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.

Figure 1. Polyaddition reaction of biscarbodiimides with diamines.

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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 \((4S,8aS)\) -decahydroquinoxaline\(^1\)\(^4\), 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/polymer, 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 \(N,N^{\prime}\)-dialyl substituted monocarbodiimides occurred smoothly under catalyst-free conditions\(^1\)^\(^5\), 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 3a\(^{PG}\) in 91% yield since absorption peaks reasonable for guanidine were observed without any bands around 2100 cm\(^{-1}\) distinctive for carbodiimide. However, 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 3b\(^{PG}\) obtained in 95% yield was soluble in a few solvents including chloroform \((\text{CHCl}_3)\) under dryer heating. For comparison, its monomeric analogue 3b\(^{2G}\) \((2G \text{ stands for two guanidino groups})\) was prepared (Figure 2). Note that the tautomerism of guanidino groups in the given structure of 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 3b\(^{2G}\) and 3b\(^{PG}\) indicated their high-level spectral similarity, which convinced us that the present polyaddition reaction took place without serious side reactions. The number-average molar mass \((M_n)\), weight-average molar mass \((M_w)\), and dispersity \((M_w/M_n)\) of 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 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.\(^1\)^\(^6\)^\(^7\) Such a situation in the present system might come from the reactivity of the

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Figure 2. Characterization of 3b\(^{PG}\) as compared to 3b\(^{2G}\) (Ar = 1-naphthyl): (a) IR spectra of 2b, 3b\(^{2G}\), and 3b\(^{PG}\), (b) \(^1\)H NMR spectra for 3b\(^{2G}\) (ca. 25 °C) and 3b\(^{PG}\) (50 °C) in CDCl\(_3\), (c) SEC chromatogram of 3b\(^{PG}\) (eluent, THF with 5% NEt\(_3\), polystyrene standard).
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 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 and does not explain the polyaddition behavior that proceeds very fast to 1-(2b-1)nPG 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 1-(2b-1)) was prepared by reacting 2b with 3 equivalents of (S,S)-1 in CH2Cl2 at room temperature followed by the removal of water-soluble unreacted (S,S)-1 through extraction (Figure 4a, 1st elongation). Subsequently, 1-2b-1 was treated with 0.5 equivalents of 2b under similar conditions, which afforded a mixture containing only molecular chains represented by 1-(2b-1)n after removal of the solvent (Figure 4a, 2nd elongation, the value of n was determined to be 3 on average by 1H NMR spectroscopy). Likewise, the 1-(2b-1)n was further extended to 1-(2b-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 1H NMR spectroscopy). Note that all these reaction systems were homogeneous. No reaction took place when 1-(2b-1)7 was mixed with 3 equivalents of (S,S)-1 in CDCl3 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, 1-(2b-1)3, and 1-(2b-1)7 containing an amino group at both ends were quantitatively end-capped by reacting with 1-naphthylphenyl-carbodiimide to derive into the corresponding oligoguanidines 3b4G, 3b8G, and 3b16G, 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 3bPG. Not surprisingly, the SEC profile of 3b4G (the theoretical molar mass, Mtheo, is 1180 g mol⁻¹) formed via the 1st elongation was relatively sharp and unimodal, which was detected with a Mn of 0.66 kg mol⁻¹, a Mw of 0.82 kg mol⁻¹, and the dispersity of 1.2 (Figure 4c, purple). By contrast, the SEC signal for 3b8G was multimodal having three characteristic peaks that could be attributed to 3b12G,8G,4G derived from 1-(2b-1)5, 1-(2b-1)3, and 1-2b-1 in ascending order of elution time (Figure 4c, 5th elongation).
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-(2b-1)₃ much more selectively than 1-(2b-1)₅. The turned reactivity was arguably taken over the third elongation since 3b₁₆G 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 π−π/π−π* interactions between one main chain and the other side chain (see Supporting Information, chapter VI), can be involved in the present polyaddition to provide 3b₄G with the large dispersity.

With not only 3b₂G but also 3b₄G, 3b₈G, and 3b₁₆G in hand, the spectroscopic characterization of 3b₄G was continued to explore its optical and conformational properties. In contrast to the above-mentioned IR and ¹H NMR studies, there was an arguable difference between 3b₂G and 3b₄G in their ultraviolet (UV) spectra; an absorption band with a peak at 312 nm assignable to π−π* transition of the naphthyl ring was shared by both cases, whereas the peak for 3b₄G remained broad around 280 nm possibly due to the π−π* transition of the p-phenylene moiety in the main chain (Figure 5a, lower). A clearer difference was observed in their circular dichroism (CD) spectra; 3b₂G showed a non-split negative Cotton effect with a line shape according to its UV absorption, while 3b₄G 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 3b₄G/₈G/₁₆G to become more apparent that there is another absorption at around 280 nm except 3b₂G. 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 3b₄G through molecular mechanics calculation, suggesting that two tautomers in 3b₄G 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 3b₄G 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. DOSY spectra of 3b₂G/₄G/₈G/₁₆G were recorded with a solute concentration of 1 w/v % in CDCl₃ 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. The resulting self-diffusion coefficients (D, μm² S⁻¹) were found to be 573 (3b₂G), 431 (3b₄G), 295 (3b₈G), and 221 (3b₁₆G), respectively, which were well correlated with the corresponding Mₘ₆₈ in good accordance with the theory that D is proportional to M.
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 3b$_{4G}$ on the calculation (Figure 5b) is adopted to give the structures of 3b$_{4G/8G/16G}$ and 3b$_{8G}$ in this article.

Finally, we explored the potential use of 3b$_{2G/4G/8G/16G}$ and 3b$_{8G}$ as a chiral Bronsted base organocatalyst.22−−25 The conjugate addition reaction between trans-$\beta$-nitrostyrene (4) and acetylacetone (5) was chosen as a test catalytic reaction. In the presence of 10 mol % of 3b$_{2G}$, the reaction of 4 (0.5 M) with 5 (1.0 M) in CH$_2$Cl$_2$ at room temperature proceeded smoothly to give the corresponding adduct (5)-6 after 1.5 and 24 h in 4 and 84% yields, respectively, with an enantioselectivity of 16% ee (Figure 6a). Interestingly, 3b$_{3PG}$ 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 3b$_{2G/4G/8G/16G}$ in their initial reaction stage (Figure 6b), which indicated that the enhanced catalytic activity of 3b$_{3PG}$ could originate from the chain length. It should be noted that the stereoselectivity of 3b$_{3PG}$ (23% ee) was much higher than 1-2b-1 (7% ee) and comparable to 3b$_{8G}$ (25% ee), indicating that the involvement of terminal amino groups in the catalysis of 3b$_{3PG}$ may be negligible, although the terminal structure of 3b$_{3PG}$ 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 3b$_{3PG}$ and its analogues 3b$_{2G/4G/8G/16G}$, 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 macro-sized 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-ECD-400S (1H, 400 MHz and 13C, 100 MHz) and JNM-ECA-500 W spectrometers (1H, 500 MHz and 13C, 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 ($M_n$) 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 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 NMRT nebook with DOSY module ver. 2.8 (NMR tec.). Spartan18 (Wavefunction, Inc.; Irvine, California, USA) was used for computational calculations. (4aS,8aS)-Decahydroquinuoxaline, (S,S)-I, was prepared according to the literature.
procedure. 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-phenylenediamine-N'-phenylthiourea as a colorless solid (3.40 g, 97%). M.p. 213 °C (decomp.). 1H NMR (500 MHz, DMSO-d_6, 50 °C): δ = 7.13 (t, J = 7.5 Hz, 2H, ArH), 7.32–7.36 ppm (m, 4H, ArH). 13C 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 = 3322, 3109 (N=S), 3033, 1523 (C=S), 1491, 1449, 1335, 1289, 1234, 1129, 1103, 1095, 1070, 1022, 991, 912, 834, 757, 713, 687 cm⁻¹; elemental analysis: calculated for C_{28}H_{18}N_{4}S_{2}: C 70.26; H 4.63; N 11.71, found: C 70.08; H 4.79; N 14.84.

To a mixture of N,N'-1,4-phenylenediamine-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. After the reaction mixture was washed with water (5 mL), the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with water (5 mL) was added methanesulfonyl chloride (2.28 g, 20 mmol) at 0 °C, and the mixture was stirred at 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/Hexane) to give 2b as a yellow solid (0.91 g, 45%): M.p. 143–145 °C; 1H NMR (400 MHz, CDCl_3, rt) δ = 7.20 (bs, 4H, ArH), 7.37–7.46 (m, 4H, ArH), 7.70 (td, J = 7.9 Hz, 2H, ArH), 7.83–7.87 (m, 2H, ArH), 8.27–8.32 ppm (p, 2H, ArH); 13C NMR (125 MHz, CDCl_3) δ = 121.2, 123.4, 125.4, 125.9, 126.0, 126.6, 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_{14}H_{14}N_{2}: C 81.93; H 4.42; 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; 1H 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, 1H), 7.89 (d, J = 8.0 Hz, 2H); 13C NMR (125 MHz, DMSO-d_6, 40 °C): 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_{12}N_{2}: C 76.8; H 4.55; N 10.94; C 76.9; H 4.56; N 11.00.

To a mixture of N,N'-1,4-phenylenediamine (2.00 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 methanesulfonyl 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 yellow light solid (2.83 g, 64%): M.p. 62 °C; 1H NMR (400 MHz, CDCl_3, rt) δ = 7.18–7.26 (m, 6H, 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); 13C NMR (125 MHz, CDCl_3) δ: 121.1, 123.5, 124.3, 125.6, 125.8, 125.9, 126.5, 126.7, 128.1, 128.8, 129.7, 134.5, 138.7 ppm; IR (ATR): ν = 2135 (N=C=N), 2079, 1589, 1570, 1500, 1467, 1381, 1258, 1224, 1151, 1068, 799, 750, 688 cm⁻¹; elemental analysis: calculated for C_{14}H_{14}N_{2}: C 83.8; H 4.95; N 11.47; found: C 83.53; H 5.04; N 11.57.

**Synthesis of 3a**. (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 vial, 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 Et₂O, and dried in vacuo to give 3b²PG as a light yellow solid (66 mg, 91%). IR (ATR): ν = 3382 (N=H), 3054, 2924, 2855, 1611 (C=O), 1577 (C=O), 1490, 1387, 1342, 1295, 1225, 1166, 1151, 1099, 1063, 1040, 1014, 959, 901, 827, 732, 691 cm⁻¹.

**Synthesis of 3b²PG.** (S,S)-1 (22.5 mg, 0.16 mmol, [α]D¹⁰ = −10.94 ° (c = 1.00, CHCl₃)) 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 Et₂O, and dried in vacuo to give 3b²PG as a light beige solid (84.5 mg, 95%). Note that 3b²G is moderately soluble in DMF (see Supporting Information, Table S2): 1H NMR (500 MHz, CDCl₃, 50 °C): δ = 1.27–1.64 (br, 4H, C₄H₂ & C₃H₃), 1.64–1.85 (br, 2H, C₄H² & C₅H²), 2.81–3.03 (br, 2H, C₄H² & C₅H²), 3.07–3.42 (br, 4H, C₄H₂ & C₅H₂), 3.85–4.20 (br, 2H, C₄H² & C₅H²), 5.12–5.82 (br, 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 = 3382 (N=H), 2928, 2852, 1611 (C=O); UV/Vis (CHCl₃): λmax (ε) = 312 nm (22,050); CD (CHCl₃, 25 °C): [α]max (Δε) = 327.5 (−38.2), 286.6 mm² dm⁻¹ cm⁻¹.

To a solution of (S,S)-1 (35 mg, 50 μmol assuming a molar mass of 690.94) in CH₂Cl₂ (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 1H NMR spectroscopy to confirm complete conversion of both terminal amino groups of 1b-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 3b²G (bearing four guanidino groups on average, Mtheo = 1179.5) and 1-naphthylphenylcarbodiimide (M = 244.30) in a w/w ratio of 93:7 and no other byproducts by 1H NMR spectroscopy using the integration of a signal at 3.9–4.2 ppm assignable to four methine protons for 3b²G 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 1b-2b-1 as well as handling in a small scale, and this is not the contamination that significantly affects the results of this study: 1H NMR (500 MHz, CDCl₃, 50 °C): 1.29–1.66 (brm, 8H, C₄H₂ & C₅H₂ × 2, overlapping the peak of water), 1.67–1.83 (br, 4H, C₄H² & C₅H²), 2.89–3.13 (brm, 4H, C₄H² & C₅H²), 3.16–3.56 (brm, 4H, C₄H² & C₅H₂), 4.00–4.30 (br, 4H, C₄H² & C₅H₂), 5.24–5.88 (brm, 2H, NH), 6.68–7.08 (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); 13C NMR (125 MHz, CDCl₃, 50 °C): 25.1, 31.5, 47.1, 57.3, 116.3, 119.5, 123.2, 122.5, 124.0, 125.4, 126.1, 126.6, 128.1, 128.5, 134.8, 141.1, 146.3, 150.5 ppm; IR (ATR): ν = 3382 (N=H), 3046, 2928, 2856, 1611 (C=O), 1596 (C=O), 1580, 1656, 1495, 1388, 1345, 1298, 1230, 1027, 1011, 774, 748, 690 cm⁻¹; UV/Vis (CHCl₃): λmax (ε) = 312 nm (22,050); CD (CHCl₃, 25 °C): [α]max (Δε) = 327 (−38.2), 286.6 mm² dm⁻¹ cm⁻¹. DOSY (500 MHz, CDCl₃, 1 w/v %, 35 °C): D = 431 μm² s⁻¹; MS (MALDI-TOF): m/z calecd for C₉H₁₄N₁₂ [M + H⁺] + 1179.6; found 1179.6; SEC (THF with 5% NEt₃ polysynthetic standard): Mₙ = 0.66 kg mol⁻¹, Mₘ = 0.82 kg mol⁻¹.
A mixture was stirred at room temperature for 3 h, analyzed by 1H NMR (400 MHz, CDCl3, 50 °C): δ = 1.19–1.63 (brm, 18H, (C2H5 and C'H5) × 4, NH × 2 for amino groups, overlapping the peak of water), 1.65–1.83 (br, 10H, (C'H5 and C'H4') × 2 for end-groups, (C'H5'' and C'H6'') × 2 for internal groups), 2.45–2.67 (br, 2H, C'H × 2 for end-groups), 2.69–3.49 (brm, 24H, C'H5 × 2 for end-groups, (C'H5'' and C'H6'') × 2 for internal groups, C'H5 × 2 for end-groups, (C'H5 and C'H6) × 4), 3.86–4.16 (br, 4H, (C'H5 and C'H6) × 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). 13C NMR (125 MHz, CDCl3, 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≡C), 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 CH2Cl2 (2.5 mL) was added 1-naphthylphosphonic acid (12 mg, 50 μmol). The reaction mixture was stirred at room temperature for 3 h, analyzed by 1H 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 3b4E (bearing 16 guanidino groups on average, Mthio = 4483.8) and 1-naphthylphosphonic acid (M = 244.30) in a w/w ratio of 98:2 by 1H NMR spectroscopy using the integration of a signal at 3.94–4.20 ppm assignable to eight methine protons for 3b4E and that at 8.30 ppm assignable to an aromatic proton for 1-naphthylphosphonic acid (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: 1H NMR (400 MHz, CDCl3, 50 °C): δ = 1.10–1.65 (brm, 32H, (C2H6 and C'H6) × 8, overlapping the peak of water), 1.65–1.81 (br, 8H, (C2H6 and C'H6'') × 4, 3.09–3.51 (br, 16H, (C2H6 and C'H6) × 4), 3.94–4.20 (br, 8H, (C'H5 and C'H6) × 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≡C), 1504, 1389, 1341, 1231, 1016, 772, 748, 691, 667 cm⁻¹; UV/Vis (CHCl3): λmax (ε) = 312 nm (23,487); CD (CHCl3, 25 °C): λmax (Δε) = 329.0 (−38.8), 289.5 nm (−4.3); DOSY (500 MHz, CDCl3, 1 w/v %, 35 °C): D = 295 μm² s⁻¹; SEC (THF with 5% Nεε, polystyrene standard): Mn = 1.52 kg mol⁻¹, Mw = 2.79 kg mol⁻¹. 1-(2b-1)3 was studied by 1H 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 yellowish solid in nearly theoretical yield (61 mg including residual solvents), which was identified to contain 3b4E (bearing 16 guanidino groups on average, Mthio = 4483.8) and 1-naphthylphosphonic acid (M = 244.30) in a w/w ratio of 98:2 by 1H NMR spectroscopy using the integration of a signal at 3.94–4.20 ppm assignable to eight methine protons for 3b4E and that at 8.30 ppm assignable to an aromatic proton for 1-naphthylphosphonic acid (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: 1H NMR (400 MHz, CDCl3, 50 °C): δ = 1.10–1.65 (brm, 32H, (C2H6 and C'H6) × 8, overlapping the peak of water), 1.65–1.81 (br, 16H, (C2H6 and C'H6'') × 8), 2.78–3.06 (br, 16H, (C'H5 and C'H4') × 8), 3.06–3.55 (br, 32H, (C2H6 and C'H6) × 8), 3.87–4.21 (br, 16H, (C'H5 and C'H6) × 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 CHCl3), 7.64–7.87 (brm, 20H, ArH), 7.89–8.22 ppm (br, 12H, ArH); IR (ATR): ν = 3383 (N–H), 3048, 2928, 2857, 1604 (C≡N), 1566 (C≡C), 1499, 1389, 1341, 1231, 1016, 772, 667 cm⁻¹; UV/Vis (CHCl3): λmax (ε) = 312 nm (23,979); CD (CHCl3, 25 °C): λmax (Δε) = 329.0 (−38.8), 292.5 nm (−3.0); DOSY (500 MHz, CDCl3, 1 w/v %, 35 °C): D = 221 μm² s⁻¹; SEC (THF with 5% Nεε, polystyrene standard): Mn = 1.55 kg mol⁻¹, Mw = 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 3b4G and 3b8G, computational studies, determination of the reactivity ratio of 2b to 1-2b, monitoring the syntheses of oligomeric analogues of 3b8G, 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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