Complementary double-stranded helical oligomers bearing achiral bifunctional groups that catalyze asymmetric aldol reaction

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Abstract: Two novel chiral dimer and trimer strands composed of *m*-terphenyl groups linked through *p*-diethynylbenzene units with the chiral amidine group and achiral piperazine group introduced at the terminus or center of the strands, respectively, and its complementary achiral carboxy acid dimer and trimer were synthesized. The complementary chiral/achiral strands form an excess-handed double-helical structure as supported by intense split-type Cotton effects in the absorption regions of the conjugated backbones biased by the chiral amidinium–carboxylate salt-bridges. The double-helical trimer was found to catalyze the direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde and produce the products with a moderate enantioselectivity despite the fact that the catalytically-active bifunctional piperazine/carboxylic acid pair introduced in the middle is achiral, indicating the key role of the one-handed double-helical framework for supramolecular bifunctional organocatalysis.

Keywords: complementary double-helix, salt-bridge, supramolecular catalysis, aldol reaction, enantioselectivity

1 | INTRODUCTION

Although a variety of optically-active single-stranded helical polymers and supramolecular helical assemblies with specific functions, such as asymmetric catalysis and chiral recognition,[1,2] has been developed during the past three decades, those of the one-handed double helices reminiscent of the natural DNA double-helix still remain a challenge regarding their synthesis, structures, and functions.[1–9] The chiral framework and space generated by such a double-helical structure have the potential for developing unique and conceptually new supramolecular asymmetric catalyses,[10,11] but successful examples are quite limited until now[12–16] except for the DNA-based catalysts.[17,18]

Here we show the invaluable role of a complementary double-helical framework with a controlled helicity for supramolecular bifunctional asymmetric organocatalysis. The design and synthesis of complementary double-helical bifunctional organocatalysts is based on our modular strategy using *m*-terphenyl-based complementary double helices stabilized by chiral amidinium–achiral carboxylate salt bridges.[12,15,19–24] We anticipated that even catalytically-active achiral functional amino residues could be introduced at the terminus (edge-achiral dimer: (*R*)-**1**) or center (center-achiral trimer: (*R*)-**3**) of the chiral strands while maintaining the one-handed double-helical structures assisted by the chiral amidine residues once complexed with the corresponding achiral complementary carboxylic acid strands.[12,15,19–24] The resulting supramolecular bifunctional double-helical organocatalysts would catalyze the asymmetric direct aldol reaction due to its doubly helical chirality and cooperative effect of the two functional amino and carboxy groups arranging in close proximity to one another in a chiral fashion through a complementary one-handed double-helix formation (Figure 1).

2 | MATERIALS AND METHODS

2.1 | Synthesis and Materials

The carboxylic acid dimer (**2**[21]) and compounds **6**,[21] **7**,[21] and (*R*)-**10**[19] were prepared according to previously reported methods. The new single-stranded dimer ((*R*)-**1**) and trimer ((*R*)-**3**) bearing chiral amidine and achiral piperazine groups and achiral carboxylic acid trimer (**4**) were prepared according to the routes shown in Schemes 1–3, respectively.

Compound 8. **7**[21] (170 mg, 0.338 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (71.3 mg, 0.372 mmol), and 1-hydroxybenzotriazole monohydrate (HOBt·H_2O) (50.3 mg, 0.372 mmol) were dissolved in anhydrous CH_2Cl_2 (4.5 mL) under N_2, and to this was added dropwise a solution of piperazine (146 mg, 1.69 mmol) in anhydrous CH_2Cl_2 (1.5 mL) under N_2. After stirring at room temperature for 4 h, the mixture was diluted with CH_2Cl_2. The solution was washed with aqueous 1 N HCl and saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, *n*-hexane/EtOAc = 1/4, v/v) to give **8** as a white solid (135 mg, 69.9% yield). Mp: 71.4–72.8 °C. IR (KBr, cm^{-1}): 3431 ($\nu_{N–H}$), 3292 ($\nu_{C≡C–H}$), 2231 ($\nu_{C≡C}$), 2157 ($\nu_{C≡C}$), 1633 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.51 (d, J = 8.5 Hz, 2H, ArH), 7.48 (d, J = 8.5 Hz, 2H, ArH), 7.41–7.38 (m, 6H, ArH), 3.29–3.27 (m, 2H, CH_2), 3.12 (s, 2H, CH), 2.81–2.79 (m, 2H, CH_2), 2.46–2.44 (m, 2H, CH_2), 2.41 (t, J = 7.0 Hz, 2H, CC$H_2$$CH_2$), 2.17–2.15 (m, 2H, CH_2), 1.63–1.57 (m, 2H, CH_2), 1.52 (br s, 1H, NH), 1.48–1.42 (m, 2H, CH_2), 1.35–1.29 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3), 0.26 (s, 9H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 167.53, 140.11, 139.66, 139.22, 139.18, 133.43, 132.17, 132.14, 132.02, 129.00, 128.89, 125.11, 122.86, 121.79, 104.87, 95.36, 92.50, 83.48, 79.66, 78.16,

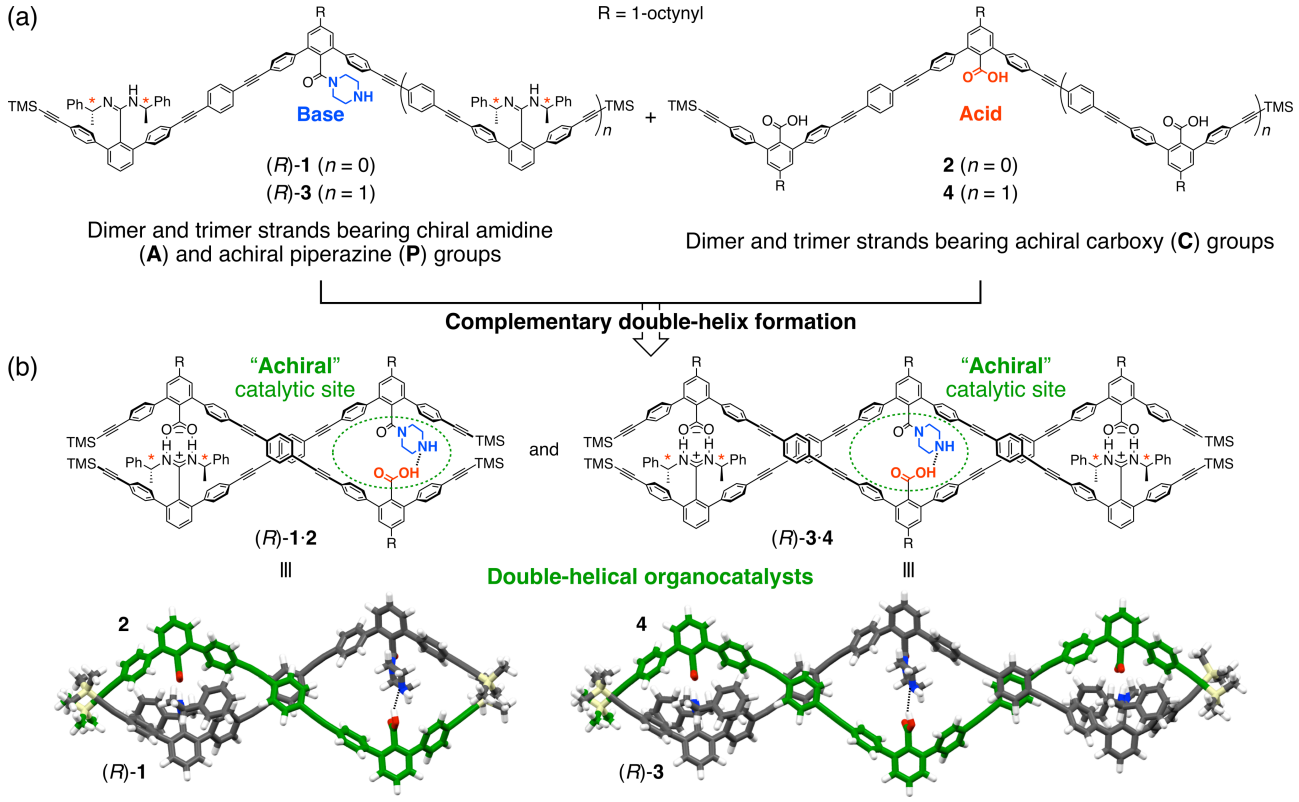
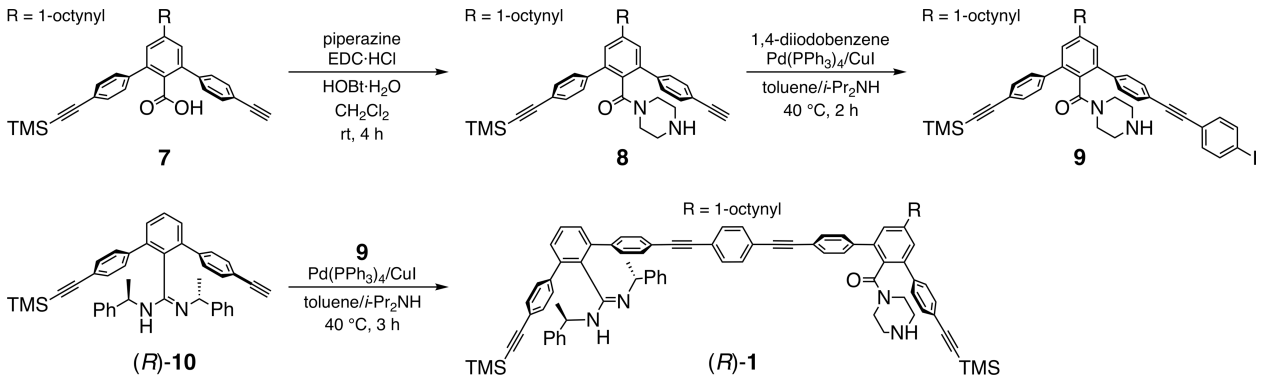


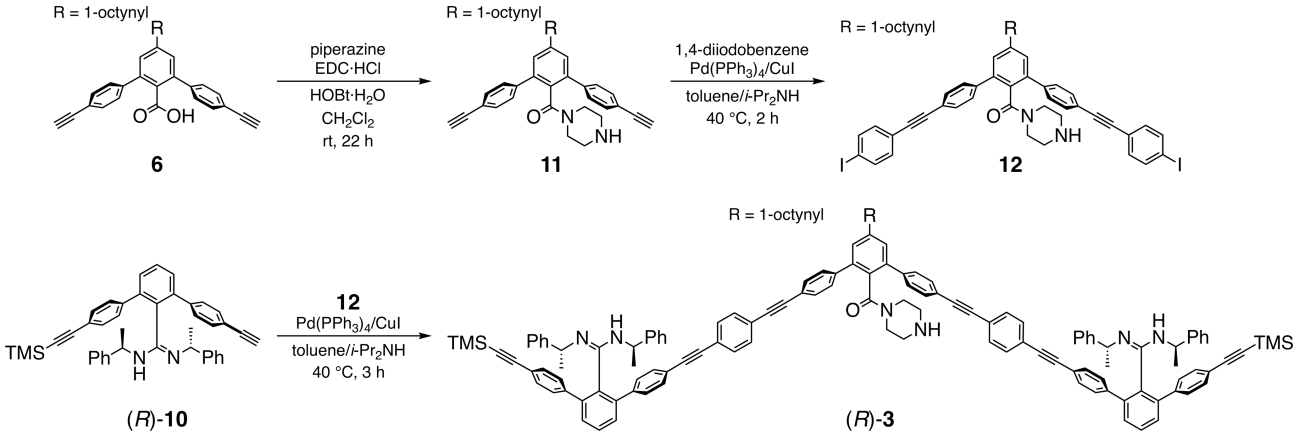
FIGURE 1 (a) Structures of *m*-terphenyl-based dimer and trimer strands bearing chiral amidine (**A**) and achiral piperazine (**P**) ((*R*)-**1** and (*R*)-**3**) and achiral carboxy (**C**) groups (**2** and **4**). (b) Complementary dimer and trimer strands form a preferred-handed double-helix stabilized by chiral amidinium–carboxylate salt bridges that promotes the asymmetric aldol reaction catalyzed by the interstrand-bifunctional achiral carboxy and secondary amino residues located inside the helical cavity. The molecular mechanics (MM)-calculated structures of the complementary right-handed double-helical (*R*)-**1**·**2** and (*R*)-**3**·**4** are also shown. The 1-octynyl chains at the *m*-terphenyl groups are replaced with hydrogen atoms to simplify the calculations.



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

78.15, 47.42, 45.66, 45.36, 42.03, 31.49, 28.77, 28.74, 22.70, 19.58, 14.22, 0.10. HRMS (ESI+): *m*/*z* calcd for $C_{38}H_{42}N_2OSi$ ($M+H^+$), 571.3145; found 571.3118.

Compound 9. To a mixture of **8** (133 mg, 0.233 mmol), 1,4-diiodobenzene (769 mg, 2.33 mmol), $Pd(PPh_3)_4$ (13.5 mg, 0.0117 mmol), and CuI (2.22 mg, 0.0117 mmol) in anhydrous toluene (6 mL) was added diisopropylamine (6 mL) under Ar. After stirring at 40 °C for 2 h, the mixture was diluted with diethyl ether (20 mL). The solution was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, *n*-hexane/EtOAc = 1/2, v/v) to give **9** as a white solid (140 mg, 77.8% yield). Mp: 93.2–94.0 °C. IR (KBr, cm^{-1}): 3447 (ν_{N-H}), 2230 ($\nu_{C\equiv C}$), 2157 ($\nu_{C\equiv C}$), 1634 ($\nu_{C=O}$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.70 (d, J = 8.5 Hz, 2H, ArH), 7.54 (d, J = 8.5 Hz, 2H, ArH), 7.49 (d, J = 8.5 Hz, 2H, ArH), 7.43 (d, J = 8.5 Hz, 2H, ArH), 7.41–7.38 (m, 4H, ArH), 7.26 (d, J = 8.5 Hz, 2H, ArH), 3.33–3.25 (m, 2H, CH_2), 2.85–2.78 (m, 2H, CH_2), 2.47–2.45 (m, 2H, CH_2), 2.42 (t, J = 7.0 Hz, 2H, CCH_2CH_2), 2.18–2.16 (m, 2H, CH_2), 1.64–1.58 (m, 2H, CH_2), 1.53 (br s, 1H, NH), 1.48–1.42 (m, 2H, CH_2), 1.37–1.28 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3), 0.26 (s, 9H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 167.56, 139.78, 139.68, 139.26, 139.20, 137.70, 133.43, 133.24, 132.15, 132.11, 132.01, 131.63, 129.10, 128.89, 125.11, 122.85, 122.82, 122.61, 104.87, 95.35, 94.40, 92.49, 90.66, 89.49, 79.67, 47.44, 45.66, 45.36, 42.06, 31.49, 28.77, 28.74, 22.69, 19.58, 14.21, 0.10. HRMS (ESI+): *m*/*z* calcd for $C_{44}H_{45}IN_2OSi$ ($M+Na^+$), 773.2424; found 773.2389.



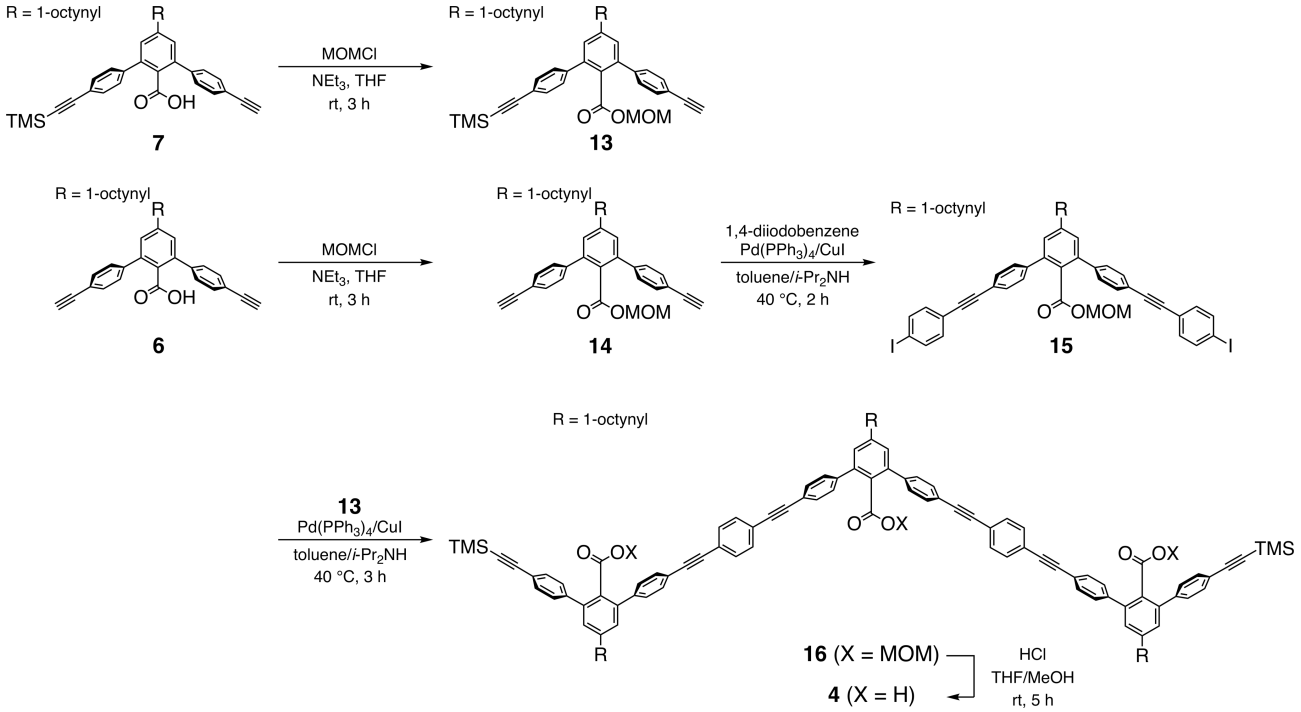
SCHEME 2 Synthesis of (*R*)-**3**

Compound (*R*)-1. To a mixture of **9** (50.0 mg, 0.0647 mmol), (*R*)-**10**[19] (42.8 mg, 0.0712 mmol), $Pd(PPh_3)_4$ (3.74 mg, 0.00324 mmol), and CuI (0.62 mg, 0.0033 mmol) in anhydrous toluene (4.0 mL) was added diisopropylamine (1.0 mL) under Ar. After stirring at 40 °C for 3 h, the mixture was diluted with EtOAc (10 mL). The solution was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (NH-SiO_2, *n*-hexane/EtOAc = 2/1, v/v) to give (*R*)-**1** as a white solid (47 mg, 58% yield). Mp: 139–141 °C. IR (KBr, cm^{-1}): 3425 (ν_{N-H}), 2157 ($\nu_{C\equiv C}$), 1637 ($\nu_{C=N}$), 1633 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, as (*R*)-**1**·CH_3CO_2H): δ 7.75 (t, J = 8.0 Hz, 1H, ArH), 7.57–7.38 (m, 16H, ArH), 7.30–7.22 (m, 10H, ArH), 7.08–7.06 (m, 4H, ArH), 6.73 (d, J = 8.5 Hz, 2H, ArH), 6.68 (d, J = 8.5 Hz, 2H, ArH), 3.95–3.90 (m, 2H, CHN), 3.36–3.25 (m, 2H, CH_2), 2.87–2.79 (m, 2H, CH_2), 2.48–2.46 (m, 2H, CH_2), 2.42 (t, J = 7.0 Hz, 2H, CCH_2CH$_2$), 2.18–2.17 (m, 2H, CH_2), 2.12 (s, 3H, CH_3CO_2), 1.64–1.58 (m, 2H, CH_2), 1.48–1.42 (m, 2H, CH_2), 1.37–1.28 (m, 4H, 2CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3), 0.74–0.71 (m, 6H, CH_3CHN), 0.27 (s, 9H, TMS), 0.26 (s, 9H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, as (*R*)-**1**·CH_3CO_2H): δ 179.48, 167.57, 162.64, 143.09, 143.01, 141.78, 141.70, 139.74, 139.71, 139.29, 139.24, 138.22, 133.45, 132.38, 132.14, 132.04, 132.01, 131.92, 131.74, 131.68, 130.71, 130.64, 129.16, 129.15, 129.12, 128.91, 128.79, 128.60, 128.05, 126.75, 126.71, 125.13, 123.45, 123.36, 123.33, 123.02, 122.86, 122.78, 122.75, 104.90, 104.35, 96.18, 95.35, 92.49, 91.25, 90.83, 90.73, 90.16, 79.70, 77.36, 55.55, 47.42, 45.62, 45.33, 42.04, 31.50, 28.78, 28.75, 24.59, 22.70, 22.46, 19.60, 14.21, 0.11, 0.05. HRMS (ESI+): *m*/*z* calcd for $C_{86}H_{84}N_4OSi_2$ ($M+H^+$), 1245.6262; found 1245.6216.

Compound 11. 6[21] (300 mg, 0.697 mmol), EDC·HCl (147 mg, 0.767 mmol), and HOBt·H_2O (104 mg, 0.770 mmol) were dissolved in anhydrous CH_2Cl_2 (7.0 mL) under N_2, and to this was added dropwise a solution of piperazine (300 mg, 3.48 mmol) in anhydrous CH_2Cl_2 (2.0 mL) under N_2. After stirring at room temperature for 22 h, the mixture was diluted with CH_2Cl_2 (10 mL). The solution was washed with aqueous 1 N HCl and saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, EtOAc) to give **11** as a white solid (284 mg, 81.6% yield). Mp: 191–192 °C. IR (KBr, cm^{-1}): 3422 (ν_{N-H}), 3277 ($\nu_{C\equiv C-H}$), 2229 ($\nu_{C\equiv C}$), 2106 ($\nu_{C\equiv C}$), 1620 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.52 (d, J = 8.5 Hz, 4H, ArH), 7.41 (d, J = 8.5 Hz, 4H, ArH), 7.40 (s, 2H, ArH), 3.30–3.28 (m, 2H, CH_2), 3.13 (s, 2H, CH), 2.83–2.81 (m, 2H, CH_2), 2.46–2.44 (m, 2H, CH_2), 2.41 (t, J = 7.0 Hz, 2H, CCH_2CH$_2$), 2.17–2.15 (m, 2H, CH_2), 1.63–1.57 (m, 2H, CH_2), 1.48–1.42 (m, 2H, CH_2), 1.37–1.27 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 167.53, 140.06, 139.16, 133.42, 132.18, 128.99, 125.16, 121.83, 92.55, 83.46, 79.63, 78.19, 47.42, 45.66, 45.35, 42.04, 31.48, 28.76, 28.73, 22.69, 19.58, 14.21. HRMS (ESI+): *m*/*z* calcd for $C_{35}H_{34}N_2O$ ($M+H^+$), 499.2749; found 499.2748.

Compound 12. To a mixture of **11** (350 mg, 0.702 mmol), 1,4-diiodobenzene (2.32 g, 7.03 mmol), $Pd(PPh_3)_4$ (40.6 mg, 0.0351 mmol), and CuI (6.68 mg, 0.0351 mmol) in anhydrous toluene (16 mL) was added diisopropylamine (16 mL) under Ar. After stirring at 40 °C for 2 h, the mixture was diluted with diethyl ether (30 mL). The solution was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (NH-SiO_2, *n*-hexane/EtOAc = 1/1, v/v) to give **12** as a white solid (442 mg, 69.7% yield). Mp: 179–180 °C. IR (KBr, cm^{-1}): 3449 (ν_{N-H}), 2229 ($\nu_{C\equiv C}$), 1630 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.70 (d, J = 8.5 Hz, 4H, ArH), 7.55 (d, J = 8.5 Hz, 4H, ArH), 7.44 (d, J = 8.5 Hz, 4H, ArH), 7.43 (s, 2H, ArH), 7.26 (d, J = 8.5 Hz, 4H, ArH), 3.32–3.30 (m, 2H, CH_2), 2.85–2.83 (m, 2H, CH_2), 2.48–2.46 (m, 2H, CH_2), 2.42 (t, J = 7.0 Hz, 2H, CCH_2CH$_2$), 2.19–2.17 (m, 2H, CH_2), 1.64–1.58 (m, 2H, CH_2), 1.52 (br s, 1H, NH), 1.48–1.42 (m, 2H, CH_2), 1.37–1.28 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 167.60, 139.76, 139.24, 137.71, 133.43, 133.24, 132.16, 131.65, 129.10, 125.17, 122.81, 122.65, 94.42, 92.55, 90.65, 89.52, 79.67, 47.46, 45.67, 45.37, 42.07, 31.49, 28.78, 28.75, 22.70, 19.59, 14.22. HRMS (ESI+): *m*/*z* calcd for $C_{47}H_{40}I_2N_2O$ ($M+H^+$), 903.1308; found 903.1296.

Compound (*R*)-3. To a mixture of **12** (78.7 mg, 0.0872 mmol), (*R*)-**10**[19] (110 mg, 0.183 mmol), $Pd(PPh_3)_4$ (6.40 mg, 0.00554 mmol), and CuI (1.05 mg, 0.00551 mmol) in anhydrous toluene (5.0 mL) was added diisopropylamine (1.0 mL) under Ar. After stirring at 40 °C for 3 h, the mixture was diluted with EtOAc (10 mL). The solution was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (NH-SiO_2, *n*-hexane/EtOAc = 2/3, v/v) to give (*R*)-**3** as a white solid (133 mg, 82.6% yield). Mp: 170–171 °C. IR (KBr, cm^{-1}): 3430 (ν_{N-H}), 2156 ($\nu_{C\equiv C}$), 1636 ($\nu_{C=N}$ and $\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, as (*R*)-**3**·$(CH_3CO_2H)_2$): δ 7.76 (t, J = 8.0 Hz, 2H, ArH), 7.57 (d, J = 8.5 Hz, 4H, ArH), 7.54–7.51 (m, 12H, ArH), 7.46 (d, J = 8.5 Hz, 4H, ArH), 7.44 (s, 2H, ArH), 7.31–7.22 (m, 20H, ArH), 7.08–7.05 (m, 8H, ArH), 6.73 (d, J = 8.5 Hz, 4H, ArH), 6.68 (d, J = 8.5 Hz, 4H, ArH), 3.95–3.90 (m, 4H, CHN), 3.36–3.34 (m, 2H, CH_2), 2.89–2.87 (m, 2H, CH_2), 2.51–2.49 (m, 2H, CH_2), 2.43 (t, J = 7.0 Hz, 2H, CCH_2CH$_2$), 2.21–2.19 (m, 2H, CH_2), 2.10 (s, 3H, CH_3CO_2),



SCHEME 3 Synthesis of **4**

1.65–1.59 (m, 2H, CH_2), 1.49–1.43 (m, 2H, CH_2), 1.38–1.29 (m, 4H, $2CH_2$), 0.91 (t, J = 7.0 Hz, 3H, CH_3), 0.74–0.71 (m, 12H, CH_3CHN), 0.26 (s, 18H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, as (*R*)-**3**·$(CH_3CO_2H)_2$): δ 178.13, 167.65, 162.67, 142.95, 142.88, 141.77, 141.69, 139.71, 139.28, 138.17, 133.36, 132.39, 132.18, 132.05, 131.98, 131.74, 131.71, 130.73, 130.65, 129.18, 129.16, 129.11, 128.78, 128.58, 128.08, 126.74, 126.71, 125.23, 123.47, 123.36, 123.35, 123.02, 122.80, 122.68, 104.33, 96.20, 92.57, 91.24, 90.85, 90.72, 90.20, 79.69, 55.58, 47.22, 45.37, 45.10, 41.85, 31.50, 28.78, 28.75, 23.57, 22.70, 22.38, 22.37, 19.60, 14.22, 0.13. HRMS (ESI+): *m*/*z* calcd for $C_{131}H_{118}N_6OSi_2$ ($M+H^+$), 1847.8984; found 1847.8906.

Compound 13. To a solution of **7**[21] (230 mg, 0.458 mmol) and NEt_3 (96 µL, 0.69 mmol) in anhydrous THF (9.5 mL) was added chloromethyl methyl ether (MOMCl) (52 µL, 0.69 mmol) at 0 °C under Ar. After stirring at room temperature for 3 h, the mixture was diluted with $CHCl_3$ (20 mL). The solution was washed with aqueous 1 N HCl, water, and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, *n*-hexane/EtOAc = 15/1, v/v) to give **13** as a colorless oil (225 mg, 90.0% yield). IR (KBr, cm^{-1}): 3293 ($\nu_{C\equiv C-H}$), 2231 ($\nu_{C\equiv C}$), 2158 ($\nu_{C\equiv C}$), 1735 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.52 (d, J = 8.5 Hz, 2H, ArH), 7.49 (d, J = 8.5 Hz, 2H, ArH), 7.38–7.36 (m, 4H, ArH), 7.35 (d, J = 8.5 Hz, 2H, ArH), 4.93 (s, 2H, OCH_2O), 3.12 (s, 1H, CH), 2.92 (s, 3H, OCH_3), 2.41 (t, J = 7.0 Hz, 2H, CCH_2CH_2), 1.63–1.57 (m, 2H, CH_2), 1.47–1.41 (m, 2H, CH_2), 1.35–1.29 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3), 0.26 (s, 9H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 168.33, 140.33, 140.01, 139.91, 139.86, 132.29, 132.13, 132.06, 131.98, 131.34, 128.66, 128.53, 125.91, 122.94, 121.89, 104.73, 95.39, 93.14, 91.84, 83.35, 79.59, 78.17, 57.58, 57.57, 31.48, 28.76, 28.70, 22.68, 19.59, 14.20, 0.09. HRMS (ESI+): *m*/*z* calcd for $C_{36}H_{38}O_3Si$ ($M+Na^+$), 569.2488; found 569.2480.

Compound 14. To a solution of **6**[21] (260 mg, 0.604 mmol) and NEt_3 (126 µL, 0.904 mmol) in anhydrous THF (12 mL) was added MOMCl (68.8 µL, 0.913 mmol) at 0 °C under Ar. After stirring at room temperature for 3 h, the mixture was diluted with $CHCl_3$ (20 mL). The solution was washed with aqueous 1 N HCl, water, and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, *n*-hexane/EtOAc = 8/1, v/v) to give **14** as a colorless oil (276 mg, 96.2% yield). IR (KBr, cm^{-1}): 3288 ($\nu_{C\equiv C-H}$), 2230 ($\nu_{C\equiv C}$), 2108 ($\nu_{C\equiv C}$), 1726 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.52 (d, J = 8.5 Hz, 4H, ArH), 7.39 (s, 2H, ArH), 7.37 (d, J = 8.5 Hz, 4H, ArH), 4.94 (s, 2H, OCH_2O), 3.12 (s, 1H, CH), 2.91 (s, 3H, OCH_3), 2.41 (t, J = 7.0 Hz, 2H, CCH_2CH_2), 1.63–1.57 (m, 2H, CH_2), 1.47–1.41 (m, 2H, CH_2), 1.37–1.27 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 168.33, 140.31, 139.90, 132.31, 132.07, 131.31, 128.65, 125.95, 121.91, 93.20, 91.86, 83.34, 79.55, 78.19, 57.564, 57.557, 31.49, 28.76, 28.69, 22.69, 19.59, 14.21. HRMS (ESI+): *m*/*z* calcd for $C_{33}H_{30}O_3$ ($M+Na^+$), 497.2093; found 497.2106.

Compound 15. To a mixture of **14** (350 mg, 0.737 mmol), 1,4-diiodobenzene (2.43 g, 7.37 mmol), $Pd(PPh_3)_4$ (42.6 mg, 0.0369 mmol), and CuI (7.02 mg, 0.0369 mmol) in anhydrous toluene (16 mL) was added diisopropylamine (16 mL) under Ar. After stirring at 40 °C for 2 h, the mixture was diluted with diethyl ether (20 mL). The solution was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, *n*-hexane/EtOAc = 15/1, v/v) to give **15** as a white solid (476 mg, 73.5% yield). Mp: 61.5–62.9 °C. IR (KBr, cm^{-1}): 2230 ($\nu_{C\equiv C}$), 1735 ($\nu_{C=O}$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.70 (d, J = 8.5 Hz, 4H, ArH), 7.55 (d, J = 8.5 Hz, 4H, ArH), 7.42 (s, 2H, ArH), 7.41 (d, J = 8.5 Hz, 4H, ArH), 7.26 (d, J = 8.5 Hz, 4H, ArH), 4.96 (s, 2H, OCH_2O), 2.95 (s, 3H, OCH_3), 2.42 (t, J = 7.0 Hz, 2H, CCH_2CH_2), 1.64–1.58 (m, 2H, CH_2), 1.48–1.42 (m, 2H, CH_2), 1.37–1.28 (m, 4H, CH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 168.41, 140.00, 139.98, 137.71, 133.25, 132.06, 131.77, 131.32, 128.74, 125.96, 122.78, 122.72, 94.44, 93.19, 91.87, 90.52, 89.52, 79.59, 57.64, 57.63, 31.49, 28.77, 28.71, 22.69, 19.61,

14.22. HRMS (ESI+): *m*/*z* calcd for $C_{45}H_{36}I_2O_3$ ($M+Na^+$), 901.0651; found 901.0652.

Compound 16. To a mixture of **15** (110 mg, 0.125 mmol), **13** (144 mg, 0.263 mmol), $Pd(PPh_3)_4$ (7.23 mg, 0.00626 mmol), and CuI (1.19 mg, 0.00625 mmol) in anhydrous toluene (5.0 mL) was added diisopropylamine (1.0 mL) under Ar. After stirring at 40 °C for 3 h, the mixture was diluted with EtOAc (20 mL). The solution was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by silica gel chromatography (SiO_2, *n*-hexane/EtOAc = 7/1, v/v) to give **16** as a white solid (203 mg, 94.4% yield). Mp: 109–110 °C. IR (KBr, cm^{-1}): 2230 ($\nu_{C\equiv C}$), 2157 ($\nu_{C\equiv C}$), 1735 ($\nu_{C=O}$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.58 (d, J = 8.5 Hz, 4H, ArH), 7.57 (d, J = 8.5 Hz, 4H, ArH), 7.53 (br s, 8H, ArH), 7.50 (d, J = 8.5 Hz, 4H, ArH), 7.44–7.39 (m, 14H, ArH), 7.36 (d, J = 8.5 Hz, 4H, ArH), 4.98 (s, 2H, OCH_2O), 4.95 (s, 4H, OCH_2O), 2.96 (s, 3H, OCH_3), 2.95 (s, 6H, OCH_3), 2.43 (t, J = 7.0 Hz, 2H, CCH_2CH_2), 2.42 (t, J = 7.0 Hz, 4H, CCH_2CH_2), 1.65–1.58 (m, 6H, CH_2), 1.49–1.42 (m, 6H, CH_2), 1.37–1.28 (m, 12H, CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3), 0.90 (t, J = 7.0 Hz, 6H, CH_3), 0.26 (s, 18H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ 168.44, 168.40, 140.02, 140.00, 139.97, 139.95, 139.94, 132.13, 132.02, 131.81, 131.80, 131.74, 131.34, 128.75, 128.54, 125.96, 125.91, 123.22, 122.93, 122.83, 122.81, 104.74, 95.39, 93.18, 93.13, 91.90, 91.86, 91.84, 91.08, 90.17, 90.15, 79.61, 57.65, 57.64, 57.635, 57.627, 31.494, 31.489, 28.78, 28.77, 28.71, 28.70, 22.70, 22.69, 19.61, 19.60, 14.21, 0.09. HRMS (ESI+): *m*/*z* calcd for $C_{117}H_{110}O_9Si_2$ ($M+Na^+$), 1737.7586; found 1737.7611.

Compound 4. To a solution of **16** (15.0 mg, 0.00874 mmol) in anhydrous THF/MeOH (1/1, v/v) (2.0 mL) was slowly added HCl (4 M in 1,4-dioxane) (0.1 mL) at 0 °C under Ar. After stirring at room temperature for 5 h, the solvents were removed under reduced pressure. The residue was diluted with $CHCl_3$ and the solution was washed with water. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to dryness. The residue was washed with *n*-hexane and MeOH, and then dried *in vacuo* to afford **4** as a white solid (13.0 mg, 94.2% yield). Mp: > 250 °C (dec.). IR (KBr, cm^{-1}): 3422 (ν_{O-H}), 2230 ($\nu_{C\equiv C}$), 2157 ($\nu_{C\equiv C}$), 1703 ($\nu_{C=O}$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.63 (d, J = 8.0 Hz, 4H, ArH), 7.60 (d, J = 8.0 Hz, 4H, ArH), 7.55 (d, J = 8.0 Hz, 4H, ArH), 7.39–7.37 (m, 22H, ArH), 7.29 (d, J = 8.0 Hz, 4H, ArH), 2.42 (t, J = 7.0 Hz, 2H, CCH_2CH_2), 2.41 (t, J = 7.0 Hz, 4H, CCH_2CH_2), 1.64–1.57 (m, 6H, CH_2), 1.48–1.41 (m, 6H, CH_2), 1.37–1.28 (m, 12H, CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3), 0.90 (t, J = 7.0 Hz, 6H, CH_3), 0.27 (s, 18H, TMS). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 175.51, 174.38, 140.05, 139.77, 139.74, 139.71, 132.13, 132.00, 131.87, 131.74, 131.66, 131.62, 130.62, 130.57, 128.57, 128.44, 126.11, 126.04, 123.18, 123.11, 123.02, 122.99, 104.97, 95.69, 93.21, 91.02, 90.94, 90.52, 90.40, 79.60, 31.49, 28.76, 28.70, 22.69, 19.61, 19.60, 14.21, 0.14. HRMS (ESI−): *m*/*z* calcd for $C_{111}H_{98}O_6Si_2$ ($M-H^-$), 1581.6824; found 1581.6843.

2.2 | General Procedure for the Preparation of Amidinium–Carboxylate Duplexes ((*R*)-1·2 and (*R*)-3·4)

A typical experimental procedure is described below. (*R*)-**1** (23.1 mg, 0.0185 mmol) and **2** (20.0 mg, 0.0185 mmol) were dissolved in $CHCl_3$ (5 mL) and the solution was stirred at ambient temperature and then poured into a large amount of *n*-hexane. The resulting precipitate was collected by centrifugation, washed with *n*-hexane, and dried *in vacuo* at ambient temperature to afford (*R*)-**1**·**2** (43.1 mg, 100% yield) as a white solid. In the same way, the (*R*)-**3**·**4** duplex (64.9 mg, 100% yield) was prepared by mixing (*R*)-**3** (35.0 mg, 0.0189 mmol) and **4** (30.0 mg, 0.0189 mmol).

2.3 | General Procedure for Asymmetric Aldol Reaction Catalyzed by Complementary Double Helices

A typical experimental procedure is described below. All experiments were performed under Ar. Stock solutions of (*R*)-**3**·**4** (4.0 mM) in anhydrous $CHCl_3$ (solution **I**) and 4-nitrobenzaldehyde (0.20 M) in anhydrous cyclohexanone (solution **II**) were prepared. A 50 μL aliquot of **I** (0.20 μmol) was transferred to a vial, and the solvent was evaporated to dryness. To this were added anhydrous cyclohexanone (100 μL) and a 100 μL aliquot of **II** (20 μmol) at 25 °C under Ar. After stirring at 25 °C for 72 h, the mixture was subjected to column chromatography (SiO_2, *n*-hexane/EtOAc (3/1, v/v)) to give a mixture of 4-nitrobenzaldehyde and a desired aldol product. The conversion of the substrate and yield of the product were estimated by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard (Table 1). The enantiomeric excess (ee) was determined to be 34% for *syn*-**5** and 34% *anti*-**5** by chiral HPLC analysis with a DAICEL CHIRALPAK AD-H column (0.46 cm (i.d.) × 25 cm) using *n*-hexane/2-propanol (95/5, v/v) as the eluent at a flow rate of 1.0 mL/min; *syn*-**5**:[25] $t_{R(2R,1'R)}$ = 31.3 min and $t_{R(2S,1'S)}$ = 41.5 min, *anti*-**5**:[26,27] $t_{R(2S,1'R)}$ = 45.2 min and $t_{R(2R,1'S)}$ = 62.0 min (run 4 in Table 1).

3 | RESULTS AND DISCUSSION

3.1 | Synthesis of Complementary Dimer and Trimer Strands

The chiral dimer and trimer strands of the *m*-terphenyl groups linked through *p*-diethynylbenzene units with the chiral amidine (**A**) and achiral piperazine (**P**) groups introduced at the terminus (edge-achiral dimer: (*R*)-**1**) and center (center-achiral trimer: (*R*)-**3**) of the strands, respectively, and its complementary achiral carboxylic acid (**C**) dimer (**2**) and trimer (**4**) strands were synthesized in a stepwise manner according to a previously reported method[21] and Schemes 1–3. All the oligomers were purified by silica gel chromatography and characterized and identified by ^1H and ^{13}C NMR spectroscopies and mass measurements (see Section 2.1 and Supporting Information).

3.2 | Complementary Double-Helix Formation

The complementary duplex formations of the chiral/achiral dimer ((*R*)-**1**) and trimer ((*R*)-**3**) with the achiral carboxylic acid dimer (**2**) and trimer (**4**), respectively, were investigated by mixing a 1:1 molar ratio and confirmed by electron-spray ionization mass spectrometry (ESI-MS) and ^1H NMR spectroscopy (Figures S1–S3). The ^1H NMR spectra of the (*R*)-**1**·**2** and (*R*)-**3**·**4** duplexes measured in $CDCl_3$ (Figures S2 and S3) were rather complicated because of the **AP** and **APA** hetero sequences of the chiral strands and relatively weak interactions between the dimer strands, respectively (Figures S2 and S3). Particularly, the signals due to the aromatic and piperazine (**P**) protons of the (*R*)-**1**·**2** dimer duplex were significantly broadened (Figure S2) when compared to that of the double-helical complex formed between the chiral amidine (**A**) and carboxylic acid (**C**) dimers.[19,21] However, these duplexes showed the characteristic N–H protons due to the amidinium–carboxylate salt-bridges at around 13.2 and 13.4 ppm, respectively (Figures S2 and S3), although the corresponding salt-

bridged N–H protons formed between the **P** and **C** units could not be clearly observed because of their weak acid-base interactions (see below). The 2D NOESY spectra of the (*R*)-**1**·**2** and (*R*)-**3**·**4** duplexes (Figures S7 and S9) displayed several NOE cross-peaks between the strands, indicating the double-helix formations stabilized by the amidinium–carboxylate salt bridges.[15,19]

The association constant (K_a) between the model monomers of piperazine (**6**) and carboxylic acid (**11**) used as the bifunctional catalytic site was estimated to be ca. 6.6×10^2 M^{-1} in $CDCl_3$ at 25 °C by ^{1}H NMR titration experiments (Figure S11), which was significantly lower than that of the (*R*)-**A**·**C** duplex (2.8×10^6 M^{-1}).[23] The K_a values of the (*R*)-**1**·**2** and (*R*)-**3**·**4** duplexes were also roughly estimated to be ca. 1×10^8 and $> 2 \times 10^{10}$ M^{-1}, respectively, in $CDCl_3$ at room temperature by the CD dilution experiments (Figure S12); the former K_a value was several orders of magnitude lower than that of the (*R*)-**AA**·**CC** duplex (3.0×10^{12} M^{-1})[23] as anticipated from the low K_a value of the **6**·**11** duplex, while the dissociation of (*R*)-**3**·**4** into single strands was negligible within the concentration range from 0.10 mM to 0.49 μM (Figure S12).

Interestingly, the circular dichroism (CD) spectra of the (*R*)-**1**·**2** and (*R*)-**3**·**4** duplexes exhibited intense split-type Cotton effects in the absorption regions of the conjugated backbones (ca. 250–375 nm) in $CDCl_3$, despite the fact that the achiral **P** unit was located at the terminus (edge-achiral dimer: (*R*)-**1**) or center (center-achiral trimer: (*R*)-**3**) of the strands (Figure 2a,b). The optically-active single strands (*R*)-**1** and (*R*)-**3** showed very weak CD signals in the same absorption regions as anticipated (Figure 2a,b). These results suggest that the chirality of the amidine units is efficiently transferred to the next achiral piperazine unit when complexed with the complementary achiral carboxylic acid strands, resulting in an excess of the right-handed double helices induced by the chiral amidine residues with an (*R*)-configuration.[12,15,19–24] The helix-sense excesses of the (*R*)-**1**·**2** and (*R*)-**3**·**4** double helices could not be exactly estimated because their CD spectral patterns and intensities were different from those of the completely right-handed double-helical (*R*)-**AA**·**CC** complex,[12,15,19–24] but that of the (*R*)-**1**·**2** duplex was, at least, likely imperfect at 25 °C. The temperature-dependent CD spectral changes of the (*R*)-**1**·**2** and (*R*)-**3**·**4** double helices also support this presumption (Figure 2c,d); the CD intensities of (*R*)-**1**·**2** remarkably increased at the lower temperature, resulting in the formation of a double-helix with a higher helix-sense excess,

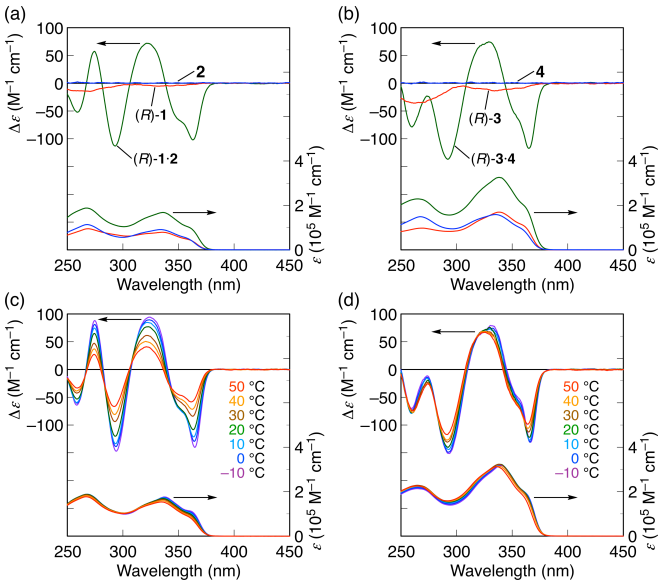


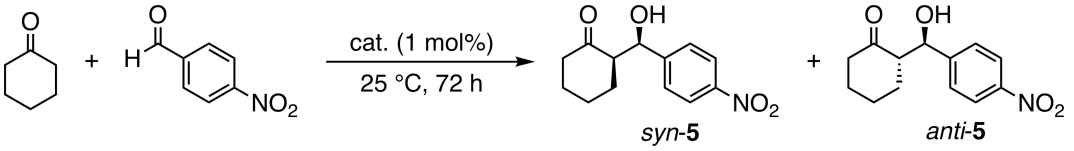
FIGURE 2 CD and absorption spectra (0.050 mM) of (a) (*R*)-**1**, **2**, and (*R*)-**1**·**2** and (b) (*R*)-**3**, **4**, and (*R*)-**3**·**4** in $CDCl_3$ at 25 °C. Temperature-dependent CD and absorption spectral changes of (c) (*R*)-**1**·**2** and (d) (*R*)-**3**·**4** (0.050 mM) in $CDCl_3$.

whereas those of (*R*)-**3**·**4** almost remained unchanged within the temperature range from 20 to –10 °C, indicating a stable double-helix formation ((*R*)-**3**·**4**) with an excess one-handedness at these temperatures.

3.3 | Asymmetric Direct Aldol Reaction

Based on this structural information (Section 3.2), the complementary right-handed double-helical dimer and trimer bearing an achiral, but catalytically-active bifunctional acid-base pair at the terminus ((*R*)-**1**·**2**) and center ((*R*)-**3**·**4**) of the double helices, respectively, were then used as organocatalysts for the asymmetric direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde at 25 °C (Table 1).[28] For comparison, the chiral trimer ((*R*)-**3**) strand and its complex with the carboxylic acid monomer ((*R*)-**3**·(**6**)$_3$) were also used as the catalysts.

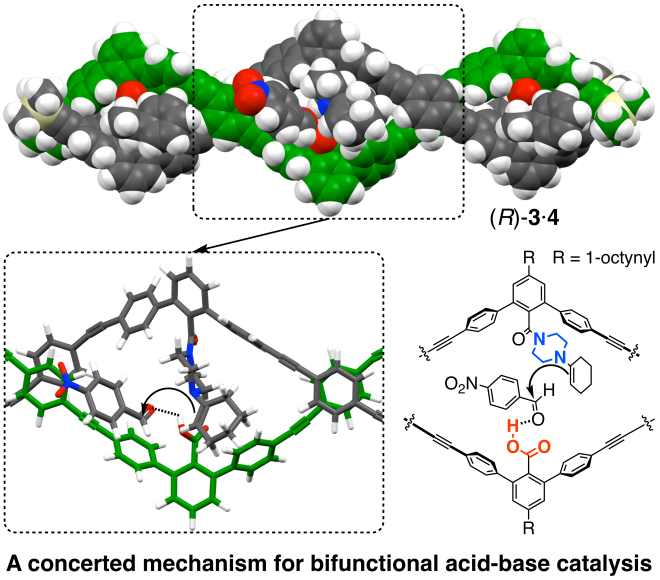
TABLE 1 Asymmetric direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by single-stranded amidine/piperazine dimer ((*R*)-**1**) and trimer ((*R*)-**3**) and complementary double helices ((*R*)-**1**·**2** and (*R*)-**3**·**4**)[a]



Run	Catalyst	Conversion (%)[b]	Yield (%)[b]	dr (%)[b] *syn*-5/*anti*-5	ee (%)[c] *syn*-5 [(2*R*,1'*R*)-rich][25]	ee (%)[c] *anti*-5 [(2*S*,1'*R*)-rich][26,27]
1	(*R*)-**1**·**2**	22	6	34/66	10	14
2	(*R*)-**3**	13	2	75/25	2	8
3[d]	(*R*)-**3**·(**6**)$_3$	13	2	67/33	2	0
4	(*R*)-**3**·**4**	62	57	23/77	34	34
5[e]	L-proline	–	65	37/63	67	89

[a]The reaction was carried out in cyclohexanone with 4-nitrobenzaldehyde (0.1 M) in the presence of a catalyst (1 mol%) at 25 °C for 72 h. The catalyst concentration [cat.] = 1 mM. [b]Conversion, yield, and diastereomeric ratio (dr) were estimated by ^{1}H NMR. [c]Determined by chiral HPLC. [d]3 mol% of **6** was used. [e]Cited from ref. 26: the reaction was done in DMSO containing 20 vol% of cyclohexanone with 4-nitrobenzaldehyde (0.1 M) in the presence of L-proline (20 mol%) at rt for 24–48 h.

The double-helical trimer with the catalytically-active piperazine/carboxy unit in the middle (*R*)-**3**·**4** efficiently catalyzed the direct aldol reaction to produce the *syn*- and *anti*-hydroxy ketone adducts (**5**) (*syn*/*anti* = 23/77) in 57% yield with the moderate enantioselectivities of 34 (*syn*-**5**) and 34% enantiomeric excess (ee) (*anti*-**5**) (run 4 in Table 1), whereas the double-helical dimer catalyst with the piperazine/carboxy unit at the terminal ((*R*)-**1**·**2**) afforded the products (*syn*/*anti* = 34/66) in poor yield (6%) with lower enantioselectivities (10 (*syn*-**5**) and 14% ee (*anti*-**5**)) (run 1 in Table 1) because the interstrand piperazine/carboxy pair located at the edge of the dimer duplex may be too flexible to maintain its bifunctional catalytic and enantioselective activities (Figure 1b, left). As anticipated, the chiral amidine/achiral piperazine trimer strand ((*R*)-**3**) and its model complexed with **6** ((*R*)-**3**·(**6**)$_3$) hardly catalyzed the aldol reaction to give the product in 2% yield with a poor enantioselectivity (0 – 8% ee) (runs 2 and 3 in Table 1). These results clearly revealed the key role of the one-handed double-helical framework for supramolecular bifunctional organocatalysis (Figure 1b, right) through which an achiral acid-base pair at the center of the (*R*)-**3**·**4** double-helix is situated in the chiral space generated and stabilized by the neighboring chiral amidinium–carboxylate salt-bridges, thereby enabling the achiral catalytic site to function as an asymmetric organocatalyst like the optically-active L-proline (Figure 3).[10,28] Therefore, the catalytic activity and enantioselectivity of the (*R*)-**3**·**4** trimer double-helix were remarkably enhanced compared to those of the dimer (*R*)-**1**·**2** double-helix, although the enantioselectivity was lower than that catalyzed by L-proline (run 5 in Table 1).[26]



A concerted mechanism for bifunctional acid-base catalysis

FIGURE 3 A proposed transition state model for the asymmetric aldol reaction. Interstrand bifunctional carboxy and secondary amino residues located inside the helical cavity largely contribute to the enantioselective aldol reaction in a concerted manner like molecular catalysts such as D- or L-proline.

4 | CONCLUSION

In conclusion, we have synthesized two novel double-helical dimer and trimer composed of chiral and achiral complementary strands. The chiral strands consisting of chiral amidine/achiral piperazine introduced at the terminus or center of the strands form a preferred-handed double-helical structure when complexed with their complementary carboxylic acid strands stabilized by the chiral amidinium–carboxylate salt-bridges. The chiral trimer strand showed almost negligible catalytic and enantioselective activities for the direct asymmetric aldol reaction. However, once complexed with the achiral complementary carboxylic acid strand, the catalytic activity and enantioselectivity were significantly enhanced due to the one-handed double-helix formation stabilized by chiral salt-bridges through which interstrand achiral piperazine and carboxylic acid residues serve as a bifunctional supramolecular asymmetric organocatalyst. Apparently, the observed enantioselectivity of the double-helical catalyst was not satisfactory high. However, we believe that the present approach will provide a promising and conceptually new way to develop more effective and specific bifunctional asymmetric organocatalysts by even introducing suitable bifunctional achiral units in a one-handed double-helical framework. Further studies along this line are now underway in our laboratory.

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CONFLICT OF INTEREST

There are no conflicts to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.