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Enantioselective synthesis of tripodal cyclophanes and pyridinophanes by intramolecular [2+2+2] cycloaddition

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ABSTRACT

An enantioselective intramolecular [2+2+2] cycloaddition of 2-aminophenol-tethered triynes and diyne-nitriles proceeded using the chiral Rh catalysts, and tripodal cyclophanes and pyridinophanes with a long ansa chain (up to [16]pyridinophane) were obtained in acceptable yield with high to almost perfect ee. In the reaction of triynes, we elucidated that the oxygen atom at the alkyne terminus is essential for the excellent enantioselectivity. For the construction of cage-type molecule, the choice of rigid tether, which connects 1,6-diyne moiety with a side carbon chain having alkyne or cyano group on its terminus, was important, and 8-amino-2-naphthol moiety was also a preferable tether.

1. Introduction

Cyclophane is a cage-type molecule, where non-adjacent multi-substituents on benzene ring are connected with ansa chain(s).[1] When the ansa chain cannot flip around the benzene ring, planar chirality is created. The use of chiral dipodal cyclophanes was already reported, and chiral discriminator,[2] chiral polymers,[3] and chiral ligand[4] are the representative examples. The major protocol for the preparation of these planar-chiral cyclophanes had been resolution of racemic compounds or diastereomers, however, catalytic and enantioselective synthesis was reported in these years: Tanaka reported a Rh- or Pd-catalyzed coupling of dithiol with dibromide for the synthesis of paracyclophanes.[5] He further disclosed a Rh-catalyzed [2+2+2] cycloaddition for the synthesis of *meta*- and paracyclophanes.[6] We also developed two strategies for the enantioselective construction of chiral paracyclophane skeletons: consecutive Sonogashira coupling using a chiral Pd catalyst[7] and *ortho*-lithiation using sparteine.[8] In contrast to these achievements of dipodal cyclophane chemistry, tripodal cyclophane remains unexplored. A simple approach to the tripodal cyclophane synthesis is an intramolecular [2+2+2] cycloaddition of branched triynes, and Huber disclosed the first report using Ziegler catalyst in 1966.[9] But the mixture of symmetrical 1,3,5- and unsymmetrical 1,2,4-isomers were obtained in low yield. Damrauer realized relatively high regioselectivity (7:1) in the reaction of silicon-tethered triynes, but the yield was low (ca. 30%).[10] Mascal achieved the improved yield of 50% by using a stoichiometric amount of [$CoCp(CO)_2$] under the highly diluted condition at high temperature, but the regioselectivity was low.[11,12]

Against these backgrounds, we focused on the development of the first enantioselective synthesis of tripodal cyclophanes by intramolecular [2+2+2] cycloaddition of branched triynes. We designed triyne **1** as a preferable substrate: the oxidative coupling proceeds selectively at nitrogen-tethered 1,6-diyne moiety. The rigid tether of 2-aminophenol controls the orientation of the alkyl side chain, and intramolecular alkyne insertion smoothly proceeds prior to intermolecular one. Further, methoxymethyl group at the alkyne terminus activates the alkyne moiety and facilitates the reaction. Subsequent reductive elimination gives planar-chiral tripodal cyclophane **2** (Scheme 1).

In the precedent communication,[13] we reported that Rh-MeDUPHOS catalyst realized the high yield and excellent enantioselectivity, and that chiral tripodal compounds with various lengths of ansa chains were obtained. In this manuscript, we scrutinized the role of methoxymethyl group for the enantioselective induction. Then, we further examined the hetero-[2+2+2] cycloaddition of 1,6-diyne-nitriles for the enantioselective synthesis of tripodal pyridinophanes, where the three substituents at 2, 4, and 5-positions of pyridine ring were connected together. Transition metal-catalyzed hetero-[2+2+2] cycloaddition of two alkynes and a cyano compound is an atom-economical and reliable protocol for

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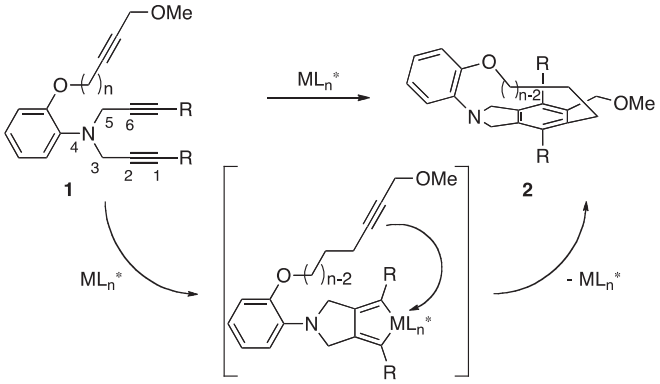


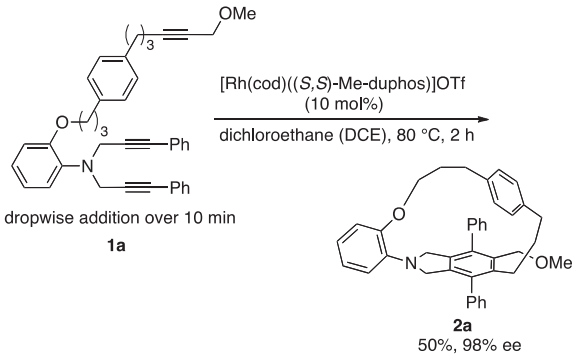
Scheme 1. Design of an appropriate triyne for the synthesis of tripodal cyclophane.

the synthesis of multi-substituted pyridine since the first report of Co-catalyzed reaction by Yamazaki in 1973.[14,15] Ru, Ni, and Fe-catalyzed reactions were also reported.[16] Maryanoff used the Co-catalyzed reaction for the synthesis of dipodal pyrdinophanes: the cycloaddition of yne-nitriles with alkynes selectively provided 2,4-pyridinophanes,[17a] and the cycloaddition of diynes with cyano compounds did 2,5-pyridinophanes.[17b] But there is no example of catalytic and enantioselective synthesis of pyridinophanes. In contrast, the planar chirality of pyridinophane is a promising chiral motif, and their applications as a coenzyme NADH model[18a,b] and chiral ligands[18c] were already reported. Therefore, efficient asymmetric synthesis of chiral pyridinophanes is strongly desired.

2. Results and discussion

2.1. Effect of side chain structure on the enantioselectivity

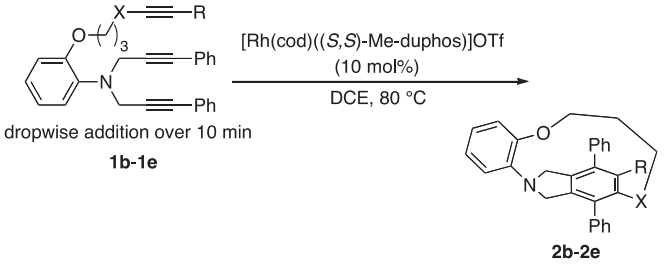
We achieved the extremely high enantioselectivity in the intramolecular reaction of triynes, which have 3-methoxypropyn-1-yl group at the end of alkyl side chain derived from the phenolic oxygen atom.[13] The side chain with paraphenylene moiety could be also installed, and the reaction of triyne **1a** proceeded to give macrocyclic tripodal cyclophane **2a** with excellent ee (Scheme 2).



Scheme 2. Reaction of triyne **1a** possessing a paraphenylene-containing tether.

We scrutinized the effect of side chain structure on the enantioselectivity (Table 1). In the precedent communication,[13] we installed an oxygen atom to the propargylic position in the carbon side chain of all triynes, and the result of triyne **1b** having phenyl-substituted diyne termini was listed as a selected example at entry 1. The absolute configuration of bromophenyl-substituted cycloadduct was determined by X-ray diffraction analysis.[13] We next examined triyne **1c**, where the oxygen atom was located at another propargylic position, under the same reaction conditions (entry 2).

Table 1
Effect of oxygen atom on the enantioselectivity



Entry	X	R	Triyne	Time/h[a]	Yield/%	ee/%
1	CH_2CH_2	CH_2OMe	**1b**	2	88 (**2b**)	98
2	OCH_2	Me	**1c**	0.5	55 (**2c**)	88
3	CH_2	Me	**1d**	1	81 (**2d**)	88
4	CH_2	H	**1e**	2	78 (**2e**)	94

[a] Reaction time after completion of dropwise addition of triynes **1**.

As a result, the corresponding cycloadduct **2c** was obtained, and its ee was still high, but significantly lower than entry 1. When triyne **1d** with no oxygen atom at both propargylic positions was subjected, the reaction smoothly proceeded to give cycloadduct **2d** in good yield with the same ee as entry 2 (entry 3). Triyne **1e** with unsubstituted alkyne terminus was also a good substrate, and the ee of the corresponding tripodal product **2e** was higher ee than entries 2 and 3, but lower than entry 1 (entry 4).[19]

In the present catalysis, planar chirality is induced by the direction of the alkyne insertion to the metallacyclopentadiene intermediate. The results of Table 1 indicate that the carbon side chain without oxygen atom can control the enantioselectivity by the aid of the chiral Rh catalyst, and the ee of about 90% was achieved. The coordination of oxygen atom at the appropriate propargylic position to metal center improved it up to 98% (Fig. 1).

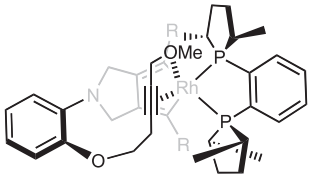
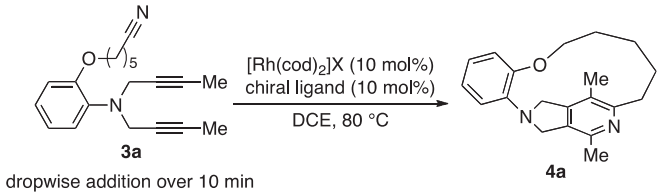


Fig. 1. Effective asymmetric induction by the coordination of oxygen to the metal center.

2.2. Screening of chiral ligands for the hetero-[2+2+2] cycloaddition of a diyne-nitrile

As an extension of our work, we examined a hetero-[2+2+2] cycloaddition of diyne-nitriles. There is no example of planar-chirality induction along with the construction of pyridine ring.[20] We chose diyne-nitrile **3a** with five-carbon chain between phenolic oxygen and a cyano group as a model substrate, and subjected it to the optimal conditions for the reaction of triynes, but the desired cycloadduct **4a** could not be detected (entry 1 in Table 2). When we switched MeDUPHOS to BINAP, tripodal **4a** was obtained in moderate yield with high ee (entry 2). Counter anion of Rh did not affect the enantioselectivity but BARF gave the best yield in shorter reaction time (entries 2–4). After screening several BINAP derivatives (entries 5–8), we were pleased to find that Cy-BINAP achieved the excellent enantioselectivity (entry 8). Among BINAP derivatives, only Cy-BINAP showed the opposite enantioinduction. When BARF was used in place of OTf, triyne **3a** was completely consumed right after dropwise addition of **3a** over 10 min (entry 9).[19]

Table 2
Screening of chiral catalysts for the hetero-[2+2+2] cycloaddition



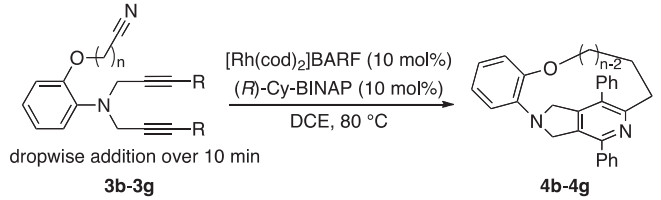
Entry	X	Chiral ligand	Time/h[a]	Yield/%	ee/%
1	OTf	(*S*,*S*)-MeDUPHOS	4	ND[b]	—
2	OTf	(*S*)-BINAP	2	52	94 (*R*)
3	BF_4	(*S*)-BINAP	2	66	95 (*R*)
4	BARF[c]	(*S*)-BINAP	0.5	77	94 (*R*)
5	OTf	(*S*)-tolBINAP	2	62	92 (*R*)
6	OTf	(*S*)-H_8-BINAP	2	57	92 (*R*)
7	OTf	(*S*)-SEGPHOS[d]	3	Trace	
8	OTf	(*S*)-Cy-BINAP	2	57	95 (*S*)
9	BARF[c]	(*R*)-Cy-BINAP	0	79	97 (*R*)

[a] Reaction time after completion of dropwise addition of diyne-nitrile **3a**.
[b] Not detected.
[c] Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.
[d] 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodi-oxole.

2.3. Scope of diyne-nitriles in the hetero-[2+2+2] cycloaddition for the synthesis of pyridinophanes

The optimal reaction conditions were in hand, and we examined the substrate scope (Table 3). Diyne-nitrile **3b** with phenyl-substituted diyne termini was also transformed into tripodal pyridinophane **4b** with almost perfect ee, but there was a lack of reproducibility in yield (14–78% for four-time experiments) (entry 1).[21] Regarding the length of carbon chain (from n=3–6), the reaction of diyne-nitriles **3c**–**e** smoothly proceeded to give the cycloadducts **4c**–**e** in high yield with excellent ee (entries 2–4). Even diyne-nitrile **3f** with further longer carbon chain (n=11) underwent an intramolecular reaction to give [16]pyridinophane **4f** in high yield, but its value of specific rotation was almost zero, and racemic isomers could not be resolved by HPLC analysis using several chiral columns, which means that the enantiomers probably interconvert each other at room temperature (entry 5). To stop the flipping of the long ansa chain, we used diyne-nitrile **3g** with phenyl-substituted diyne termini and ascertained the asymmetric induction, but it was moderate (66% ee) (entry 6). The high enantioselectivity was achieved by using BINAP in this case (entry 7).

Table 3
Substrate scope of diyne-nitriles in the hetero-[2+2+2] cycloaddition

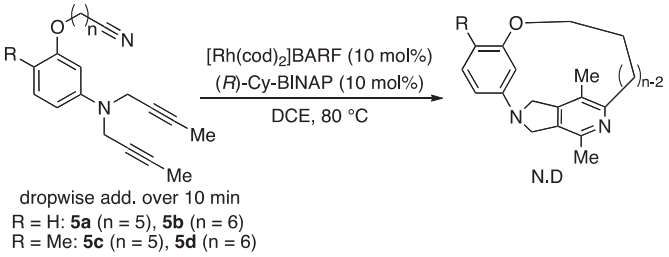


Entry	n	R		Time/h[a]	Yield/%	ee/%[b]
1	5	Ph	**3b**	0	Up to 78(**4b**)	99
2	3	Me	**3c**	0	79 (**4c**)	98
3	4	Me	**3d**	0	85 (**4d**)	97
4	6	Me	**3e**	0	89 (**4e**)	97
5	11	Me	**3f**	0	84 (**4f**)	—
6	11	Ph	**3g**	2.5	81 (**4g**)	66
7[c]	11	Ph	**3g**	1	84 (**4g**)	91

[a] Reaction time after completion of dropwise addition of diyne-nitriles **3**.
[b] The absolute configuration is not determined.
[c] BINAP was used in place of Cy-BINAP.

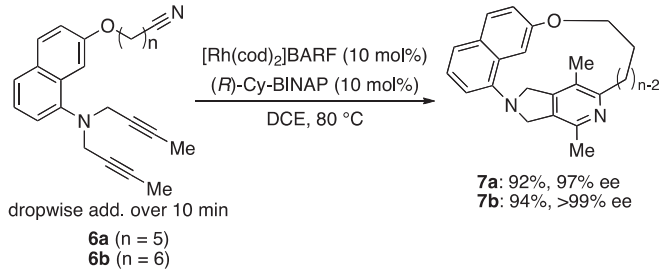
2.4. Rigid tether other than 2-aminophenol moiety

ortho-Phenylene moiety as a rigid tether is probably important for the efficient intramolecular cycloaddition of diyne-nitriles possessing very long ansa chains. We next subjected 3-aminophenol-tethered diyne-nitriles **5a**, **5b** under the same reaction conditions (Scheme 3). They were immediately consumed, but the desired cycloadducts could not be detected in the complex mixture. To suppress the flexibility of the side chain, we installed a methyl group at its *ortho* position, but the reaction of **5c**, **5d** also gave a complex mixture without the formation of desired cycloadducts (Scheme 3).



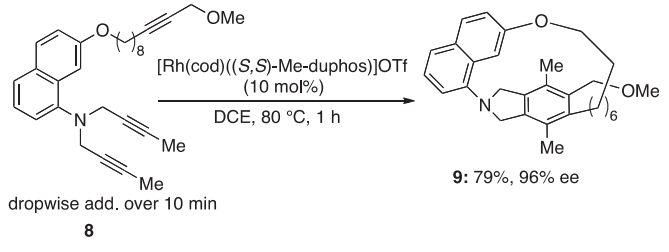
Scheme 3. Reaction of 3-aminophenol-tethered diyne-nitriles.

We next used 8-amino-2-naphthol as a rigid tether, because the orientation of two substituents at the 1 and 7 positions of naphthalene ring are the same as that of 1 and 2 positions of benzene ring (Scheme 4). As a result, an intramolecular reaction of diyne-nitriles **6a**, **6b** efficiently proceeded to give the corresponding tripodal pyridinophane **7a**, **7b** in high yield with excellent ee.



Scheme 4. Reaction of 8-amino-2-naphthol-tethered diyne-nitriles.

The same tether also worked well in the alkyne trimerization, and triyne **8** underwent an intramolecular reaction to give tripodal cyclophane **9** in high yield with excellent ee (Scheme 5).



Scheme 5. Reaction of 8-amino-2-naphthol-tethered triyne.

3. Conclusions

We have comprehensively studied the enantioselective intramolecular [2+2+2] cycloaddition of branched triynes and diyne-

nitriles for the synthesis of planar-chiral tripodal compounds. In the reaction of triynes, methoxymethyl group played an important role for the induction of the extremely high enantioselectivity. The reaction of diyne-nitriles also proceeded with excellent enantioselectivity, and even a [16]pyridinophane could be obtained. This is the first example of catalytic and enantioselective synthesis of pyridinophanes. The rigid tether in substrate, such as *ortho*-phenylene and 1,7-naphthylene moiety, was found to be very important for the efficient construction of cage-type macrocyclic molecules.

4. Experimental section

4.1. General

Anhydrous 1,2-dichloroethane (DCE) was purchased and dried over activated molecular sieves 4 Å. All solvents were degassed by argon bubbling prior to use. All reactions were carried out under an atmosphere of argon in oven-dried glassware with a magnetic stirring bar.

IR spectra were recorded with a JASCO FT/IR-4100 spectrometer. NMR spectra were recorded with a JEOL AL-400 (400 MHz), Lambda-500 (500 MHz), or Bruker Avance-600 (600 MHz) spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. High-resolution mass spectra (HRMS) were measured on a JEOL JMS-SX102A with FAB (Fast Atomic Bombardment) method. Optical rotations were measured with Jasco DIP-1000 or DIP-2000 polarimeter.

4.2. Typical experimental procedure for the [2+2+2] cycloaddition

4.2.1. [2+2+2] Cycloaddition of the triynes. [Rh(cod)((*S*,*S*)-MeDUPHOS)]OTf (6.7 mg, 0.010 mmol) was placed in a Schlenk tube, which was then evacuated and backfilled with argon. To the reaction vessel was added dichloromethane (1.0 mL). While stirring the solution at room temperature for 5 min, hydrogen gas was introduced, and the solution was further stirred for 30 min at room temperature. After removal of the solvent and hydrogen gas under reduced pressure, argon gas was introduced. DCE (0.5 mL) was added and the reaction vessel was immersed in an oil bath at 80 °C for 5 min. Then, triyne (0.10 mmol) in DCE (2.1 mL) was added dropwise via syringe pump over 10 min. After the reaction mixture was stirred at the temperature, the solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give pure cycloadduct. The ee was determined by HPLC analysis using a chiral column.

4.2.2. Hetero-[2+2+2] cycloaddition of the diyne-nitriles. [$Rh(cod)_2$]BARF (5.7 mg, 0.010 mmol) and Cy-BINAP (6.8 mg, 0.010 mmol) were placed in a Schlenk tube, which was then evacuated and backfilled with argon. To the reaction vessel was added dichloromethane (1.0 mL). While stirring the solution at room temperature for 5 min, hydrogen gas was introduced, and the solution was further stirred for 30 min at room temperature. After removal of the solvent and hydrogen gas under reduced pressure, argon gas was introduced. DCE (0.5 mL) was added and the reaction vessel was immersed in an oil bath at 80 °C for 5 min. Then, diyne-nitrile (0.10 mmol) in DCE (2.1 mL) was added dropwise via syringe pump over 10 min. After the reaction mixture was stirred at the temperature, the solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give pure cycloadduct. The ee was determined by HPLC analysis using a chiral column.

4.3. Physical properties of substrates and cycloadducts

*4.3.1. 2-(3-(4-(6-Methoxyhex-4-ynyl)phenyl)propyloxy)-N,N-bis(3-phenylprop-2-ynyl)benzenamine (**1a**).* Brown solid. Mp 53–54 °C; IR (CH_2Cl_2) 3055, 2312, 1599, 1363, 1244, 1093 cm^{-1}; ^1H NMR δ 1.76–1.85 (m, 2H), 2.17–2.26 (m, 4H), 2.67 (dd, *J*=6.3, 8.0 Hz, 2H), 2.87 (dd, *J*=6.5, 8.8 Hz, 2H), 3.38 (s, 3H), 4.06 (t, *J*=6.3 Hz, 2H), 4.10 (t, *J*=2.2 Hz, 2H), 4.38 (s, 4H), 6.87 (ddd, *J*=1.7, 7.8, 7.8 Hz, 1H), 6.94 (ddd, *J*=1.7, 7.8, 7.8 Hz, 1H), 7.01 (ddd, *J*=1.7, 7.8, 7.8 Hz, 1H), 7.04–7.17 (m, 4H), 7.26–7.32 (m, 7H), 7.38–7.42 (m, 4H); ^{13}C NMR δ 18.1, 30.1, 31.0, 32.0, 34.3, 41.7, 57.3, 60.1, 67.4, 76.2, 84.9, 85.5, 86.6, 112.3, 120.4, 120.6, 123.2, 123.4, 127.9, 128.1, 128.5, 131.7, 138.5, 139.0, 151.7 (two pairs of aromatic peaks are overlapped); HRMS (FAB, positive) *m*/*z* calcd for $C_{40}H_{40}NO_2$, 566.3059 ($[M+1]^+$); found, 566.3058 ($[M+1]^+$).

*4.3.2. 2-(4-Oxa-6-octynyloxy)-N,N-bis(3-phenylprop-2-ynyl)benzenamine (**1c**).* Yellow oil. IR (CH_2Cl_2) 3059, 2227, 1595, 1500, 1362, 1242, 1138, 1092 cm^{-1}; ^1H NMR δ 1.81 (t, *J*=2.2 Hz, 3H), 2.19 (tt, *J*=6.1, 6.1 Hz, 2H), 3.76 (t, *J*=6.1 Hz, 2H), 4.11 (q, *J*=2.2 Hz, 2H), 4.16 (t, *J*=6.1 Hz, 2H), 4.34 (s, 4H), 6.90–6.97 (m, 2H), 7.02 (ddd, *J*=1.7, 7.7, 7.7 Hz, 1H), 7.26–7.30 (m, 7H), 7.39–7.44 (m, 4H); ^{13}C NMR δ 3.5, 29.6, 41.6, 58.7, 65.1, 66.6, 75.2, 82.3, 84.9, 85.5, 112.4, 120.5, 120.6, 123.1, 123.5, 128.0, 128.1, 131.7, 138.5, 151.7; HRMS (FAB, positive) *m*/*z* calcd for $C_{31}H_{30}NO_2$, 448.2277 ($[M+1]^+$); found, 448.2282 ($[M+1]^+$).

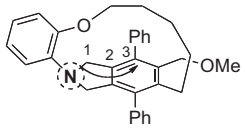
*4.3.3. 2-(5-Heptynyloxy)-N,N-bis(3-phenylprop-2-ynyl)benzenamine (**1d**).* Yellow oil. IR (CH_2Cl_2) 3059, 2235, 1595, 1500, 1365, 1240, 1140, 1107 cm^{-1}; ^1H NMR δ 1.74 (t, *J*=2.5 Hz, 3H), 1.71–1.78 (m, 2H), 1.97–2.05 (m, 2H), 2.22 (tq, J_t=2.5 Hz, J_q=2.5 Hz, 2H), 4.07 (t, *J*=6.3 Hz, 2H), 4.35 (s, 4H), 6.89 (dd, *J*=1.5, 7.7 Hz, 1H), 6.93 (ddd, *J*=1.5, 7.7, 7.7 Hz, 1H), 7.02 (ddd, *J*=1.5, 7.7, 7.7 Hz, 1H), 7.26–7.30 (m, 7H), 7.38–7.43 (m, 4H); ^{13}C NMR δ 3.4, 18.5, 25.7, 28.5, 41.7, 67.8, 75.9, 78.7, 84.9, 85.5, 112.3, 120.5, 120.6, 123.2, 123.5, 127.9, 128.1, 131.7, 138.5, 151.8; HRMS (FAB, positive) *m*/*z* calcd for $C_{31}H_{29}NO$, 431.2249 (M); found, 431.2230 (M).

*4.3.4. 2-(5-Hexynyloxy)-N,N-bis(3-phenylprop-2-ynyl)benzenamine (**1e**).* Yellow oil. IR (CH_2Cl_2) 3059, 2227, 1595, 1500, 1365, 1240, 1138, 1107 cm^{-1}; ^1H NMR δ 1.76–1.85 (m, 2H), 1.94 (t, *J*=2.7 Hz, 1H), 1.99–2.08 (m, 2H), 2.29 (dt, *J*=2.7, 7.1 Hz, 2H), 4.07 (t, *J*=6.3 Hz, 2H), 4.34 (s, 4H), 6.89 (dd, *J*=1.5, 7.7 Hz, 1H), 6.94 (ddd, *J*=1.5, 7.7, 7.7 Hz, 1H), 7.02 (ddd, *J*=1.5, 7.7, 7.7 Hz, 1H), 7.25–7.30 (m, 7H), 7.38–7.43 (m, 4H); ^{13}C NMR δ 18.2, 25.2, 28.4, 41.7, 67.7, 68.7, 84.1, 84.9, 85.5, 112.4, 120.6, 120.7, 123.2, 123.5, 128.0, 128.2, 131.7, 138.6, 151.8; HRMS (FAB, positive) *m*/*z* calcd for $C_{30}H_{27}NO$, 417.2093 (M); found, 417.2091 (M).

*4.3.5. 2,6-(1,2-o-Benzo-3-oxa-7-o-phenylenedecano)-4,7-diphenyl-5-(methoxymethyl)isoindoline (**2a**).* Brown solid. Mp 61–62 °C; IR (CH_2Cl_2) 3055, 2866, 2819, 1599, 1211 cm^{-1}; ^1H NMR δ 1.42–1.56 (m, 1H), 1.85–2.03 (m, 2H), 2.42–2.71 (m, 4H), 2.96–3.11 (m, 2H), 3.28 (s, 3H), 3.56–3.63 (m, 1H), 3.75–3.85 (m, 1H), 4.01–4.18 (m, 3H), 4.27 (d, *J*=10.0 Hz, 1H), 4.29 (dd, *J*=1.7, 13.2 Hz, 1H), 4.43 (dd, *J*=1.7, 13.2 Hz, 1H), 4.52 (d, *J*=10.0 Hz, 1H), 6.42 (d, *J*=6.6 Hz, 1H), 6.57–6.68 (m, 2H), 6.74–6.85 (m, 2H), 6.86–6.94 (m, 4H), 7.13–7.19 (m, 1H), 7.26–7.47 (m, 6H), 7.47–7.57 (m, 2H); ^{13}C NMR δ 27.5, 28.7, 31.4, 31.7, 32.9, 54.1, 54.1, 58.0, 68.9, 69.9, 119.3, 120.7, 121.4, 123.4, 126.7, 127.1, 127.7, 127.9, 128.0, 128.0, 128.1, 128.8, 129.0, 129.1, 129.2, 129.5, 133.1, 136.8, 137.0, 137.6, 138.7, 138.8, 139.7, 139.9, 140.6, 151.7; HRMS (EI, positive) *m*/*z* calcd for $C_{40}H_{40}NO_2$, 566.3059 ($[M+1]^+$); found, 566.3080 ($[M+1]^+$); $[\alpha]_D^{21}$ 41.5 (*c* 0.40, $CHCl_3$, 98% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IC-H(double): 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow

rate: 0.5 mL/min, retention time: 16 min for major isomer and 16.5 min for minor isomer).

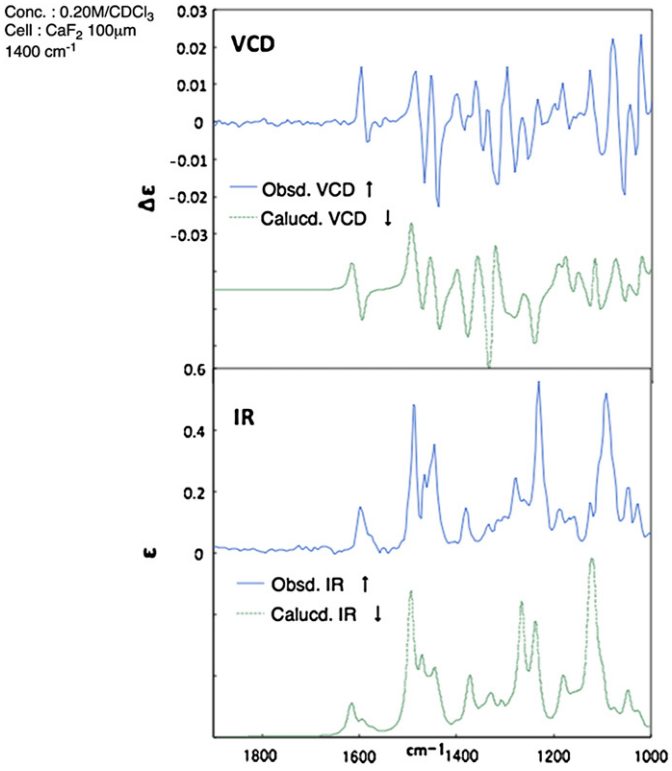
*4.3.6. (S)-2,6-(1,2-o-Benzo-3-oxaoctano)-4,7-diphenyl-5-(methoxymethyl)isoindoline (**2b**).*[13]



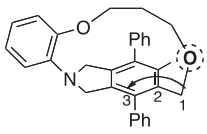
2b

The pilot atom is the nitrogen (dotted circle) of pyrrolidine ring, and we determined the above enantiomer as *R* isomer.

The observed VCD and IR spectra of (+)-**2b** showed good agreements with the calculated IR and VCD ones of (*R*)-**2b**.



*4.3.7. (S)-2,6-(1,2-o-Benzo-3,7-dioxaoctano)-4,7-diphenyl-5-methylisoindoline (**2c**).*



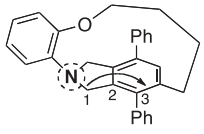
2c

The pilot atom is the oxygen (dotted circle) at the benzylic position on the tether, and we determined the above enantiomer as *S* isomer.

White solid. Decomp. 184 °C; IR (CH_2Cl_2) 2929, 1595, 1487, 1228, 1093 cm^{-1}; ^1H NMR δ 0.59–0.71 (m, 1H), 1.66–1.79 (m, 1H), 2.37 (s, 3H), 3.34 (ddd, *J*=2.7, 12.0, 12.0 Hz, 1H), 3.43 (ddd, *J*=8.3, 10.5, 12.0 Hz, 1H), 3.49–3.56 (m, 1H), 3.60 (t, *J*=10.5 Hz, 1H), 3.74 (d, *J*=15.7 Hz, 1H), 4.36 (d, *J*=12.0 Hz, 1H), 4.36–4.43 (m, 1H), 4.53 (dd, *J*=2.7, 15.7 Hz, 1H), 4.63 (d, *J*=15.7 Hz, 1H), 4.87 (d, *J*=12.0 Hz, 1H), 6.78 (dd, *J*=1.5, 8.3 Hz, 1H), 6.82 (ddd, *J*=1.5, 7.6, 7.6 Hz, 1H), 7.32 (ddd, *J*=2.0 7.6, 8.3 Hz, 1H), 7.17–7.26 (m, 3H), 7.29–7.44 (m, 8H); ^{13}C NMR δ 16.4, 30.1, 60.4, 62.1, 64.3, 64.9, 67.4, 113.2, 120.4, 126.9, 127.0, 127.1, 128.4, 128.4, 132.5, 132.7, 135.7, 136.3, 137.7, 139.5, 140.2, 141.7, 143.2, 157.5; HRMS (EI, positive) *m*/*z* calcd for $C_{31}H_{30}NO_2$, 448.2277 ($[M+1]^+$); found, 448.2279 ($[M+1]^+$); $[\alpha]_D^{27}$ 97.3 (*c* 1.415, $CHCl_3$, 88% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak OD-H(double): 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 10 min for major isomer and 12 min for minor isomer).

*4.3.8. 2,6-(1,2-o-Benzo-3-oxaheptano)-4,7-diphenyl-5-methylisoindoline (**2d**).* White solid. Mp 114 °C; IR (CH_2Cl_2) 3055, 2927, 1599, 1496 cm^{-1}; ^1H NMR δ 0.93–1.06 (m, 1H), 1.29–1.38 (m, 1H), 1.51–1.61 (m, 1H), 1.69–1.80 (m, 1H), 1.83–1.96 (m, 1H), 2.21 (s, 3H), 2.76 (ddd, *J*=4.6, 11.8, 13.2 Hz, 1H), 2.97 (ddd, *J*=3.7, 3.7, 13.2 Hz, 1H), 3.43 (ddd, *J*=6.6, 8.5, 10.5 Hz, 1H), 3.69 (d, *J*=14.6 Hz, 1H), 4.21 (dd, *J*=2.2, 14.6 Hz, 1H), 4.47 (dd, *J*=2.2, 14.6 Hz, 1H), 5.18 (d, *J*=14.6 Hz, 1H), 6.87 (dd, *J*=1.7, 7.7 Hz, 1H), 6.92 (ddd, *J*=1.7, 7.7, 7.7 Hz, 1H), 6.98 (d, *J*=2.0, 7.7, 7.7 Hz, 1H), 7.10 (dd, *J*=2.0, 7.7 Hz, 1H), 7.12 (d, *J*=7.7 Hz, 2H), 7.27–7.40 (m, 4H), 7.44 (dd, *J*=7.7, 7.7 Hz, 2H), 7.71 (s, br, 2H); ^{13}C NMR δ 16.4, 26.0, 26.8, 31.3, 57.6, 63.9, 77.2, 124.0, 125.4, 126.5, 126.8, 128.2, 128.3, 129.3, 131.0, 131.3, 131.8, 136.9, 137.0, 137.2, 137.7, 140.3, 141.6, 142.1, 145.7, 154.5 (a pair of aromatic peaks is overlapped); HRMS (EI, positive) *m*/*z* calcd for $C_{31}H_{30}NO$, 432.23274 ($[M+1]^+$); found, 432.23116 ($[M+1]^+$); $[\alpha]_D^{24}$ 174.1 (*c* 1.21, $CHCl_3$, 88% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 7 min for minor isomer and 8 min for major isomer).

*4.3.9. (R)-2,6-(1,2-o-Benzo-3-heptano)-4,7-diphenylisoindoline (**2e**).*



2e

The pilot atom is the nitrogen (dotted circle) of pyrrolidine ring, and we determined the above enantiomer as *R* isomer.

Pale yellow solid. Mp 153–154 °C; IR (CH_2Cl_2) 3057, 2927, 1599, 1500 cm^{-1}; ^1H NMR δ 0.95–1.09 (m, 1H), 1.46 (t, *J*=8.3 Hz, 1H), 1.58–1.74 (m, 2H), 1.75–1.89 (m, 1H), 2.70–2.83 (m, 2H), 3.36 (ddd, *J*=6.3, 9.0, 10.5 Hz, 1H), 4.01 (d, *J*=14.5 Hz, 1H), 4.29 (dd, *J*=2.0, 14.5 Hz, 1H), 4.91 (dd, *J*=2.0, 14.5 Hz, 1H), 5.17 (d, *J*=14.5 Hz, 1H), 6.82 (dd, *J*=2.0, 7.6 Hz, 1H), 6.90 (ddd, *J*=2.0, 7.6, 7.6 Hz, 1H), 6.95 (ddd, *J*=2.0, 7.6, 7.6 Hz, 1H), 7.16 (dd, *J*=2.0, 7.6 Hz, 1H), 7.28–7.51 (m, 9H), 7.69 (d, *J*=7.6 Hz, 2H); ^{13}C NMR δ 25.7, 30.0, 33.9, 57.6, 64.1, 76.7, 123.3, 123.8, 125.7, 126.6, 126.8, 127.4, 128.1, 128.4, 128.7, 131.0, 131.5, 136.1, 137.2, 137.4, 138.7, 139.9, 140.7, 145.1, 146.3, 154.7; HRMS (FAB, positive) *m*/*z* calcd for $C_{30}H_{27}NO$, 417.2093 (M); found, 417.2093 (M); $[\alpha]_D^{20}$ 136.7 (*c* 0.82, $CHCl_3$, 94% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak OD-H(double): 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 16 min for minor isomer and 18 min for major isomer).

*4.3.10. 6-{2-[Bis(but-2-ynyl)amino]phenoxy}hexanenitrile (**3a**).* Yellow oil. IR (neat) 3060, 2245, 1593, 1500, 1367, 1240, 1130 cm^{-1}; ^1H NMR δ 1.66–1.80 (m, 4H), 1.82 (t, *J*=2.0 Hz, 3H×2), 1.91 (tt, *J*=6.2, 6.2 Hz, 2H), 2.40 (t, *J*=6.8 Hz, 2H), 3.99 (q, *J*=2.0 Hz, 2H×2), 4.01 (t, *J*=6.2 Hz, 2H), 6.83 (dd, *J*=1.6, 7.6 Hz, 1H), 6.90 (ddd,

J=1.6, 7.6, 7.6 Hz, 1H), 6.98 (ddd, J=1.6, 7.6, 7.6 Hz, 1H), 7.16 (dd, J=1.6, 7.6 Hz, 1H); ^{13}C NMR δ 3.7, 17.1, 25.3, 25.5, 28.5, 40.8, 67.6, 75.0, 80.3, 112.3, 119.6, 120.2, 120.8, 123.0, 139.0, 151.5; HRMS (FAB, positive) m/z calcd for $C_{20}H_{24}N_2O$, 309.1967 (M); found, 309.1963 (M).

*4.3.11. 6-{2-[Bis(3-phenylprop-2-ynyl)amino]phenoxy}hexanenitrile (**3b**).* Yellow oil. IR (CH_2Cl_2) 3059, 2245, 1595, 1500, 1365, 1240, 1107 cm^{-1}; ^{1}H NMR δ 1.71–1.73 (m, 4H), 1.91–1.94 (m, 2H), 2.28–2.33 (m, 2H), 4.05 (t, J=6.2 Hz, 2H), 4.34 (s, 2H×2), 6.88 (d, J=7.5 Hz, 1H), 6.95 (dd, J=7.1, 7.2 Hz, 1H), 7.03 (dd, J=7.1, 7.5 Hz, 1H), 7.25–7.30 (m, 7H), 7.40–7.42 (m, 4H); ^{13}C NMR δ 14.6, 22.9, 23.2, 26.2, 39.3, 65.4, 82.5, 83.1, 110.1, 117.2, 118.2, 118.5, 120.7, 121.1, 125.7, 125.8, 129.2, 136.3, 149.3; HRMS (FAB, positive) m/z calcd for $C_{30}H_{29}N_2O$, 433.2280 ([M+1]$^+$); found, 433.2243 ([M+1]$^+$).

*4.3.12. 4-{2-[Bis(but-2-ynyl)amino]phenoxy}butanenitrile (**3c**).* Yellow oil. IR (CH_2Cl_2) 3062, 2247, 1595, 1500, 1369, 1240, 1130 cm^{-1}; ^{1}H NMR δ 1.83 (t, J=2.2 Hz, 3H×2), 2.15–2.21 (m, 2H), 2.72 (t, J=7.4 Hz, 2H), 3.94 (q, J=2.2 Hz, 2H×2), 4.09 (t, J=5.6 Hz, 2H), 6.84 (dd, J=1.6, 7.6 Hz, 1H), 6.90–6.94 (m, 2H), 7.19 (dd, J=2.0, 7.2 Hz, 1H); ^{13}C NMR δ 3.4, 14.0, 25.5, 40.8, 65.9, 74.9, 80.3, 112.9, 119.3, 120.0, 121.3, 122.9, 139.3, 150.9; HRMS (FAB, positive) m/z calcd for $C_{18}H_{20}N_2O$, 280.1576 (M); found, 280.1564 (M).

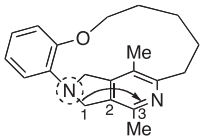
*4.3.13. 5-{2-[Bis(but-2-ynyl)amino]phenoxy}pentanenitrile (**3d**).* Yellow oil. IR (CH_2Cl_2) 3062, 2245, 1593, 1500, 1367, 1240, 1130 cm^{-1}; ^{1}H NMR δ 1.82 (t, J=2.0 Hz, 3H×2), 1.92–2.04 (m, 4H), 2.49 (t, J=6.8 Hz, 2H), 3.96 (q, J=2.0 Hz, 2H×2), 4.03 (t, J=5.6 Hz, 2H), 6.83 (dd, J=1.7, 7.7 Hz, 1H), 6.91 (ddd, J=1.7, 7.6, 7.7 Hz, 1H), 6.97 (ddd, J=1.7, 7.6, 7.7 Hz, 1H), 7.16 (dd, J=1.7, 7.7 Hz, 1H); ^{13}C NMR δ 3.5, 17.0, 22.6, 28.3, 40.8, 67.2, 74.8, 80.3, 112.5, 119.5, 120.3, 121.0, 123.0, 139.1, 151.4; HRMS (FAB, positive) m/z calcd for $C_{19}H_{23}N_2O$, 295.1810 ([M+1]$^+$); found, 295.1812 ([M+1]$^+$).

*4.3.14. 7-{2-[Bis(but-2-ynyl)amino]phenoxy}heptanenitrile (**3e**).* Yellow oil. IR (CH_2Cl_2) 3060, 2245, 1593, 1500, 1367, 1240, 1130 cm^{-1}; ^{1}H NMR δ 1.50–1.61 (m, 4H), 1.67–1.74 (m, 2H), 1.82 (t, J=2.0 Hz, 3H×2), 1.85–1.93 (m, 2H), 2.36 (t, J=7.0 Hz, 2H), 3.99–4.01 (m, 6H), 6.83 (d, J=7.5 Hz, 1H), 6.89 (dd, J=7.3, 7.8 Hz, 1H), 6.97 (dd, J=7.3, 7.5 Hz, 1H), 7.15 (d, J=7.8 Hz, 1H); ^{13}C NMR δ 3.5, 16.9, 25.2, 25.4, 28.3, 28.9, 40.6, 67.7, 74.9, 80.2, 112.1, 119.6, 120.1, 120.5, 122.9, 138.8, 151.5; HRMS (FAB, positive) m/z calcd for $C_{21}H_{27}N_2O$, 323.2123 ([M+1]$^+$); found, 323.2122 ([M+1]$^+$).

*4.3.15. 12-{2-[Bis(but-2-ynyl)amino]phenoxy}dodecanenitrile (**3f**).* Yellow oil. IR (CH_2Cl_2) 3060, 2245, 1593, 1500, 1367, 1240, 1130 cm^{-1}; ^{1}H NMR δ 1.30–1.36 (m, 10H), 1.40–1.45 (m, 2H), 1.47–1.53 (m, 2H), 1.61–1.67 (m, 2H), 1.80 (t, J=2.3 Hz, 3H×2), 1.83–1.89 (m, 2H), 2.31 (t, J=7.4 Hz, 2H), 3.96–4.00 (m, 6H), 6.83 (dd, J=1.4, 8.0 Hz, 1H), 6.87 (ddd, J=1.4, 7.6, 7.7 Hz, 1H), 6.96 (ddd, J=1.5, 7.7, 8.0 Hz, 1H), 7.13 (dd, J=1.5, 7.6 Hz, 1H); ^{13}C NMR δ 3.7, 17.1, 25.4, 26.2, 28.6, 28.7, 29.3, 29.3, 29.4, 29.4, 29.5, 40.8, 68.1, 75.0, 80.2, 112.0, 120.2, 120.4, 123.0, 138.9, 151.8 (a pair of aromatic peaks is overlapped); HRMS (FAB, positive) m/z calcd for $C_{26}H_{37}N_2O$, 393.2906 ([M+1]$^+$); found, 393.2887 ([M+1]$^+$).

*4.3.16. 12-{2-[Bis(3-phenylprop-2-ynyl)amino]phenoxy}dodecanenitrile (**3g**).* Yellow oil. IR (CH_2Cl_2) 3059, 2245, 1595, 1500, 1367, 1242, 1107 cm^{-1}; ^{1}H NMR δ 1.26–1.42 (m, 12H), 1.49–1.55 (m, 2H), 1.58–1.65 (m, 2H), 1.90 (tt, J=7.2, 7.6 Hz, 2H), 2.15 (t, J=7.2 Hz, 2H), 4.04 (t, J=6.4 Hz, 2H), 4.35 (s, 2H×2), 6.89 (d, J=7.7 Hz, 1H), 6.93 (dd, J=7.4, 7.6 Hz, 1H), 7.02 (dd, J=7.6, 7.7 Hz, 1H), 7.23–7.33 (m, 7H), 7.39–7.42 (m, 4H); ^{13}C NMR δ 17.1, 25.3, 26.3, 28.6, 28.7, 29.2, 29.3, 29.4, 29.5, 41.7, 68.2, 84.9, 85.6, 112.2, 119.8, 120.5, 123.2, 123.5, 128.0, 128.1, 131.7, 138.5, 151.9 (two pairs of aliphatic peaks and aromatic peaks are overlapped); HRMS (FAB, positive) m/z calcd for $C_{36}H_{41}N_2O$, 517.3219 ([M+1]$^+$); found, 517.3226 ([M+1]$^+$).

*4.3.17. (R)-2,6-(1,2-o-Benzo-3-oxaoctano)-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**4a**).*



4a

The pilot atom is the nitrogen (dotted circle) of pyrrolidine ring, and we determined the above enantiomer as *R* isomer.

Colorless oil. IR (CH_2Cl_2) 2924, 1593, 1487, 1227 cm^{-1}; ^{1}H NMR δ 0.02–0.10 (m, 1H), 0.81–0.89 (m, 1H), 1.03–1.13 (m, 1H), 1.21–1.31 (m, 1H), 1.44–1.54 (m, 1H), 1.87–1.95 (m, 1H), 2.24 (s, 3H), 2.37 (s, 3H), 2.93 (dd, J=7.6, 12.8 Hz, 1H), 3.02–3.10 (m, 1H), 3.41–3.48 (m, 2H), 3.98 (d, J=15.6 Hz, 1H), 4.18 (d, J=15.6 Hz, 1H), 4.54 (d, J=15.6 Hz, 1H), 4.72 (d, J=15.6 Hz, 1H), 6.68 (d, J=7.7 Hz, 1H), 6.84 (ddd, J=1.6, 7.7, 7.7 Hz, 1H), 7.09 (ddd, J=1.6, 7.7, 7.7 Hz, 1H), 7.29 (dd, J=1.6, 7.7 Hz, 1H); ^{13}C NMR δ 16.3, 21.5, 23.2, 26.5, 29.5, 30.7, 60.7, 60.9, 68.4, 112.8, 120.1, 123.8, 127.0, 131.9, 133.1, 142.8, 147.1, 152.4, 156.8, 157.1; HRMS (FAB, positive) m/z calcd for $C_{20}H_{24}N_2O$, 309.1967 (M); found, 309.1951 (M); $[\alpha]_D^{28}$ 40.2 (c 0.40, $CHCl_3$, 94% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 9 min for major isomer and 12 min for minor isomer).

*4.3.18. 2,6-(1,2-o-Benzo-3-oxaoctano)-2,3-dihydro-4,7-diphenyl-1H-pyrrolo[3,4-c]pyridine (**4b**).* Yellow solid. Decomp. 209 °C; IR (CH_2Cl_2) 2931, 1595, 1489, 1230 cm^{-1}; ^{1}H NMR δ 0.27–0.34 (m, 1H), 0.87–0.90 (m, 1H), 1.08–1.11 (m, 2H), 1.36–1.45 (m, 1H), 1.70–1.74 (m, 1H), 2.74–2.82 (m, 1H), 3.02–3.06 (m, 1H), 3.46 (dd, J=7.8, 7.8 Hz, 1H), 3.66 (dd, J=8.6, 8.6 Hz, 1H), 4.11 (d, J=15.2 Hz, 1H), 4.37 (d, J=16.0 Hz, 1H), 4.65 (d, J=16.0 Hz, 1H), 5.12 (d, J=15.2 Hz, 1H), 6.72 (d, J=8.1 Hz, 1H), 6.82 (dd, J=7.6, 7.7 Hz, 1H), 7.08 (ddd, J=1.6, 7.7, 8.1 Hz, 1H), 7.26–7.47 (m, 9H), 7.88 (d, J=7.8 Hz, 2H); ^{13}C NMR δ 23.6, 27.4, 29.2, 32.5, 59.6, 61.8, 69.0, 112.9, 120.2, 127.1, 127.2, 128.1, 128.5, 129.9, 131.3, 132.3, 132.6, 138.9, 139.7, 142.2, 149.6, 153.5, 156.6, 157.2 (two pairs of aromatic peaks are overlapped); HRMS (FAB, positive) m/z calcd for $C_{30}H_{29}N_2O$, 433.2280 ([M+1]$^+$); found, 433.2277 ([M+1]$^+$); $[\alpha]_D^{16}$ 8.4 (c 0.3, $CHCl_3$, 98% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 8 min for minor isomer and 9 min for major isomer).

*4.3.19. 2,6-(1,2-o-Benzo-3-oxahexano)-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**4c**).* Pale yellow oil. IR (CH_2Cl_2) 2937, 1591, 1479, 1217 cm^{-1}; ^{1}H NMR δ 1.77–1.85 (m, 1H), 2.12–2.22 (m, 1H), 2.31 (s, 3H), 2.37 (s, 3H), 2.69–2.76 (m, 1H), 2.99 (dd, J=9.6 9.6 Hz, 1H), 3.43–3.48 (m, 1H), 3.72 (d, J=13.4 Hz, 1H), 3.81 (dd, J=7.8, 7.8 Hz, 1H), 4.02 (d, J=14.6 Hz, 1H), 4.39 (d, J=14.6 Hz, 1H), 4.58 (d, J=13.4 Hz, 1H), 6.68 (d, J=8.1 Hz, 1H), 6.81 (dd, J=7.6, 7.7 Hz, 1H), 6.97 (ddd, J=1.8, 7.7, 8.1 Hz, 1H), 7.20 (dd, J=1.8, 7.6 Hz, 1H); ^{13}C NMR δ 16.1, 21.3, 27.6, 33.8, 58.7, 62.4, 67.5, 114.8, 121.4, 126.3, 129.0, 131.9, 132.5, 141.5, 148.1, 155.3, 155.9, 157.7; HRMS (FAB, positive) m/z calcd for $C_{18}H_{21}N_2O$, 281.1654 ([M+1]$^+$); found, 281.1642 ([M+1]$^+$); $[\alpha]_D^{33}$ 43.9 (c 0.79, $CHCl_3$, 98% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H:

4×250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane+0.1 vol % diethylamine, flow rate: 1.0 mL/min, retention time: 20 min for minor isomer and 24 min for major isomer).

*4.3.20. 2,6-(1,2-o-Benzo-3-oxaheptano)-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**4d**).* Pale yellow oil. IR (CH_2Cl_2) 2941, 1591, 1481, 1217 cm^{-1}; ^1H NMR δ 1.20–1.39 (m, 3H), 1.70–1.83 (m, 2H), 2.36 (s, 3H), 2.40 (s, 3H), 2.81–2.85 (m, 1H), 3.19–3.23 (m, 1H), 3.26–3.31 (m, 1H), 3.98 (d, *J*=14.4 Hz, 1H), 4.34 (d, *J*=15.1 Hz, 1H), 4.47 (d, *J*=15.1 Hz, 1H), 4.67 (d, *J*=14.4 Hz, 1H), 6.75 (dd, *J*=1.2, 8.0 Hz, 1H), 6.92–7.00 (m, 2H), 7.21 (dd, *J*=2.0, 7.6 Hz, 1H); ^{13}C NMR δ 16.6, 21.4, 25.4, 27.3, 33.5, 58.5, 62.0, 75.2, 121.9, 123.4, 125.4, 126.0, 131.3, 132.0, 144.6, 148.1, 154.7, 154.9, 156.9; HRMS (FAB, positive) *m/z* calcd for $C_{19}H_{23}N_2O$, 295.1810 ($[M+1]^+$); found, 295.1812 ($[M+1]^+$); $[\alpha]_D^{35}$ 17.7 (*c* 1.07, $CHCl_3$, 97% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AS-H×2: 4×250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 30 min for minor isomer and 34 min for major isomer).

*4.3.21. 2,6-(1,2-o-Benzo-3-oxanonano)-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**4e**).* Pale yellow oil. IR (CH_2Cl_2) 2927, 1550, 1488, 1226 cm^{-1}; ^1H NMR δ −0.16 to −0.07 (m, 1H), 0.51–0.60 (m, 1H), 1.00–1.07 (m, 1H), 1.28–1.38 (m, 2H), 1.41–1.47 (m, 1H), 1.69–1.78 (m, 2H), 2.27 (s, 3H), 2.36 (s, 3H), 2.79–2.85 (m, 1H), 3.19–3.24 (m, 1H), 3.54–3.58 (m, 1H), 3.69–3.73 (m, 1H), 4.08 (d, *J*=14.8 Hz, 1H), 4.32 (d, *J*=15.8 Hz, 1H), 4.52 (d, *J*=15.8 Hz, 1H), 4.70 (d, *J*=14.8 Hz, 1H), 6.75 (d, *J*=7.9 Hz, 1H), 6.86 (dd, *J*=7.7, 7.7 Hz, 1H), 7.11 (ddd, *J*=1.7, 7.7, 7.9 Hz, 1H), 7.29 (dd, *J*=1.7, 7.7 Hz, 1H); ^{13}C NMR δ 15.1, 21.4, 24.9, 25.2, 27.6, 29.3, 35.2, 60.1, 61.3, 68.0, 112.0, 120.1, 122.7, 126.9, 131.7, 133.2, 142.1, 147.2, 151.4, 156.5, 157.9; HRMS (FAB, positive) *m/z* calcd for $C_{21}H_{27}N_2O$, 323.2123 ($[M+1]^+$); found, 323.2081 ($[M+1]^+$); $[\alpha]_{436}^{27}$ 29.0 (*c* 1.25, $CHCl_3$, 97% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 5 min for major isomer and 8 min for minor isomer).

*4.3.22. 2,6-(1,2-o-Benzo-3-oxatetradecano)-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**4f**).* White solid. Mp 105–106 °C; IR (CH_2Cl_2) 2925, 1549, 1452, 1230 cm^{-1}; ^1H NMR δ 0.94–1.16 (m, 10H), 1.26–1.28 (m, 2H), 1.39–1.41 (m, 1H), 1.50–1.52 (m, 1H), 1.70–1.83 (m, 4H), 2.26 (s, 3H), 2.46 (s, 3H), 2.76–2.79 (m, 1H), 3.00–3.05 (m, 1H), 3.95–3.97 (m, 1H), 4.06–4.14 (m, 2H), 4.49 (d, *J*=12.2 Hz, 1H), 4.61 (d, *J*=12.2 Hz, 1H), 5.24 (d, *J*=14.4 Hz, 1H), 6.93–7.03 (m, 4H); ^{13}C NMR δ 15.1, 21.6, 26.4, 26.6, 27.7, 28.2, 28.3, 28.5, 29.2, 29.9, 30.0, 33.7, 53.8, 55.4, 70.1, 114.8, 118.3, 121.5, 121.6, 122.8, 130.4, 138.7, 147.9, 148.6, 151.9, 158.3; HRMS (FAB, positive) *m/z* calcd for $C_{26}H_{37}N_2O$, 393.2906 ($[M+1]^+$); found, 393.2943 ($[M+1]^+$).

*4.3.23. 2,6-(1,2-o-Benzo-3-oxatetradecano)-2,3-dihydro-4,7-diphenyl-1H-pyrrolo[3,4-c]pyridine (**4g**).* White solid. Mp 64–65 °C; IR (CH_2Cl_2) 2929, 1597, 1502, 1228 cm^{-1}; ^1H NMR δ 0.94–1.03 (m, 6H), 1.05–1.33 (m, 7H), 1.35–1.42 (m, 1H), 1.50–1.58 (m, 1H), 1.59–1.66 (m, 2H), 1.89–2.01 (m, 1H), 2.86 (t, *J*=4.8 Hz, 2H), 3.95–4.03 (m, 3H), 4.67 (d, *J*=13.2 Hz, 1H), 4.85 (d, *J*=13.2 Hz, 1H), 5.05 (d, *J*=12.8 Hz, 1H), 6.88–6.99 (m, 4H), 7.33–7.51 (m, 8H), 7.87 (d, *J*=7.2 Hz, 2H); ^{13}C NMR δ26.6, 26.7, 27.3, 28.1, 28.2, 28.3, 29.1, 29.7, 30.0, 34.1, 55.1, 55.7, 70.4, 115.1, 120.1, 121.6, 122.6, 127.4, 128.1, 128.4, 128.5, 129.3, 130.4, 130.7, 138.0, 138.5, 139.7, 149.7, 150.1, 153.0, 157.8 (a pair of aromatic peaks is overlapped); HRMS (FAB, positive) *m/z* calcd for $C_{36}H_{40}N_2O$, 516.3141 (M); found, 516.3118 (M); $[\alpha]_D^{28}$ −6.4 (*c* 1.60, $CHCl_3$, 65% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 9 min for major isomer and 11 min for minor isomer).

*4.3.24. 6-{8-[Bis(but-2-ynyl)amino]-2-naphthoxy}hexanenitrile (**6a**).* Brown solid. Mp 103–104 °C; IR (CH_2Cl_2) 3060, 2247, 1599, 1512, 1358, 1254, 1134 cm^{-1}; ^1H NMR δ 1.69–1.83 (m, 4H), 1.86 (t, *J*=2.1 Hz, 3H×2), 1.88–1.93 (m, 2H), 2.41 (t, *J*=6.8 Hz, 2H), 4.01 (q, *J*=2.1 Hz, 2H×2), 4.16 (t, *J*=6.2 Hz, 2H), 7.11 (dd, *J*=2.4, 9.0 Hz, 1H), 7.24–7.34 (m, 2H), 7.50 (d, *J*=8.0 Hz, 1H), 7.53 (d, *J*=2.4 Hz, 1H), 7.72 (d, *J*=9.0 Hz, 1H); ^{13}C NMR δ 3.8, 17.2, 25.3, 25.6, 28.6, 42.6, 67.4, 75.2, 80.7, 103.1, 117.6, 118.7, 119.8, 123.2, 123.8, 130.0, 130.2, 130.4, 146.1, 157.0; HRMS (FAB, positive) *m/z* calcd for $C_{24}H_{26}N_2O$, 358.2045 (M); found, 358.2029 (M).

*4.3.25. 7-{8-[Bis(but-2-ynyl)amino]-2-naphthoxy}heptanenitrile (**6b**).* Brown solid. Mp 78–79 °C; IR (CH_2Cl_2) 3066, 2249, 1597, 1508, 1360, 1252, 1134 cm^{-1}; ^1H NMR δ 1.54–1.61 (m, 4H), 1.69–1.74 (m, 2H), 1.85 (t, *J*=2.1 Hz, 3H×2), 1.88–1.91 (m, 2H), 2.37 (t, *J*=7.0 Hz, 2H), 4.01 (q, *J*=2.1 Hz, 2H×2), 4.15 (t, *J*=6.2 Hz, 2H), 7.11 (dd, *J*=2.6, 9.0 Hz, 1H), 7.25 (dd, *J*=7.5, 7.9 Hz, 1H), 7.32 (d, *J*=7.5 Hz, 1H), 7.50 (d, *J*=7.9 Hz, 1H), 7.53 (d, *J*=2.6 Hz, 1H), 7.72 (d, *J*=9.0 Hz, 1H); ^{13}C NMR δ 3.6, 17.0, 25.2, 25.4, 28.4, 28.9, 42.4, 67.5, 75.0, 80.5, 102.9, 117.3, 118.5, 119.7, 123.0, 123.6, 129.8, 129.9, 130.2, 145.8, 156.9; HRMS (FAB, positive) *m/z* calcd for $C_{25}H_{28}N_2O$, 372.2202 (M); found, 372.2191 (M).

*4.3.26. 2,6-[1,4-(1,7-Naphthylene)-5-oxadecano]-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**7a**).* Pale yellow solid. Mp 135 °C; IR (CH_2Cl_2) 2945, 1595, 1508, 1221 cm^{-1}; ^1H NMR δ 1.35–1.47 (m, 3H), 1.51–1.57 (m, 1H), 1.74–1.80 (m, 1H), 2.06–2.12 (m, 1H), 2.24 (s, 3H), 2.42 (s, 3H), 2.62–2.67 (m, 1H), 2.70–2.76 (m, 1H), 2.94–2.99 (m, 1H), 3.21–3.25 (m, 1H), 4.40 (d, *J*=14.9 Hz, 1H), 4.50 (d, *J*=16.2 Hz, 1H), 4.79 (d, *J*=16.2 Hz, 1H), 4.90 (d, *J*=14.9 Hz, 1H), 6.25 (d, *J*=2.4 Hz, 1H), 6.99 (dd, *J*=2.4, 8.9 Hz, 1H), 7.24 (dd, *J*=7.2, 8.1 Hz, 1H), 7.49 (d, *J*=7.2 Hz, 1H), 7.63 (d, *J*=8.1 Hz, 1H), 7.74 (d, *J*=8.9 Hz, 1H); ^{13}C NMR δ 14.8, 20.9, 21.9, 25.9, 28.8, 35.5, 60.7, 61.1, 67.7, 101.8, 118.7, 123.3, 123.4, 126.8, 129.4, 130.9, 131.1, 131.5, 133.9, 148.3, 148.7, 151.3, 157.5, 158.6; HRMS (FAB, positive) *m/z* calcd for $C_{24}H_{26}N_2O$, 358.2045 (M); found, 358.2058 (M); $[\alpha]_D^{22}$ −32.7 (*c* 1.63, $CHCl_3$, 97% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 10 min for minor isomer and 12 min for major isomer).

*4.3.27. 2,6-[1,4-(1,7-Naphthylene)-5-oxaundecano]-2,3-dihydro-4,7-dimethyl-1H-pyrrolo[3,4-c]pyridine (**7b**).* White solid. Mp 60–61 °C; IR (CH_2Cl_2) 2941, 1595, 1508, 1227 cm^{-1}; ^1H NMR δ 1.01–1.06 (m, 1H), 1.14–1.32 (m, 3H), 1.53–1.60 (m, 2H), 1.76–1.82 (m, 1H), 1.89–1.96 (m, 1H), 2.22 (s, 3H), 2.42 (s, 3H), 2.80–2.85 (m, 1H), 3.08–3.23 (m, 3H), 4.55 (d, *J*=14.5 Hz, 1H), 4.63 (d, *J*=16.4 Hz, 1H), 4.77 (d, *J*=16.4 Hz, 1H), 4.89 (d, *J*=14.5 Hz, 1H), 6.63 (d, *J*=2.4 Hz, 1H), 7.04 (dd, *J*=2.4, 8.7 Hz, 1H), 7.26 (dd, *J*=7.6, 8.0 Hz, 1H), 7.51 (d, *J*=7.6 Hz, 1H), 7.65 (d, *J*=8.0 Hz, 1H), 7.78 (d, *J*=8.7 Hz, 1H); ^{13}C NMR δ 15.2, 21.8, 24.3, 24.5, 26.7, 26.8, 32.1, 60.4, 61.0, 68.1, 101.6, 118.9, 123.4, 123.4, 126.7, 129.3, 131.0, 131.1, 131.2, 132.2, 147.4, 148.8, 149.7, 157.5, 158.3; HRMS (FAB, positive) *m/z* calcd for $C_{25}H_{28}N_2O$, 372.2202 (M); found, 372.2203 (M); $[\alpha]_D^{24}$ −3.6 (*c* 1.365, $CHCl_3$, >99% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 17 min for minor isomer and 20 min for major isomer).

*4.3.28. N,N-Bis(but-2-ynyl)-2-(11-methoxyundec-9-ynyloxy)benzenamine (**8**).* Yellow oil. IR (CH_2Cl_2) 3050, 2931, 1458, 1211 cm^{-1}; ^1H NMR δ 1.37–1.43 (m, 6H), 1.50–1.57 (m, 4H), 1.84–1.88 (m, 8H), 2.21–2.25 (m, 2H), 3.37 (s, 3H), 4.02 (q, *J*=2.0 Hz, 4H), 4.08 (t, *J*=1.8 Hz, 2H), 4.14 (t, *J*=6.6 Hz, 2H), 7.12 (dd, *J*=2.2, 8.8 Hz, 1H),

7.23–7.33 (m, 2H), 7.50 (d, J=8.0 Hz, 1H), 7.53 (d, J=2.2 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H); ^{13}C NMR δ 3.7, 18.7, 26.1, 28.6, 28.8, 29.1, 29.3, 42.5, 57.4, 60.2, 68.0, 75.1, 75.7, 80.5, 87.1, 103.0, 117.3, 118.7, 122.9, 123.6, 129.8, 130.0, 130.3, 145.9, 157.1 (a pair of aliphatic peaks is overlapped); HRMS (FAB, positive) m/z calcd for $C_{30}H_{37}N_2O$, 443.2824 (M); found, 443.2842 (M).

*4.3.29. 2,6-[1,4-(1,7-Naphthylene)-5-oxatridecano]-4,7-dimethyl-5-(methoxymethyl)isoindoline (**9**).* White solid. Mp 46–47 °C; IR (CH_2Cl_2) 2929, 1599, 1506, 1227 cm^{-1}; ^{1}H NMR δ 0.95–1.34 (m, 8H), 1.59–1.75 (m, 4H), 2.20 (s, 3H), 2.29 (s, 3H), 2.86–2.96 (m, 2H), 3.43 (s, 3H), 3.55–3.67 (m, 2H), 4.51–4.53 (m, 2H), 4.58 (d, J=10.2 Hz, 1H), 4.65 (d, J=13.0 Hz, 1H), 4.79–4.85 (m, 2H), 6.88 (d, J=2.3 Hz, 1H), 7.07 (dd, J=2.3, 8.8 Hz, 1H), 7.28 (d, J=6.9, 8.1 Hz, 1H), 7.46 (d, J=6.9 Hz, 1H), 7.61 (d, J=8.1 Hz, 1H), 7.78 (d, J=8.8 Hz, 1H); ^{13}C NMR δ 16.0, 16.6, 24.3, 25.7, 27.2, 27.9, 28.0, 28.2, 29.1, 58.3, 59.2, 60.8, 68.3, 69.1, 102.4, 118.8, 123.5, 125.4, 125.5, 128.1, 129.8, 130.8, 130.8, 131.3, 133.5, 137.1, 139.5, 139.5, 146.1, 157.1; HRMS (FAB, positive) m/z calcd for $C_{30}H_{37}NO_2$, 443.2824 (M); found, 443.2812 (M); $[\alpha]_D^{24}$ −12.3 (c 1.40, $CHCl_3$, 96% ee). ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 11 min for major isomer and 12 min for minor isomer).

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Supplementary material

Synthetic scheme of diyne-nitriles, amino-2-naphthol-tethered diyne-nitriles, and triyne, and the IR and VCD spectra of **2c**, **2e**, and **4a**. Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.01.046.

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