DOI: 10.1002/ejoc.200600232

Synthesis of Polyether Cyclophanes through Rhodium-Catalyzed Cross-Alkyne Cyclotrimerization

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Keywords: Alkynes / Catalysis / Cyclophanes / Cyclotrimerization / Rhodium

Cross-cyclotrimerizations of ether-linked α,ω-diynes and dimethyl acetylenedicarboxylate in the presence of a catalytic amount of cationic rhodium(I)/H_8-BINAP complex give [7]–[21]polyether cyclophanes in good yield. [8]–[9]Ester cyclophanes were also synthesized from the corresponding α,ω-diynes. The ratio of para-, meta-, and orthocyclophanes depends on the length and the structure of the α,ω-diyne tether chain, whilst the effect of concentration on the yield of polyether cyclophanes appears to be small. X-ray analysis revealed that a single crystal of [15]metacyclophane **4g** was the chiral form and that of [5.5]metacyclophane **4k** the racemic form, due to an absence of ring flip in the crystals.

Introduction

Cyclophanes have been paid substantial attention in view of their fascinating chemical, physicochemical, and biological properties.[1] Although a number of synthetic methods have been developed, the preparation of these compounds has suffered from multiple reaction steps and low overall yields.[2] Among the methods reported, the transition metal-catalyzed or -mediated annulation strategy is one of the more attractive routes for their synthesis.[3–6] In particular, [2+2+2] cycloaddition with α,ω-diynes is a potentially straightforward route, but such reactions have been achieved with limited success.[7] Shinokubo, Oshima, and co-worker reported $RhCl(PPh_3)_3$-catalyzed macrocyclizations to form ortho- and metacyclophanes through intramolecular [2+2+2] cycloadditions of triynes in an aqueous–organic biphasic system,[8] whilst Maryanoff et al. reported novel cobalt-catalyzed macrocyclizations forming cyclophanes through intermolecular [2+2+2] cycloaddition between α,ω-diynes and nitriles,[9–10] isocyanates,[10–11] or alkynes.[10] However, the substrate scope (restricted to benzene-linked α,ω-diynes), the efficiency [high dilutions (0.005 M) and high catalyst loadings (15 mol%) are required], and the selectivity (12–36% yield with use of 5–10 equiv. of monoalkynes) for intermolecular cycloadditions between α,ω-diynes and alkynes still remain to be improved.

We recently reported cationic rhodium(I)/H_8-BINAP [2,2′-bis(diphenylphosphanyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl][12] complex-catalyzed cross-cyclotrimerizations of terminal alkynes with dialkyl acetylenedicarboxylates and their application to the synthesis of carbacyclophanes from the corresponding α,ω-diynes.[13–16] This successful synthesis of carbacyclophanes prompted us to investigate the synthesis of practically more important polyether cyclophanes, which are found in natural products and are used for a variety of host–guest chemistries. In this paper we describe the synthesis of [7]–[21]polyether cyclophanes through intermolecular cross-cyclotrimerization of the corresponding α,ω-diynes **2** and dimethyl acetylenedicarboxylate (**1**) catalyzed by the cationic rhodium(I)/H_8-BINAP complex.

Results and Discussion

In our previous report we observed that the formation of [7]–[12]carbacyclophanes is very rapid (reactions can be completed at room temperature within 1 h) and that the yields of cyclophanes are highly dependent on concentration (Table 1, Entries 1–3).[13b] Although [7]carbacyclophanes were obtained in 23% yield at a concentration of 0.01 M (Entry 1), cyclophanes were obtained either in 14% yield or not at all at higher concentrations (0.02 M: Entry 2, and 0.1 M: Entry 3). On the other hand, the formation of [7]polyether cyclophanes was slow and the effect of concentration on the cyclophane yield appeared to be smaller than that of [7]carbacyclophanes (Entries 4–6). Although the highest yield of cyclophanes was obtained at a concentration of 0.01 M (Entry 4), a similar yield of cyclophanes was obtained at a concentration of 0.02 M (Entry 5) and

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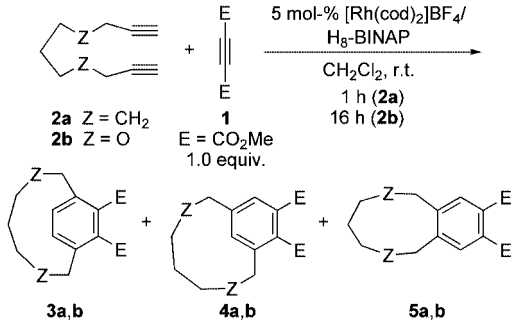
cyclophanes could be obtained in 36% yield even at a concentration of 0.1 M (Entry 6). The ratio of para-, meta-, and orthocyclophanes did not depend on concentration.

Table 1. Effect of concentration on yield and regioselectivity of [7]-cyclophanes.[a]



Entry	Diyne	Conc. [M]	% yield (**3**:**4**:**5**)[b]
1[c]	**2a**	0.01	23 (54:46:0)
2[c]	**2a**	0.02	14 (50:50:0)
3[c]	**2a**	0.1	0
4	**2b**	0.01	58 (61:35:4)
5	**2b**	0.02	50 (57:39:4)
6	**2b**	0.1	36 (57:40:3)

[a] $[Rh(cod)_2]BF_4$ (0.0125 mmol), H_8-BINAP (0.0125 mmol), **2** (0.25 mmol), **1** (0.25 mmol), and CH_2Cl_2 (2.5 mL: 0.1 M, 12.5 mL: 0.02 M, 25 mL: 0.01 M) were used. [b] Isolated yield. [c] Ref.[13b].

We next investigated the formation of [9]polyether cyclophanes from α,ω-diynes **2d** and **2e** in the presence of various modified BINAP ligands (Figure 1) as shown in Table 2. In general, the yields of cyclophanes and the ratios of the paracyclophane obtained from **2d** were higher than those from **2e**. The use of H_8-BINAP or Segphos [(4,4′-bi-1,3-benzodioxol)-5,5′-diylbis(diphenylphosphane)][17] as ligands furnished para- or metacyclophanes as major products (Entries 1, 2, 4, and 5), but the use of BINAP as ligand furnished meta- or orthocyclophanes as major products (Entries 3 and 6).

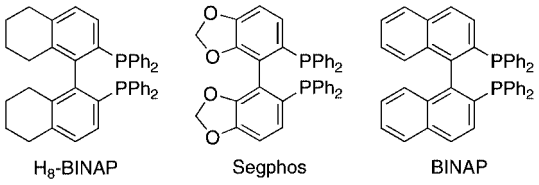
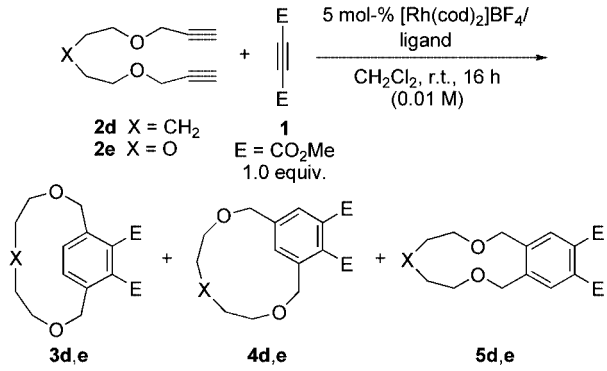


Figure 1. Structures of modified BINAP ligands.

The reactions between ether-linked α,ω-diynes **2b**–**i** and **1** were investigated in the presence of 5 mol% $[Rh(cod)_2]BF_4/H_8$-BINAP at room temperature (Table 3). The use of α,ω-diynes **2b**–**d**, containing two oxygen atoms in their tether chains, furnished mixtures of para-, meta-, and orthocyclophanes in 48–58% yields, with paracyclophanes **3b**–**d** being obtained as major products (Entries 1–3). The increased length of the polyether chain of **2** increases the yields of meta- and/or orthocyclophanes (Entries 4, 6, 8, 9, and 11). In the case of the largest [21]polyether cyclophanes, the orthocyclophane **5i** was obtained as the major product (Entry 11). This successful synthesis of the crown-like [18]- and [21]polyether cyclophanes through the macrocyclizations is noteworthy. The use of a large amount of **1** (4 equiv.) significantly increased the yields of cyclophanes (Entries 5, 7, 10 and 12).

Table 2. Effect of ligands on yield and regioselectivity of [9]polyether cyclophanes.[a]



Entry	Diyne	Ligand	% yield (**3**:**4**:**5**)[b]
1	**2d**	H_8-BINAP	48 (69:28:3)
2	**2d**	Segphos	43 (48:48:4)
3	**2d**	BINAP	45 (33:51:16)
4	**2e**	H_8-BINAP	32 (44:49:7)
5	**2e**	Segphos	16 (42:49:9)
6	**2e**	BINAP	31 (15:42:43)

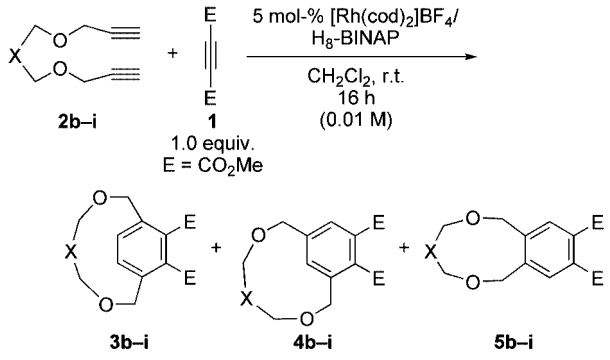
[a] $[Rh(cod)_2]BF_4$ (0.0125 mmol), ligand (0.0125 mmol), **2** (0.25 mmol), **1** (0.25 mmol), and CH_2Cl_2 (25 mL) were used. [b] Isolated yield.

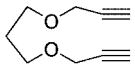
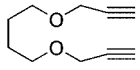
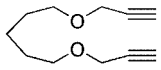
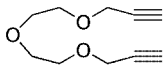
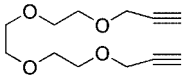
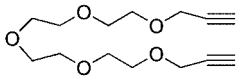
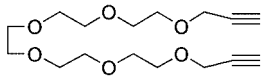
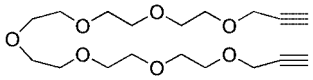
The same trend was observed with the ether-linked α,ω-diynes **2j** and **2k**, containing benzene rings in their tether chains (Table 4, Entries 1 and 2). The yields and regioselectivities of cyclophanes derived from **2j** and **2k** (Table 4, Entries 1 and 2) and from **2c** and **2f** (Table 3, Entries 2 and 6) are very close to each other. The use of a large amount of **1** (4 equiv.) significantly increased the yield of cyclophanes (Entry 3). Interestingly, the reaction between α,ω-diyne **2l**, prepared from homopropargylic alcohol, and **1** furnished a mixture of para- and metacyclophanes in high yield with high regioselectivity, with paracyclophane **3l** being obtained as major product (Entry 4).

It is well known that, if the tether chain of an asymmetrical cyclophane resides on one side of the aromatic ring (no ring flip to another side), it can exhibit planar chirality.[1] As the large macrocycles undergo rapid ring flip in solution, they exhibit no planar chirality. If the ring flip were to cease in a crystal, however, a chiral or racemic crystal of the asymmetrical cyclophane might be obtained. Indeed, we determined by X-ray analysis that a single crystal of [15]metacyclophane **4g** was the chiral form ($P2_1$ space group, Figure 2), whilst that of [5.5]metacyclophane **4k** was the racemic form ($P2_1/c$ space group, Figure 3).

The synthesis of ester cyclophanes was also investigated, as shown in Table 5. The reactions between α,ω-diynes **2n** and **2o** and **1** were carried out in the presence of 5 mol%

Table 3. Synthesis of [7]–[21]polyether cyclophanes through rhodium-catalyzed cross alkyne cyclotrimerization.[a]



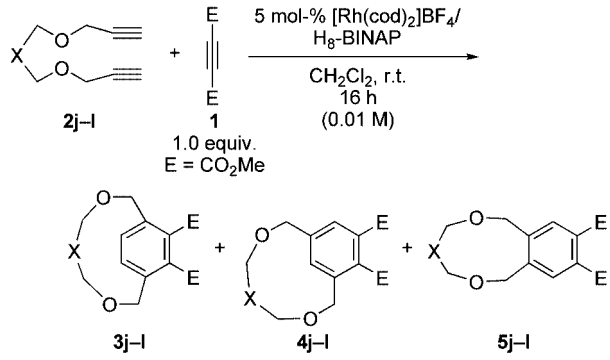
Entry	Diyne		% yield (**3**:**4**:**5**)[b]
1		**2b**	58 (61:35:4)
2		**2c**	51 (59:41:0)
3		**2d**	48 (69:28:3)
4 5[c]		**2e**	32 (44:49:7) 61 (57:39:4)
6 7[c]		**2f**	35 (0:100:0) 79 (0:100:0)
8		**2g**	48 (3:78:19)
9 10[c]		**2h**	31 (8:42:50) 64 (4:50:46)
11 12[c]		**2i**	28 (7:36:57) 62 (3:37:60)

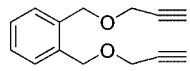
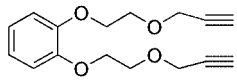
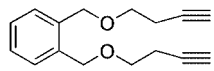
[a] $[Rh(cod)_2]BF_4$ (0.0125 mmol), H_8-BINAP (0.0125 mmol), **2** (0.25 mmol), **1** (0.25 mmol), and CH_2Cl_2 (25 mL, 0.01 M) were used. [b] Isolated yield. [c] **1** (1.00 mmol) was used.

$[Rh(cod)_2]BF_4/H_8$-BINAP at room temperature, and gave [8]- and [9]ester cyclophanes, both in 53% yield (Entries 2 and 3). Although [8]- and [9]ester cyclophanes could be isolated by silica gel chromatography, the [7]ester paracyclophane **3m** could not be isolated by silica gel chromatography, due to decomposition (Entry 1). Contrary to the steric demand, the longer length of the ester chain of **2** decreased the yield of paracyclophanes **3** and increased the yield of metacyclophanes **4**.

Scheme 1 depicts possible intermediates **A** and **B**, generated from α,ω-diyne **2** and dimethyl acetylenedicarboxylate (**1**), giving cyclophanes **3**–**5**.[18] In the case of the syntheses of [7]–[12]carbacyclophanes, intermediate **A** is proposed as a predominant intermediate, giving a paracyclophane **3** as major product. Indeed, although cross-cyclotrimerization products were obtained in good yields at a low concentration (0.01 M, Table 1, Entry 1), they were not obtained at

Table 4. Synthesis of [3.3]–[5.5]polyether cyclophanes through rhodium-catalyzed cross alkyne cyclotrimerization.[a]



Entry	Diyne		% yield (**3**:**4**:**5**)[b]
1		**2j**	46 (33:35:32)
2 3[c]		**2k**	35 (6:94:0) 74 (6:94:0)
4		**2l**	70 (83:17:0)

[a] $[Rh(cod)_2]BF_4$ (0.0125 mmol), H_8-BINAP (0.0125 mmol), **2** (0.25 mmol), **1** (0.25 mmol), and CH_2Cl_2 (25 mL, 0.01 M) were used. [b] Isolated yield. [c] Compound **1** (1.00 mmol) was used.

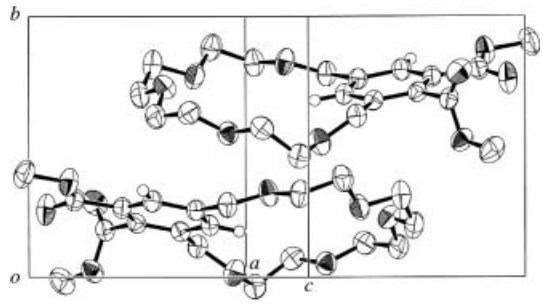


Figure 2. ORTEP diagram of the chiral crystal of [15]metacyclophane **4g** ($P2_1$ space group). Hydrogen atoms of alkyl groups have been omitted for clarity.

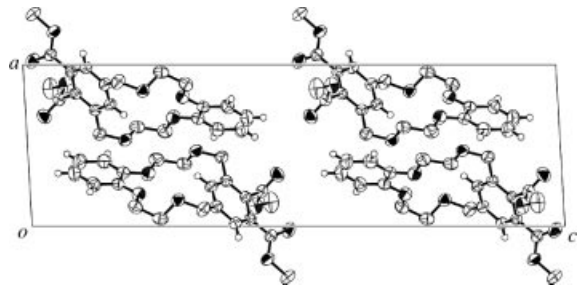
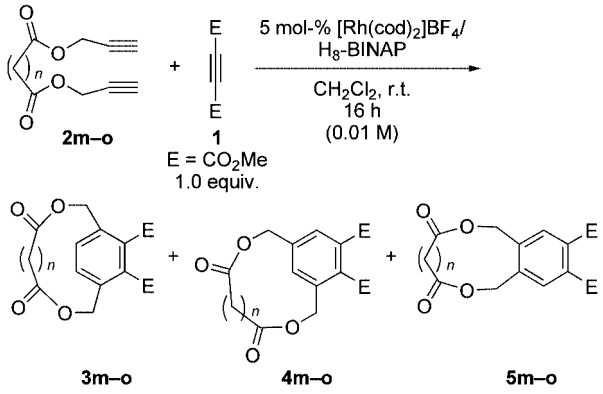


Figure 3. ORTEP diagram of the racemic crystal of [5.5]metacyclophane **4k** ($P2_1/c$ space group). Hydrogen atoms of alkyl groups have been omitted for clarity.

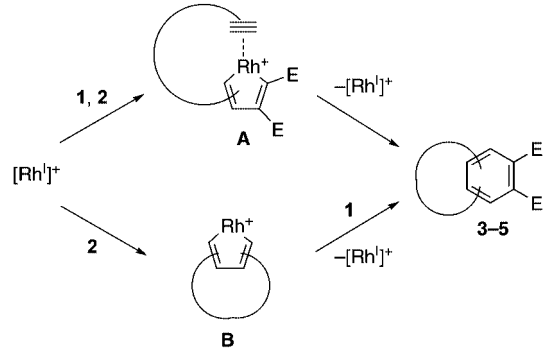
Table 5. Synthesis of [7]–[9]ester cyclophanes through rhodium-catalyzed cross-alkyne cyclotrimerization.[a]



Entry	Diyne	% yield (**3**:**4**:**5**)[b]
1	**2m** (n = 1)	<10 (100:0:0)
2	**2n** (n = 2)	53 (68:30:2)
3	**2o** (n = 3)	53 (39:55:6)

[a] $[Rh(cod)_2]BF_4$ (0.0125 mmol), H_8-BINAP (0.0125 mmol), **2** (0.25 mmol), **1** (0.25 mmol), and CH_2Cl_2 (25 mL, 0.01 M) were used. [b] Isolated yield.

high concentrations (0.1 M, Table 1, Entry 3), presumably due to the failure of the second *intramolecular* cyclization step. On the other hand, in the case of the α,ω-diynes **2**, with oxygen-containing linkers, the formation of intermediate **B** should be rapid due to their high coordination capability with the cationic rhodium.[13b] As the second step here is an *intermolecular* reaction in the cross-cyclotrimerization through intermediate **B**, the effect of concentrations on the yield of cyclophanes **3**–**5** should be small if the reaction proceeds through this intermediate **B**. Indeed, cyclophanes were obtained in 36% yield even at a high concentration (0.1 M, Table 1, Entry 6), and the yield of cyclophanes significantly increased on use of excess **1** (Table 2, Entries 5, 7, 10, and 12; Table 3, Entry 3). Intermediate **B** is thus proposed as at least one of the possible intermediates giving polyether cyclophanes.



Scheme 1. Possible mechanism for rhodium-catalyzed cross-cyclotrimerization of ether-linked α,ω-diynes and dimethyl acetylenedicarboxylate.

Conclusions

In conclusion, a series of [7]–[21]polyether cyclophanes have been efficiently synthesized through a cationic rhodium(I)/H_8-BINAP complex-catalyzed cross-cyclotrimerization of α,ω-diynes and dimethyl acetylenedicarboxylate. The successful synthesis of the crown-like [18]- and [21]-polyether cyclophanes through the macrocyclization is particularly noteworthy. [8]–[9]Ester cyclophanes were also synthesized from the corresponding α,ω-diynes. The ratio of para-, meta-, and orthocyclophanes depends on the length and the structure of the tether chains of the α,ω-diynes. Importantly, the effect of concentration on the yield of polyether cyclophanes appears to be small. X-ray analysis revealed that a single crystal of [15]metacyclophane **4g** was the chiral form and that of [5.5]metacyclophane **4k** the racemic form due to an absence of ring flip in the crystal state. As α,ω-diynes can be prepared in one step from commercially available reagents, this method allows a two-step synthesis of [7]–[21]cyclophanes with oxygen-containing linkers.

Experimental Section

General Methods: ^1H NMR spectra were recorded at 300 MHz (JEOL AL 300) and ^{13}C NMR spectra were obtained with complete proton decoupling at 75 MHz (JEOL AL 300). HRMS data were obtained with a JEOL JMS-700 instrument. Infrared spectra were obtained with a JASCO A-302 instrument. H_8-BINAP and Segphos were obtained from Takasago International Corporation, anhydrous CH_2Cl_2 was obtained from Aldrich (No. 27,099-7) and used as received. All reagents were obtained from commercial sources and used as received unless otherwise indicated. All reactions were carried out under argon or nitrogen in oven-dried glassware unless otherwise indicated.

Starting Materials: α,ω-Diynes **2b**,[19] **2c**,[19] **2d**,[19] **2e**,[19] **2f**,[20] **2 g**,[21] **2h**,[22] **2i**,[23] **2j**,[19] **2k**,[10] **2l**,[10] **2m**,[24] **2n**,[24] and **2o**[25] were prepared according to the literature.

Representative Procedure for Cross-Cyclotrimerization of α,ω-Diyne 2 and 1 (Table 3, Entry 1): A CH_2Cl_2 (1.0 mL) solution of H_8-BINAP (7.9 mg, 0.0125 mmol) was added at room temperature under Ar to a CH_2Cl_2 (1.0 mL) solution of $[Rh(cod)_2]BF_4$ (5.1 mg, 0.0125 mmol). The mixture was stirred at room temperature for 5 min and the resulting solution was placed under H_2 in a Schlenk tube. After stirring at room temperature for 0.5 h, the resulting solution was concentrated to dryness and the residue was dissolved in CH_2Cl_2 (20 mL). A CH_2Cl_2 (2.0 mL) solution of diyne **2b** (38.1 mg, 0.250 mmol) and **1** (35.5 mg, 0.250 mmol) was added dropwise to this solution over 1 min, and remaining substrate was washed away with CH_2Cl_2 (3.0 mL). The mixture was stirred at room temperature for 16 h and the resulting solution was concentrated and purified by preparative TLC (hexane/EtOAc, 1:1), which furnished [7]paracyclophane **3b** (26.0 mg, 0.0883 mmol, 35%) and a mixture of [7]metacyclophane **4b** and [7]orthocyclophane **5b** (16.5 mg, 0.0561 mmol, 23%, **4b**/**5b** = 89:11).

[7]Paracyclophane 3b: Yield 35% (26.0 mg). Colorless solid; m.p. 116.0–117.2 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.64 (s, 2 H), 5.11 (d, J = 11.1 Hz, 2 H), 4.28 (d, J = 11.1 Hz, 2 H), 3.92 (s, 6 H), 3.20 (dt, J = 12.4, 7.3 Hz, 2 H), 2.74 (ddd, J = 12.4, 7.3, 4.2 Hz, 2 H), 1.16–1.36 (m, 1 H), 0.12–0.18 (m, 1 H) ppm. ^{13}C NMR

($CDCl_3$, 75 MHz): δ = 167.0, 139.6, 135.2, 135.0, 71.5, 64.6, 52.8, 32.0 ppm. IR (neat): $\tilde{\nu}$ = 2890, 1720, 1440, 1280, 1180, 1110, 1020 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}O_6$ $[M+Na]^+$ 317.1001; found 317.1004.

[7]Metacyclophane 4b and [7]Orthocyclophane 5b (4b/5b 89:11): Yield 23% (16.5 mg). Colorless solid; m.p. 86.8–89.0 °C. ^1H NMR ($CDCl_3$, 300 MHz, **4b**): δ = 8.38 (s, 1 H), 7.67 (s, 1 H), 4.67 (s, 4 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.01–3.51 (m, 4 H), 1.52 (s, 2 H) ppm; aryl protons of **5b**: δ = 7.54 (s, 2 H) ppm; benzyl protons of **5b**: δ = 4.86 (s, 4 H) ppm; methyl protons of **5b**: δ = 3.89 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 183.3, 167.9, 167.0, 142.4, 140.1, 136.3, 132.0, 130.3, 130.0, 127.4, 72.4, 72.3, 70.7, 69.7, 69.6, 69.5, 52.7, 52.6, 34.0, 29.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1430, 1280, 1200, 1130, 1060 cm^{-1}. $C_{15}H_{18}O_6$ (294): calcd. for C 61.22, H 6.16; found C 60.78, H 6.44.

[8]Paracyclophane 3c: Yield 30% (22.9 mg). Colorless solid; m.p. 112.0–112.9 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.66 (s, 2 H), 4.88 (d, J = 11.7 Hz, 2 H), 4.44 (d, J = 11.7 Hz, 2 H), 3.91 (s, 6 H), 3.07 (quint, J = 6.0 Hz, 2 H), 2.90 (quint, J = 6.0 Hz, 2 H), 0.70–0.86 (m, 2 H), 0.52–0.70 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.4, 139.5, 135.1, 133.5, 70.0, 65.6, 52.7, 26.2 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1440, 1280, 1180, 1030 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{20}O_6$ $[M+Na]^+$ 331.1158; found 331.1160.

[8]Metacyclophane 4c: Yield 21% (16.0 mg). Colorless solid; m.p. 70.1–72.0 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.27 (s, 1 H), 7.64 (s, 1 H), 4.74 (s, 2 H), 4.71 (s, 2 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.23 (t, J = 5.4 Hz, 2 H), 3.20 (t, J = 5.4 Hz, 2 H), 1.63–1.81 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.2, 166.9, 141.5, 138.7, 132.1, 131.9, 129.9, 127.1, 71.1, 69.6, 64.7, 64.3, 52.62, 52.60, 25.9, 25.7 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1430, 1270, 1190, 1080 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{20}O_6$ $[M+Na]^+$ 331.1158; found 331.1162.

[9]Paracyclophane 3d: Yield 33% (32.6 mg). Colorless solid; m.p. 96.5–97.4 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.63 (s, 2 H), 4.97 (d, J = 12.0 Hz, 2 H), 4.40 (d, J = 12.0 Hz, 2 H), 3.90 (s, 6 H), 3.39 (ddd, J = 11.7, 8.7, 5.4 Hz, 2 H), 3.16 (ddd, J = 11.7, 8.7, 5.4 Hz, 2 H), 0.92–1.05 (m, 2 H), 0.49–0.78 (m, 2 H), 0.22–0.40 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.5, 138.6, 134.6, 133.0, 69.9, 66.0, 52.7, 28.2, 20.8 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1430, 1280, 1190, 1110, 1020 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{22}O_6$ $[M+Na]^+$ 345.1314; found 345.1319.

[9]Metacyclophane 4d and [9]Orthocyclophane 5d (4d/5d 91:9): Yield 15% (12.3 mg). Colorless solid; m.p. 91.4–95.5 °C. ^1H NMR ($CDCl_3$, 300 MHz, **4d**): δ = 8.38 (s, 1 H), 7.65 (s, 1 H), 4.69 (s, 2 H), 4.65 (s, 2 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.41–3.52 (m, 4 H), 1.74–1.96 (m, 2 H), 1.17–1.39 (m, 4 H) ppm; aryl protons of **5d**: δ = 7.66 (s, 2 H) ppm; benzyl protons of **5d**: δ = 4.59 (s, 4 H) ppm; methyl protons of **5d**: δ = 3.90 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.7, 166.5, 142.6, 139.5, 131.6, 130.1, 128.2, 126.3, 72.2, 70.1, 69.9, 69.3, 52.60, 52.56, 28.21, 28.18, 20.7 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1420, 1250, 1180, 1090 cm^{-1}. $C_{17}H_{22}O_6$ (322): calcd. for C 63.34, H 6.88; found C 63.20, H 6.89.

[9]Paracyclophane 3e, [9]Metacyclophane 4e, and [9]Orthocyclophane 5e (3e/4e/5e 57:39:4): Yield 61% (49.4 mg). Colorless solid; m.p. 68.7–73.8 °C. ^1H NMR ($CDCl_3$, 300 MHz, **3e**): δ = 7.58 (s, 2 H), 4.81 (d, J = 12.0 Hz, 2 H), 4.53 (d, J = 12.0 Hz, 2 H), 3.89 (s, 6 H), 2.84–3.67 (m, 8 H) ppm; aryl protons of **4e**: δ = 8.64 (s, 1 H), 7.63 (s, 1 H) ppm; aryl protons of **5e**: δ = 7.68 (s, 2 H) ppm; benzyl protons of **4e**: δ = 4.73 (s, 2 H), 4.70 (s, 2 H) ppm; benzyl protons of **5e**: δ = 4.76 (s, 4 H) ppm; methyl protons of **4e**: δ = 3.92 (s, 3 H), 3.89 (s, 3 H) ppm; methyl protons of **5e**: δ = 3.90 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.6, 168.0, 167.4, 166.4, 141.4, 140.5, 138.6, 138.5, 138.3, 134.0, 132.2, 131.3, 131.0, 130.8, 127.9, 125.8, 73.5, 71.9, 71.3, 70.7, 70.5, 70.0, 69.8, 69.7, 69.6, 69.41, 69.35, 68.9, 52.6, 52.54, 52.48 ppm. IR (neat): $\tilde{\nu}$ = 2850, 1720, 1430, 1260, 1200, 1100, 1080 cm^{-1}. $C_{16}H_{20}O_7$ (324): calcd. for C 59.25, H 6.22; found C 59.32, H 6.23.

[12]Metacyclophane 4f: Yield 35% (32.0 mg). Pale yellow solid; m.p. 74.2–76.5 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.34 (s, 1 H), 7.67 (s, 1 H), 4.67 (s, 2 H), 4.65 (s, 2 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.62–3.81 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.9, 166.2, 140.7, 137.6, 131.6, 130.0, 127.7, 126.5, 71.3, 70.6, 70.5, 70.2, 70.1, 70.0, 69.8, 68.8, 52.6, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2850, 1720, 1430, 1260, 1200, 1120 cm^{-1}. $C_{18}H_{24}O_8$ (368): calcd. for C 58.69, H 6.57; found C 58.83, H 6.69.

[15]Paracyclophane 3g and [15]Metacyclophane 4g (3g/4g = 4:96): Yield 39% (40.2 mg). Pale yellow solid; m.p. 74.0–78.3 °C. ^1H NMR ($CDCl_3$, 300 MHz, **4g**): δ = 8.04 (s, 1 H), 7.76 (s, 1 H), 4.69 (s, 2 H), 4.66 (s, 2 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.61–3.76 (m, 16 H) ppm; aryl protons of **3g**: δ = 7.80 (s, 2 H) ppm; benzyl protons of **3g**: δ = 4.76 (s, 4 H) ppm; methyl protons of **3g**: δ = 3.90 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.1, 168.1, 166,3, 140.6, 140.2, 137.3, 132.1, 130.7, 130.5, 128.2, 128.1, 127.3, 71.9, 71.5, 71.1, 70.9, 70.81, 70.77, 70.74, 70.70, 70.5, 70.11, 70.05, 69.9, 69.8, 69.6, 69.4, 52.6, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2850, 1710, 1430, 1350, 1240, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{28}O_9$ $[M+Na]^+$ 435.1631; found 435.1663.

[15]Orthocyclophane 5g: Yield 9% (9.6 mg). Pale yellow solid; m.p. 94.3–95.1 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.31 (s, 2 H), 4.77 (s, 4 H), 3.86 (s, 6 H), 3.62–3.78 (m, 16 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.1, 137.2, 130.0, 129.3, 71.3, 70.4, 70.2, 69.2, 68.9, 52.3 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1430, 1350, 1260, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{28}O_9$ $[M+Na]^+$ 435.1631; found 435.1635.

[18]Paracyclophane 3h and [18]Metacyclophane 4h (3h/4h = 16:84): Yield 15% (16.8 mg). Pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz, **4h**): δ = 7.84 (s, 1 H), 7.82 (s, 1 H), 4.66 (s, 2 H), 4.64 (s, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.57–3.77 (m, 20 H) ppm; aryl protons of **3h**: δ = 7.76 (s, 2 H) ppm; benzyl protons of **3h**: δ = 4.74 (s, 4 H) ppm; methyl protons of **3h**: δ = 3.90 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.1, 166.3, 140.5, 140.2, 139.0, 137.1, 132.5, 130.8, 129.0, 128.4, 127.7, 72.3, 71.10, 71.05, 71.0, 70.98, 70.87, 70.8, 70.7, 70.4, 70.2, 70.1, 69.8, 52.61, 52.57, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1430, 1350, 1260, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{32}O_{10}$ $[M+Na]^+$ 479.1893; found 479.1895.

[18]Orthocyclophane 5h: Yield 16% (18.4 mg). Pale yellow solid; m.p. 75.3–77.2 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.98 (s, 2 H), 4.73 (s, 4 H), 3.86 (s, 6 H), 3.77 (s, 4 H), 3.58–3.75 (m, 16 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.9, 137.1, 129.8, 129.5, 71.3, 71.0, 70.6, 70.5, 69.5, 69.4, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2850, 1720, 1430, 1350, 1280, 1150 cm^{-1}. $C_{22}H_{32}O_{10}$ (456): calcd. for C 57.88, H 7.07; found C 57.91, H 6.98.

[21]Paracyclophane 3i and [21]Metacyclophane 4i (3i/4i = 16:84): Yield 12% (14.7 mg). Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz, **4i**): δ = 7.83 (s, 1 H), 7.81 (s, 1 H), 4.65 (s, 2 H), 4.63 (s, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.42–3.74 (m, 24 H) ppm; aryl protons of **3i**: δ = 7.77 (s, 2 H) ppm; benzyl protons of **3i**: δ = 4.71 (s, 4 H) ppm; methyl protons of **3i**: δ = 3.90 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.9, 167.8, 166.2, 140.3, 137.0, 132.5, 130.9, 130.7, 128.8, 128.4, 127.8, 72.2, 70.92, 70.89, 70.83, 70.79, 70.76, 70.64, 70.60, 70.3, 70.2, 70.1, 70.0, 69.8, 52.59, 52.56 ppm. IR (neat): $\tilde{\nu}$ = 2850, 1720, 1430, 1350, 1280, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{36}O_{11}$ $[M+Na]^+$ 523.2155; found 523.2180.

[21]Orthocyclophane (5i): Yield 16% (19.4 mg). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.83 (s, 2 H), 4.73 (s, 4 H), 3.86 (s, 6 H), 3.59–3.75 (m, 24 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.9, 137.1, 129.92, 129.89, 71.0, 70.9, 70.8, 70.7, 70.6, 69.9, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2850, 1720, 1430, 1350, 1260, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{36}O_{11}$ $[M+Na]^+$ 523.2155; found 523.2162.

[3.3]Paracyclophane 3j, [3.3]Metacyclophane 4j, and [3.3]Orthocyclophane 5j (3j/4j/5j 33:35:32): Yield 46% (41.4 mg). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.04 (s, 1 H, **4j**), 7.68 (s, 1 H, **4j**), 7.58 (s, 2 H, **5j**), 7.28 (s, 2 H, **3j**), 6.90–7.56 (m, 12 H, **3j**+**4j**+**5j**), 4.99 (d, J = 11.4 Hz, 2 H, **3j**), 4.71 (d, J = 11.4 Hz, 2 H, **3j**), 4.09 (d, J = 14.1 Hz, 2 H, **3j**), 3.52 (d, J = 14.1 Hz, 2 H, **3j**), 4.00–4.76 (m, 16 H, **4j**+**5j**), 3.89–3.93 (m, 18 H, **3j**+**4j**+**5j**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.8, 167.4, 167.1, 166.8, 140.6, 140.5, 137.8, 137.6, 136.7, 135.4, 135.4, 135.3, 133.3, 132.1, 132.04, 131.99, 131.1, 131.0, 130.6, 129.9, 129.8, 128.9, 128.8, 128.2, 126.5, 126.3, 73.0, 71.8, 69.8, 68.6, 68.0, 65.9, 65.6, 61.2, 52.8, 52.6, 52.6 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1440, 1280, 1200, 1160, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{20}O_6$ $[M+Na]^+$ 379.1158; found 379.1159.

[5.5]Paracyclophane 3k: Yield 2% (2.0 mg). Colorless solid; m.p. 149.2–151.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84 (s, 2 H), 6.78–6.87 (m, 2 H), 6.72–6.78 (m, 2 H), 4.72 (d, J = 13.8 Hz, 2 H), 4.62 (d, J = 13.8 Hz, 2 H), 4.16 (t, J = 9.9 Hz, 2 H), 3.94–4.02 (m, 2 H), 3.89 (s, 6 H), 3.53–3.68 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.2, 148.2, 137.4, 133.3, 130.4, 120.4, 111.7, 68.6, 68.3, 68.1, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1440, 1250, 1120, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}O_8$ $[M+Na]^+$ 439.1369; found 439.1365.

[5.5]Metacyclophane 4k: Yield 33% (34.4 mg). Colorless solid; m.p. 137.9–139.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.47 (s, 1 H), 7.75 (s, 1 H), 6.83–6.96 (m, 4 H), 4.77 (s, 2 H), 4.75 (s, 2 H), 4.14–4.27 (m, 4 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.86–3.98 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.1, 166.4, 148.7, 148.6, 140.6, 137.6, 132.0, 130.5, 128.2, 127.1, 121.0, 120.9, 112.4, 71.0, 68.8, 68.7, 68.34, 68.27, 68.1, 52.6, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1500, 1440, 1250, 1130, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}O_8$ $[M+Na]^+$ 439.1369; found 439.1386.

[4.4]Paracyclophane 3l and [4.4]Metacyclophane 4l (3l/4l 83:17): Yield 70% (67.6 mg). Colorless solid; m.p. 137.2–142.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, **3l**): δ = 7.27–7.39 (m, 2 H), 7.14–7.27 (m, 2 H), 7.12 (s, 2 H), 4.10 (ddd, J = 11.4, 5.1, 2.4 Hz, 2 H), 3.96 (d, J = 11.1 Hz, 2 H), 3.89 (s, 6 H), 3.45 (dt, J = 11.4, 2.4 Hz, 2 H), 3.23 (dt, J = 13.2, 2.4 Hz, 2 H), 3.13 (d, J = 11.1 Hz, 2 H), 2.85 (dd, J = 13.2, 5.1 Hz, 2 H) ppm; aryl protons of **4l**: δ = 7.95(s, 1 H), 7.69 (s, 1 H) ppm; benzyl protons of **4l**: δ = 4.33 (s, 2 H), 4.32 (s, 2 H) ppm; methyl protons of **4l**: δ = 3.93 (s, 3 H), 3.89 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.0, 168.5, 166.5, 141.2, 137.4, 137.3, 136.8, 136.5, 136.4, 135.3, 134.1, 132.5, 131.2, 131.1, 130.8, 128.5, 128.4, 128.0, 127.9, 127.5, 127.3, 71.63, 71.57, 71.0, 70.8, 70.6, 70.2, 52.41, 52.37, 52.3, 35.9, 35.7, 33.2 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1440, 1270, 1200, 1090, 1060, 750 cm^{-1}. $C_{22}H_{24}O_6$ (384): calcd. for C 68.74, H 6.29; found C 68.29, H 6.27.

[8]Paracyclophane 3n, [8]Metacyclophane 4n, and [8]Orthocyclophane 5n (3n/4n/5n 68:30:2): Yield 53% (44.4 mg). Colorless solid; m.p. 92.2–96.1 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, **3n**): δ = 7.51 (s, 2 H), 5.40 (d, J = 10.8 Hz, 2 H), 5.22 (d, J = 10.8 Hz, 2 H), 3.93 (s, 6 H), 2.06–2.80 (m, 4 H) ppm; aryl protons of **4n**: δ = 7.80 (s, 1 H), 7.68 (s, 1 H) ppm; aryl protons of **5n**: δ = 7.73 (s, 2 H) ppm; benzyl protons of **4n**: δ = 5.30 (s, 4 H) ppm; benzyl protons of **5n**: δ = 5.18 (s, 4 H) ppm; methyl protons of **4n**: δ = 3.91 (s, 3 H), 3.88 (s, 3 H) ppm; methyl protons of **5n**: δ = 3.95 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2, 172.9, 171.6, 167.3, 166.5, 166.4, 141.5, 139.0, 136.4, 135.0, 134.1, 131.5, 130.6, 129.3, 127.0, 67.0, 66.2, 65.0, 52.7, 52.6, 32.53, 32.49 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1720, 1430, 1350, 1270, 1150, 1120 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{16}O_8$ $[M+Na]^+$ 359.0743; found 359.0747.

[9]Paracyclophane 3o: Yield 21% (18.2 mg). Colorless solid; m.p. 135.1–136.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.58 (s, 2 H), 5.40 (d, J = 11.1 Hz, 2 H), 5.16 (d, J = 11.1 Hz, 2 H), 3.93 (s, 6 H), 2.01 (ddd, J = 16.5, 8.1, 5.1 Hz, 2 H), 1.86 (ddd, J = 16.5, 8.1, 5.1 Hz, 2 H), 1.31–1.46 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.3, 166.7, 137.7, 134.3, 133.1, 66.3, 52.8, 32.8, 18.5 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1710, 1440, 1410, 1280, 1200, 1130 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{18}O_8$ $[M+Na]^+$ 373.0899; found 373.0903.

[9]Metacyclophane 4o and [9]Orthocyclophane 5o (4o/5o 90:10): Yield 32% (28.3 mg). Colorless solid; m.p. 169.1–172.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, **4o**): δ = 7.60 (s, 1 H), 7.24 (s, 1 H), 5.29 (s, 2 H), 5.27 (s, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.52–2.71 (m, 4 H), 2.14–2.33 (m, 2 H) ppm; aryl protons of **5o**: δ = 7.78 (s, 2 H) ppm; benzyl protons of **5o**: δ = 5.17 (s, 4 H) ppm; methyl protons of **5o**: δ = 3.93 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.57, 172.55, 172.0, 167.6, 167.0, 166.7, 139.3, 139.0, 136.7, 132.6, 132.4, 130.9, 129.5, 125.3, 124.9, 64.5, 63.8, 63.5, 52.8, 52.7, 52.6, 34.7, 34.6, 34.4, 21.5, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1420, 1270, 1200, 1170, 1080 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{18}O_8$ $[M+Na]^+$ 373.0899; found 373.0905.

X-ray Crystallographic Studies of 4g and 4k: Crystals suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2/*n*-pentane. CCDC-601703 (for **4g**) and -601704 (for **4k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR spectra of cyclophanes.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We thank Takasago International Corporation for the gift of H_8-BINAP and Segphos.

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Received: March 16, 2006
Published Online: June 13, 2006

