 124.3, 125.6, 125.8, 125.9, 126.5, 126.7, 128.1, 128.8, 129.7, 134.5, 134.7, 138.7 ppm; IR (ATR): ν = 2135 (N═C═N), 2097, 1589, 1570, 1500, 1467, 1381, 1258, 1224, 1151, 1068, 799, 769, 750, 688 cm^{-1}; elemental analysis: calculated for $C_{17}H_{12}N_2$: C 83.58; H 4.95; N 11.47, found: C 83.53; H 5.04; N 11.57.

Synthesis of 3a^{PG}. (*S,S*)-**1** (22 mg, 0.16 mmol, $[\alpha]_D^8$ = −10.94 ° (c = 1.00, $CHCl_3$)) and **2a** (50 mg, 0.16 mmol) were placed in a glass vessel, and DMF (0.3 mL) was added to mix them by stirring at room temperature. The mixture became highly viscous like a gel and unstirrable within a minute, which was left as it is for an hour in total. Afterward, the solidified

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mixture was crushed in a mortar, washed with MeOH and Et_2O, and dried *in vacuo* to give **3a^{PG}** as a light yellow solid (66 mg, 91%): IR (ATR): ν = 3382 (N−H), 3054, 2924, 2855, 1611 (C═N), 1577 (C═N), 1490, 1387, 1342, 1295, 1225, 1166, 1151, 1099, 1063, 1040, 1014, 959, 901, 827, 732, 691 cm^{-1}.

Synthesis of 3b^{PG}. (*S*,*S*)-**1** (22.5 mg, 0.16 mmol, $[\alpha]_D^8$ = −10.94 ° (*c* = 1.00, $CHCl_3$)) and **2b** (66.5 mg, 0.16 mmol) were placed in a glass vessel, and DMF (0.3 mL) was added to mix them by stirring at room temperature. The mixture became highly viscous like a gel and unstirrable within a minute, which was left as it is for an hour in total. Afterward, the solidified mixture was crushed in a mortar, washed with MeOH and Et_2O, and dried in *vacuo* to give **3b^{PG}** as a light beige solid (84.5 mg, 95%). Note that **3b^{PG}** is moderately soluble in DMF (see Supporting Information, Table S2): ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 1.27−1.64 (br, 4H, C^6H_2 & C^7H_2), 1.64−1.85 (br, 2H, C^5H^{ax} & C^8H^{ax}), 2.81−3.03 (br, 2H, C^5H^{eq} & C^8H^{eq}), 3.07−3.42 (br, 4H, C^2H_2 & C^3H_2), 3.85−4.20 (br, 2H, $C^{4a}H$ & $C^{8a}H$), 5.12−5.82 (brm, 2H, NH), 6.68−6.98 (br, 6H, ArH), 7.16−7.59 (brm, 9H, ArH), 7.64−7.82 (br, 2H, ArH), 7.93−8.17 ppm (br, 1H, ArH); IR (ATR): ν = 3384 (N−H), 3050, 2928, 2859, 1611 (C═N), 1577 (C═N), 1494, 1435, 1390, 1342, 1298, 1225, 1170, 1099, 1066, 1040, 1014, 956, 901, 827, 732, 694 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 312 (23,650), 282 nm (21,750); CD ($CHCl_3$, 25 °C): λ_{max} ($\Delta\varepsilon$) = 329.5 (−39.9), 292.5 nm (−0.7); DOSY (500 MHz, $CDCl_3$, 1 w/v %, 35 °C): *D* = 103 μm^2 S^{-1}; SEC (THF with 5% NEt_3, polystyrene standard): M_n = 14.9 kg mol^{-1}, M_w = 93.5 kg mol^{-1}.

Synthesis of 3b^{2G}. To a solution of (*S*,*S*)-**1** (50 mg, 0.36 mmol, $[\alpha]_D^8$ = −10.94 ° (*c* = 1.00, $CHCl_3$)) in CH_2Cl_2 (2.6 mL) was added 1-naphthylphenylcarbodiimide (0.19 g, 0.79 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel using a mixture of $CHCl_3$ and MeOH (98:2) as eluent to give **3b^{2G}** as a light yellow solid (M = 628.82, 71 mg, 32%): M.p. 115−116 °C; $[\alpha]_D^9$ = −559.16 ° (*c* = 0.100, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rt): 1.40−1.69 (br, 4H, C^6H_2 & C^7H_2), 1.69−1.83 (br, 2H, C^5H^{ax} & C^8H^{ax}), 2.98−3.13 (brm, 2H, C^5H^{eq} & C^8H^{eq}), 3.16−3.56 (brm, 4H, C^2H_2 & C^3H_2), 4.00−4.30 (br, 2H, $C^{4a}H$ & $C^{8a}H$), 5.24−5.88 (brm, 2H, NH), 6.82−7.08 (m, 8H, ArH), 7.17−7.29 (m, 4H, ArH), 7.31−7.63 (m, 8H, ArH), 7.81 (d, *J* = 8.0 Hz, 2H, ArH), 7.94−8.16 ppm (br, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt): 25.1, 31.5, 47.1, 57.3, 116.3, 119.5, 122.3, 122.5, 124.0, 125.4, 126.1, 126.6, 128.1, 128.5, 129.4, 134.8, 141.1, 146.3, 150.5 ppm; IR (ATR): ν = 3386 (N−H), 3046, 2928, 2856, 1611 (C═N), 1596 (C═N), 1580, 1566, 1495, 1388, 1345, 1298, 1230, 1027, 1013, 774, 748, 690 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 312 nm (19,850); CD ($CHCl_3$, 25 °C): λ_{max} ($\Delta\varepsilon$) = 317 nm (−27.4); DOSY (500 MHz, $CDCl_3$, 1 w/v %, 35 °C): *D* = 573 μm^2 S^{-1}; SEC (THF with 5% NEt_3, polystyrene standard): M_n = 0.34 kg mol^{-1}, M_w = 0.41 kg mol^{-1}.

Synthesis of 3b^{4G}. To a solution of (*S*,*S*)-**1** (200 mg, 1.42 mmol, $[\alpha]_D^8$ = −10.94 ° (*c* = 1.00, $CHCl_3$)) in CH_2Cl_2 (27 mL) was added a solution of **2b** (194 mg, 0.47 mmol) in CH_2Cl_2 (20 mL) dropwise at room temperature over 1 h. The reaction mixture was stirred at room temperature for 6 h and washed with water (10 × 20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **1-2b-1** as a beige solid, which was identified to be a mixture of **1-2b-1** (M = 690.94) and **1-(2b-1)$_2$** in ratio of 13:≤1 (315 mg, 96%) and used for the next reaction without further purification: $[\alpha]_D^9$ = −632.96 ° (*c* = 0.100, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, rt): δ = 1.20−1.59 (br, 8H, (C^6H_2 & C^7H_2) × 2), 1.66−1.82 (br, 6H, (C^5H_2 & C^8H^{ax}) × 2), 2.45−2.66 (br, 2H, $C^{4a}H$ × 2), 2.66−3.11 (brm, 10H, C^8H^{eq} × 2, (C^2H_2 & C^3H_2) × 2), 3.16−3.35 (br, 2H, $C^{8a}H$ × 2), 5.21−6.08 (br, 2H, NH of guanidino groups), 6.69−7.08 (br, 6H, ArH), 7.30−7.56 (m, 8H, ArH), 7.73−7.86 (brm, 2H, ArH), 8.00−8.15 ppm (br, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt): δ = 25.2, 29.6, 32.9, 45.7, 51.9, 59.8, 62.3, 63.1, 115.7, 116.6, 120.6, 121.5, 122.4, 123.9, 126.1, 128.0, 134.5, 135.4, 145.6, 152.2 ppm; IR (ATR): ν = 3382 (N−H), 3046, 2924, 2852, 1611 (C═N), 1566 (C═N), 1501, 1444, 1384, 1346, 1335, 1297, 1232, 1138, 1016, 956, 910, 770 cm^{-1}.

To a solution of **1-2b-1** (35 mg, 50 μmol assuming a molar mass of 690.94) in CH_2Cl_2 (5.0 mL) was added 1-naphthylphenylcarbodiimide (24 mg, 100 μmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h, analyzed by ^{1}H NMR spectroscopy to confirm complete conversion of both terminal amino groups of **1-2b-1**, and briefly concentrated under reduced pressure to give a beige solid in nearly theoretical yield (62 mg including residual solvents), which was identified to contain **3b^{4G}** (bearing four guanidino groups on average, M^{theo} = 1179.5) and 1-naphthylphenylcarbodiimide (M = 244.30) in a w/w ratio of 93:7 and no other byproducts by ^{1}H NMR spectroscopy using the integration of a signal at 3.90−4.20 ppm assignable to four methine protons for **3b^{4G}** and that at 8.30 ppm assignable to an aromatic proton for 1-naphthylphenylcarbodiimide (see Supporting Information, Figure S35). This material was used without further purification except the removal of residual volatiles under reduced pressure prior to use. Note that the residual carbodiimide is due to experimental error in stoichiometry that can be caused by the underestimated molar mass of **1-2b-1** as well as handling in a small scale, and this is not the contamination that significantly affects the results of this study: ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): 1.29−1.66 (brm, 8H, (C^6H_2 & C^7H_2) × 2, overlapping the peak of water), 1.67−1.83 (br, 4H, (C^5H^{ax} & C^8H^{ax}) × 2), 2.82−3.06 (brm, 4H, (C^5H^{eq} & C^8H^{eq}) × 2), 3.09−3.53 (brm, 8H, (C^2H_2 & C^3H_2) × 2), 3.95−4.20 (br, ($C^{4a}H$ & $C^{8a}H$) × 2), 5.33−5.82 (brm, 4H, NH of guanidino groups), 6.67−7.05 (brm, 14H, ArH), 7.14−7.57 (brm, 20H, ArH), 7.70−8.22 ppm (brm, 8H, ArH), IR (ATR): ν = 3382 (N−H), 3043, 2924, 2857, 1600 (C═N), 1566 (C═N), 1499, 1389, 1346, 1295, 1231, 1016, 772, 748, 691 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 312 nm (22,050); CD ($CHCl_3$, 25 °C): λ_{max} ($\Delta\varepsilon$) = 327.5 (−38.2), 286.5 nm (−7.1); DOSY (500 MHz, $CDCl_3$, 1 w/v %, 35 °C): *D* = 431 μm^2 S^{-1}; MS (MALDI-TOF): *m*/*z* calcd for $C_{78}H_{74}N_{12}$ [M + H]$^+$ 1179.6, found 1179.6; SEC (THF with 5% NEt_3, polystyrene standard): M_n = 0.66 kg mol^{-1}, M_w = 0.82 kg mol^{-1}.

Synthesis of 3b^{8G}. To a solution of **1-2b-1** (49 mg, 71 μmol) in CH_2Cl_2 (2.6 mL) was added a solution of **2b** (15 mg, 35 μmol) in CH_2Cl_2 (1.0 mL) dropwise at room temperature over 15 min. The reaction mixture was stirred at room temperature for 8 h. After confirming the consumption of **2b** by TLC analysis as well as ^{1}H NMR spectroscopy, the reaction mixture was concentrated under reduced pressure to give a beige solid (65 mg, 101%), which was identified to be **1-(2b-**

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1)$_3$ (on average) and used for the next reaction without further purification: $[\alpha]_D^9$ = −669.12 ° (c = 0.100, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 1.19−1.63 (brm, 18H, (C^6H_2 & C^7H_2) × 4, NH × 2 for amino groups, overlapping the peak of water), 1.65−1.83 (br, 10H, (C^5H_2 & C^8H^{ax}) × 2 for end-groups, (C^5H^{ax} & C^8H^{ax}) × 2 for internal groups), 2.45−2.67 (br, 2H, $C^{4a}H$ × 2 for end-groups), 2.69−3.49 (brm, 24H, C^8H^{eq} × 2 for end-groups, (C^5H^{eq} & C^8H^{eq}) × 2 for internal groups, $C^{8a}H$ × 2 for end-groups, (C^2H_2 & C^3H_2) × 4), 3.86−4.16 (br, 4H, ($C^{4a}H$ & $C^{8a}H$) × 2 for internal groups), 5.35−6.03 (br, 6H, NH of guanidino groups), 6.64−7.06 (brm, 18H, ArH), 7.22−7.60 (brm, 24H, ArH), 7.62−7.89 (br, 8H, ArH), 7.91−8.23 ppm (br, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt): δ = 24.9, 29.1, 30.8, 32.7, 45.4, 47.0, 51.5, 56.9, 59.6, 62.4, 116.1, 120.8, 122.2, 123.7, 125.1, 125.9, 127.9, 134.5, 135.5, 145.1, 146.1, 150.8, 151.9 ppm; IR (ATR): ν = 3387 (N−H), 3047, 2924, 2857, 1609 (C═N), 1566 (C═N), 1504, 1446, 1389, 1346, 1298, 1236, 1136, 1016, 772, 734 cm^{-1}.

To a solution of **1**-(**2b-1**)$_3$ (45 mg, 25 μmol assuming a molar mass of 1792.4) in CH_2Cl_2 (2.5 mL) was added 1-naphthylphenylcarbodiimide (12 mg, 50 μmol). The reaction mixture was stirred at room temperature for 3 h, analyzed by ^{1}H NMR spectroscopy to confirm complete conversion of both terminal amino groups of **1**-(**2b-1**)$_3$, and briefly concentrated under reduced pressure to give a beige solid in nearly theoretical yield (61 mg including residual solvents), which was identified to contain **3b**^{8G} (bearing eight guanidino groups on average, M^{theo} = 2281.0) and 1-naphthylphenylcarbodiimide (M = 244.30) in a w/w ratio of 98:2 and no other byproducts by ^{1}H NMR spectroscopy using the integration of a signal at 3.94−4.20 ppm assignable to eight methine protons for **3b**^{8G} and that at 8.30 ppm assignable to an aromatic proton for 1-naphthylphenylcarbodiimide (see Supporting Information, Figure S38). This material was used as a pure product without further purification except removal of residual volatiles under reduced pressure prior to use: ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): 1.11−1.63 (br, 16H, (C^6H_2 & C^7H_2) × 4, overlapping the peak of water), 1.66−1.85 (br, 8H, (C^5H^{ax} & C^8H^{ax}) × 4), 2.71−3.05 (br, 8H, (C^5H^{eq} & C^8H^{eq}) × 4), 3.09−3.51 (br, 16H, (C^2H_2 & C^3H_2) × 4), 3.94−4.20 (br, 8H, ($C^{4a}H$ & $C^{8a}H$) × 4), 5.01−5.94 (br, 8H, NH of guanidino groups), 6.60−7.08 (brm, 26H), ArH, 7.11−7.21 (brm, 4H, ArH), 7.26−7.61 (brm, 32H, ArH), 7.65−7.86 (br, 10H, ArH), 7.89−8.20 ppm (br, 6H, ArH); IR (ATR): ν = 3383 (N−H), 3048, 2924, 2857, 1609 (C═N), 1566 (C═N), 1504, 1389, 1341, 1231, 1016, 772, 748, 691, 667 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 312 nm (23,487); CD ($CHCl_3$, 25 °C): λ_{max} ($\Delta\varepsilon$) = 329.0 (−38.9), 289.5 nm (−4.5); DOSY (500 MHz, $CDCl_3$, 1 w/v %, 35 °C): D = 295 μm^2 S^{-1}; SEC (THF with 5% NEt_3, polystyrene standard): M_n = 1.52 kg mol^{-1}, M_w = 2.79 kg mol^{-1}.

Synthesis of 3b^{16G}. To a solution of **1**-(**2b-1**)$_3$ (452 mg, 250 μmol) in CH_2Cl_2 (8.0 mL) was added a solution of **2b** (52 mg, 126 μmol) in CH_2Cl_2 (4.6 mL) dropwise at room temperature over 15 min. The reaction mixture was stirred at room temperature for 1.5 h. After confirming the consumption of **2b** by TLC analysis as well as ^{1}H NMR spectroscopy, the reaction mixture was concentrated under reduced pressure to give a beige solid (482 mg, 96%), which was identified to be **1**-(**2b-1**)$_7$ (on average) and used for the next reaction without further purification: $[\alpha]_D^9$ = −768.74 ° (c = 0.100, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rt): 1.07−1.95 (brm, 52H, (C^6H_2 & C^7H_2) × 8, (C^5H_2 & C^8H^{ax}) × 2 for end-groups, (C^5H^{ax} & C^8H^{ax}) × 6 for internal groups, NH × 2 for amino groups, overlapping the peak of water), 2.38−2.67 (br, 2H, $C^{4a}H$ × 2 for end-groups), 2.69−3.63 (brm, 48H, C^8H^{eq} × 2 for end-groups, (C^5H^{eq} & C^8H^{eq}) × 6 for internal groups, $C^{8a}H$ × 2 for end-groups, (C^2H_2 & C^3H_2) × 8), 3.84−4.38 (brm, 12H, ($C^{4a}H$ & $C^{8a}H$) × 6 for internal groups), 5.34−5.98 (brm, 14H, NH of guanidino groups), 6.60−7.02 (br, 42H, ArH), 7.26−7.56 (br, 56H, ArH), 7.56−7.87 (br, 18H, ArH), 7.89−8.18 ppm (br, 10H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, rt): 25.1, 29.4, 31.5, 32.9, 45.7, 47.3, 57.3, 59.8, 62.7, 116.4, 118.4, 121.0, 122.4, 124.0, 125.4, 126.2, 128.1, 134.8, 135.9, 145.4, 146.4, 151.1, 152.0 ppm; IR (ATR): ν = 3382 (N−H), 3048, 2924, 2857, 1604 (C═N), 1566 (C═N), 1504, 1389, 1341, 1227, 1011, 772 cm^{-1}.

To a solution of **1**-(**2b-1**)$_7$ (50 mg, 12.5 μmol assuming a molar mass of 3995.2) in CH_2Cl_2 (1.0 mL) was added a solution of 1-naphthylphenylcarbodiimide (6 mg, 25 μmol) in CH_2Cl_2 (0.3 mL) dropwise at room temperature over 7 min. The reaction mixture was stirred at room temperature for 2 h, analyzed by ^{1}H NMR spectroscopy to confirm complete conversion of both terminal amino groups of **1**-(**2b-1**)$_7$, and briefly concentrated under reduced pressure to give a yellowish solid in nearly theoretical yield (61 mg including residual solvents), which was identified to contain **3b**^{16G} (bearing 16 guanidino groups on average, M^{theo} = 4483.8) and 1-naphthylphenylcarbodiimide (M = 244.30) in a w/w ratio of 98:2 by ^{1}H NMR spectroscopy using the integration of a signal at 3.87−4.21 ppm assignable to 16 methine protons for **3b**^{16G} and that at 8.30 ppm assignable to an aromatic proton for 1-naphthylphenylcarbodiimide (see Supporting Information, Figure S41). This material was used as a pure product without further purification except removal of residual volatiles under reduced pressure prior to use: ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 1.10−1.65 (brm, 32H, (C^6H_2 & C^7H_2) × 8, overlapping the peak of water), 1.65−1.81 (br, 16H, (C^5H^{ax} & C^8H^{ax}) × 8), 2.78−3.06 (br, 16H, (C^5H^{eq} & C^8H^{eq}) × 8), 3.06−3.55 (br, 32H, (C^2H_2 & C^3H_2) × 8), 3.87−4.21 (br, 16H, ($C^{4a}H$ & $C^{8a}H$) × 8), 5.00−5.92 (brm, 16H, NH of guanidino groups), 6.60−7.04 (brm, 50H, ArH), 7.12−7.60 (brm, 68H, ArH, overlapping the peak of $CHCl_3$), 7.64−7.87 (brm, 20H, ArH), 7.89−8.22 ppm (brm, 12H, ArH); IR (ATR): ν = 3383 (N−H), 3048, 2928, 2857, 1604 (C═N), 1566 (C═N), 1499, 1389, 1341, 1231, 1016, 772, 667 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 312 nm (23,979); CD ($CHCl_3$, 25 °C): λ_{max} ($\Delta\varepsilon$) = 329.0 (−38.8), 292.5 nm (−3.0); DOSY (500 MHz, $CDCl_3$, 1 w/v %, 35 °C): D = 221 μm^2 S^{-1}; SEC (THF with 5% NEt_3, polystyrene standard): M_n = 1.55 kg mol^{-1}, M_w = 3.56 kg mol^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05892.

Solubility of **3a**^{PG} and **3b**^{PG}, computational studies, determination of the reactivity ratio of **2b** to **1-2b**, monitoring the syntheses of oligomeric analogues of **3b**^{PG}, an evidence for irreversibility of chain elongations, schematic interpretation of intermolecular associations, asymmetric catalysis, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Bayer, O.; Rinke, H.; Siefken, W.; Orthner, L.; Schild, H. A process for the production of polyurethanes and polyureas. *DRP* **1937**, *728981*, 13.

(2) Bayer, O. Das Di-Isocyanat-Polyadditionsverfahren (Polyurethane). *Angew. Chem.* **1947**, *59*, 257−272.

(3) Iwakura, Y.; Noguchi, K. Polyaddition Reaction of Biscarbodiimides. II. Synthesis of Polyguanidines by Polyaddition Reaction of Biscarbodiimides with Diamines. *J. Polym. Sci., Part A: Polym. Chem.* **1969**, *7*, 801−812.

(4) Iwakura, Y.; Noguchi, K. A Synthesis of Polyguanidines by Polyaddition Reaction of Biscarbodiimides with Diamines. *J. Polym. Sci., Part C: Polym. Lett.* **1967**, *5*, 821−825.

(5) Goodwin, A.; Novak, B. M. Synthesis of New Rigid Rod Helical Polymers through the Living Polymerization of Carbodiimides Using Titanium(IV) Complexes. *Macromolecules* **1994**, *27*, 5520−5522.

(6) Schlitzer, D. S.; Novak, B. M. Trapped Kinetic States, Chiral Amplification and Molecular Chaperoning in Synthetic Polymers: Chiral Induction in Polyguanidines through Ion Pair Interactions. *J. Am. Chem. Soc.* **1998**, *120*, 2196−2197.

(7) Tang, H. Z.; Lu, Y.; Tian, G.; Capracotta, M. D.; Novak, B. M. Stable Helical Polyguanidines: Poly{*N*-(1-anthryl)-*N*′-[(*R*)- and/or (*S*)-3,7-dimethyloctyl]guanidines}. *J. Am. Chem. Soc.* **2004**, *126*, 3722−3723.

(8) Tian, G.; Lu, Y.; Novak, B. M. Helix-Sense Selective Polymerization of Carbodiimides: Building Permanently Optically Active Polymers from Achiral Monomers. *J. Am. Chem. Soc.* **2004**, *126*, 4082−4083.

(9) Kim, J.; Novak, B. M.; Waddon, A. J. Lyotropic Liquid Crystalline Properties of Poly(*N*,*N*′-di-*n*-hexylguanidine). *Macromolecules* **2004**, *37*, 1660−1662.

(10) Kim, J.; Novak, B. M.; Waddon, A. J. Liquid Crystalline Properties of Polyguanidines. *Macromolecules* **2004**, *37*, 8286−8292.

(11) Tang, H. Z.; Boyle, P. D.; Novak, B. M. Chiroptical Switching Polyguanidine Synthesized by Helix-Sense-Selective Polymerization Using [(*R*)-3,3′-Dibromo-2,2′-binaphthoxy](di-*tert*-butoxy)titanium-(IV) Catalyst. *J. Am. Chem. Soc.* **2005**, *127*, 2136−2142.

(12) Arnold, L.; Marx, A.; Thiele, C. M.; Reggelin, M. Polyguanidines as Chiral Orienting Media for Organic Compounds. *Chem. − Eur. J.* **2010**, *16*, 10342−10346.

(13) Alonso-Moreno, C.; Antiñolo, A.; Carrillo-Hermosilla, F.; Otero, A. Guanidines: from Classical Approaches to Efficient Catalytic Syntheses. *Chem. Soc. Rev.* **2014**, *43*, 3406−3425.

(14) Lorentz-Petersen, L. L. R.; Nordstrøm, L. U.; Madsen, R. Iridium-Catalyzed Condensation of Amines and Vicinal Diols to Substituted Piperazines. *Eur. J. Org. Chem.* **2012**, 6752−6759.

(15) Baishya, A.; Peddarao, T.; Barman, M. K.; Nembenna, S. Catalyst Free C−N Bond Formation by the Reaction of Amines with Diimides: Bulky Guanidines. *New J. Chem.* **2015**, *39*, 7503−7510.

(16) Flory, P. J. Molecular Size Distribution in Linear Condensation Polymers. *J. Am. Chem. Soc.* **1936**, *58*, 1877−1885.

(17) Flory, P. J. Fundamental Principles of Condensation Polymerization. *Chem. Rev.* **1946**, *39*, 137−197.

(18) Peebles, L. H. Sequence Length Distribution in Segmented Block Copolymers. *Macromolecules* **1974**, *7*, 872−882.

(19) Groves, P. Diffusion Ordered Spectroscopy (DOSY) as applied to Polymers. *Polym. Chem.* **2017**, *8*, 6700−6708.

(20) Johnson, C. S., Jr. Diffusion Ordered Nuclear Magnetic Resonance Spectroscopy: Principles and Applications. *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *34*, 203−256.

(21) Brown, W.; Stilbs, P.; Johnsen, R. M. Friction Coefficients in Self-Diffusion, Velocity Sedimentation, and Mutual Diffusion for Poly(ethylene oxide) in Aqueous Solution. *J. Polym. Sci., Polym. Phys. Ed.* **1983**, *21*, 1029−1039.

(22) Nagasawa, K.; Sohtome, Y. Chiral Guanidine and AmRidine Organocatalysts, In *Science of Synthesis: Asymmetric Organocatalysis*; eds. Maruoka, K.; Thieme, S., 2012, p. 1.

(23) Sohtome, Y.; Nagasawa, K. Dynamic Asymmetric Organocatalysis: Cooperative Effects of Weak Interactions and Conformational Flexibility in Asymmetric Organocatalysts. *Chem. Commun.* **2012**, *48*, 7777−7789.

(24) Selig, P. Guanidine Organocatalysis. *Synthesis* **2013**, *45*, 703−718.

(25) Dong, S.; Feng, X.; Liu, X. Chiral Guanidines and Their Derivatives in Asymmetric Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8525−8540.

(26) Overberger, C. G.; Okamoto, Y. Solvolysis of Sodium 4-Acetoxy-3-nitrobenzenesulfonate Catalyzed by Oligo(4(5)-vinylimidazole). *Macromolecules* **1972**, *5*, 363−368.

(27) Itsuno, S.; Hassan, M. M. Polymer-Immobilized Chiral Catalysts. *RSC Adv.* **2014**, *4*, 52023−52043.

(28) Itsuno, S.; Ullah, M. S. in *Science of Synthesis: Flow Chemistry in Organic Synthesis*, eds. Jamison, T. F.; Koch, G. Thieme, Stuttgart, 2018, pp. 347−380.

(29) Ishikawa, T.; Heima, T.; Yoshida, M.; Kumamoto, T. Catalytic Performance of Polystyrene-Bound *ChibaG* Derivatives as Guanidine Organobases in Asymmetric Michael Additions. *Helv. Chim. Acta* **2014**, *97*, 307−314.

(30) Wannaporn, D.; Ishikawa, T. Polymer-Supported and Polymeric Chiral Guanidines: Preparation and Application to the Asymmetric Michael Reaction of Iminoacetate with Methyl Vinyl Ketone. *Mol. Diversity* **2005**, *9*, 321−331.

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