An Improved Method for the Regiospecific Synthesis of Polysubstituted [2.2]Paracyclophanes

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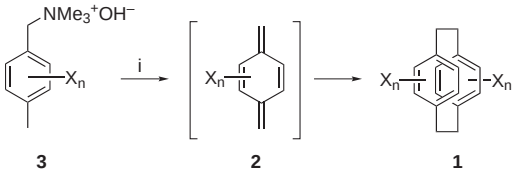
Dedicated to Prof. T. Y. Luh on the occasion of his 60th birthday

Abstract: 4,16-Disubstituted, 4,7,12,15-tetrasubstituted, 4,8,12,16-tetrasubstituted and 4,5,7,8,12,13,15,16-octasubstituted [2.2]paracyclophanes can be prepared in significantly improved yields and excellent regiospecificities via the Winberg 1,6-elimination–dimerization reaction from substituted (4-methylbenzyl)trimethylammonium hydroxides. Using 2-chloro-phenothiazine instead of phenothiazine as a polymerization inhibitor results in a doubling of product yields.

Key words: cyclophanes, dimerizations, regioselectivity

The cofacial stacking arrangement of the two aromatic rings combined with the structural rigidity of the [2.2]paracyclophane (PCP) skeleton make it an unique structural probe to investigate the through-space π-π transannular interactions[1] in many optoelectronic materials.[2,3] Optically active PCPs are also useful ligands in asymmetric synthesis with good product enantioselectivities.[4] Despite such potentials, one of the major obstacles in the development of PCP chemistry is the lack of convenient synthetic routes to substituted PCP derivatives. While mono-substituted PCPs can be prepared either by stoichiometric electrophilic aromatic substitutions[5] of [2.2]paracyclophane or by functional group interconversions[5a,b,6] from another mono-substituted PCP derivative in reasonable yields and purities, di-, tri- and tetra-substituted PCPs are difficult to obtain from electrophilic aromatic substitutions without resorting to repeated chromatographic or crystallization purification.[7] Herein we report the regiospecific syntheses of 4,16-disubstituted, 4,7,12,15-tetrasubstituted, 4,8,12,16-tetrasubstituted and 4,5,7,8,12,13,15,16-octasubstituted PCP derivatives **1** from the Winberg dimerization[8] of substituted xylylene intermediates **2** without invoking tedious purification procedures (Scheme 1). More importantly, yields of the dimerization product are doubled in the presence of 2-chlorophenothiazine instead of phenothiazine as the polymerization inhibitor.

In contrast to most literature methods, our strategy towards such substituted PCPs employs a pre-cyclization approach, i.e., the functional groups are introduced to the PCP skeleton prior to cyclophane ring formation via the Winberg reaction. This method involves the dimerization of xylylenes **2** generated in situ from a 1,6-elimination of substituted (4-methylbenzyl)trimethylammonium hydroxides **3** that in turn can be conveniently prepared in two or three steps from commercially available materials. It was also noted that similar works using this approach to prepare substituted PCP derivatives had been demonstrated previously in scattered studies by different groups.[9]



Scheme 1 *Reagents and conditions*: (i) PhMe, 2-chlorophenothiazine, reflux, 3 h.

The dimerization reaction was suggested to be a multistep process[10] and was shown to involve coupling of two xylylene molecules via their biradical resonance form.[11] Such an approach would be of little practical use if a mixture of regioisomers were to form from the dimerization of the substituted xylylene intermediate **2**. However, we envisaged that this should not be a random process. For example, a mono-substituted biradical **4** can dimerize via either a head-to-tail or a head-to-head fashion to furnish the biradical dimer **5a** or **5b**, respectively (Scheme 2). Prior to cyclization, the two aromatic rings of head-to-tail dimer **5a** must orient in a stacking arrangement to give either conformer **6a** or **6b**. Similarly, the head-to-head dimer **5b** can also adopt conformations **6c** or **6d**. Among these four isomeric biradicals, conformer **6a** is energetically more favorable than the others because the two substituents (X) are now oriented in a *pseudo-para* fashion. As a result, the cyclization process (route a) involving **6a** should be more favorable than similar reactions (routes b to d) originated from the other intermediates, producing the 4,16-disubstituted PCP derivative **7** selectively. The alternative competitive side-reaction of the dimeric biradical intermediates would be the polymerization reaction to give poly(*p*-phenyleneethylene)s. Hence, it is of practical interest to extend this concept to the systematic synthesis of PCPs of new substitution patterns, namely, 4,7,12,15-**10** and 4,8,12,16-tetrasubstituted **11** PCPs, respectively,

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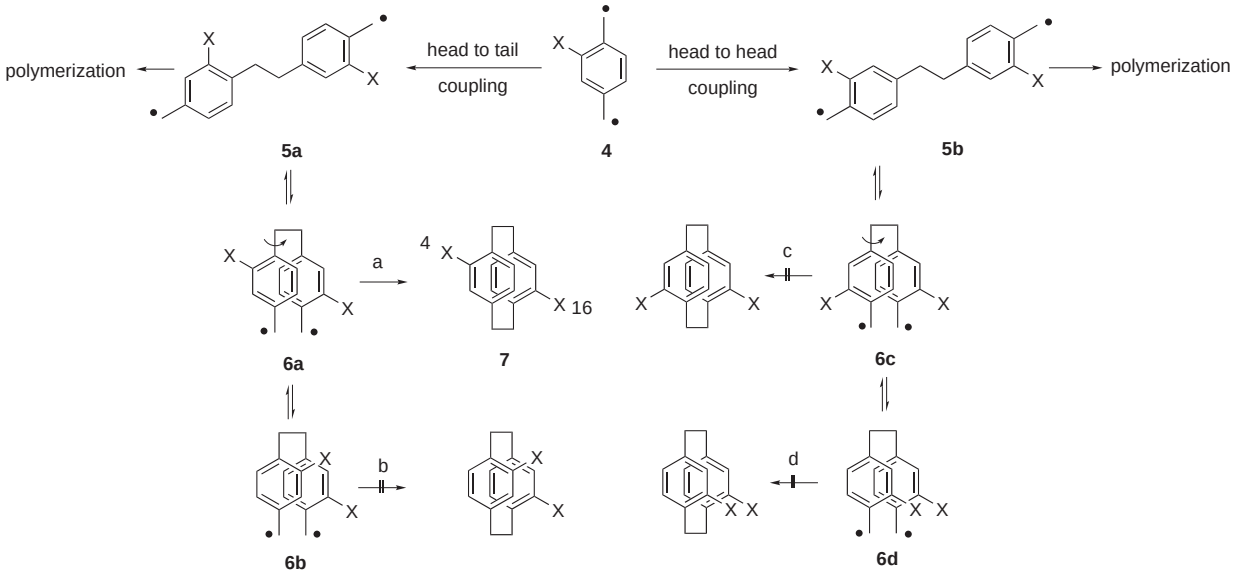
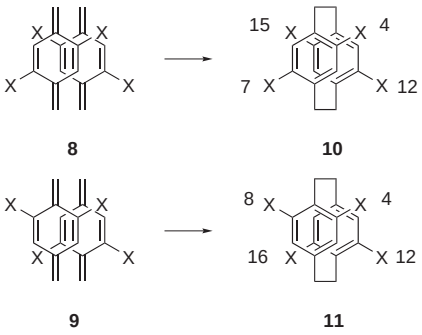


Scheme 2 Possible dimerization modes of a monosubstituted xylylene.

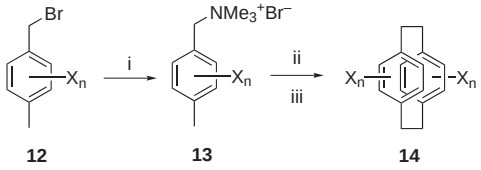
from the dimerization of 2,5-disubstituted **8** and 2,6-disubstituted xylylenes **9** (Scheme 3). Furthermore, such strategy should also be applicable to the synthesis of 4,5,7,8,12,13,15,16-octasubstituted PCPs from 2,3,5,6-tetrasubstituted xylylenes.



Scheme 3 Dimerizations of disubstituted xylylenes.

The various highly reactive xylylenes mentioned above were generated in situ from the pyrolysis of substituted (4-methylbenzyl)trimethylammonium hydroxide precursors that were prepared in quantitative yield from reaction of trimethylamine and substituted (4-methylbenzyl)bromides **12** in diethyl ether,[12] followed by anion exchange with silver oxide in water (Scheme 4). The benzyl bromides **12**, in turn, were readily prepared in 75–93% overall yield on 5–20 g scales from inexpensive and commercially available starting materials in one or two steps via bromination reactions.[13,14]

According to Winberg's original procedure,[8b] the dimerization process was conducted in the presence of phenothiazine to suppress polymerization. It happened that phenothiazine was not immediately available in our laboratory so we chose 2-chlorophenothiazine as a substitute. We then repeated the synthesis of the parent [2.2]paracy-

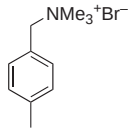
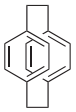
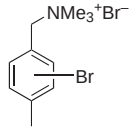
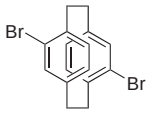
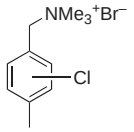
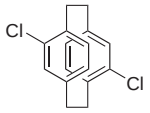
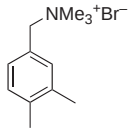
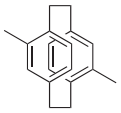
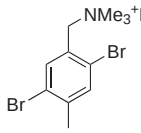
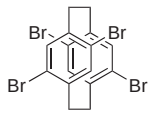
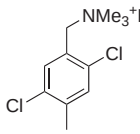
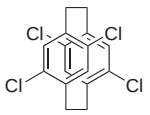
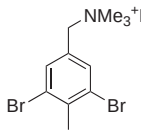
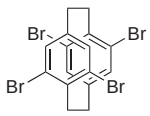
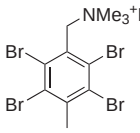
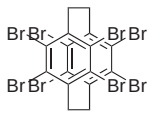


Scheme 4 *Reagents and conditions*: (i) NMe_3, Et_2O, 0 °C; (ii) Ag_2O, H_2O; (iii) toluene, 110 °C.

clophane **14a** and were surprised to find that the yield was 21% from the precursor **13a** (Table 1, entry 1). This value was roughly twice that reported in the literature.[8b] It was later confirmed that the yield of [2.2]paracyclophane **14a** dropped back to 10% when phenothiazine was again used as the inhibitor. We therefore conducted a comparative study of the cyclophane formation reactions in the presence of either 2-chlorophenothiazine or phenothiazine.[15] It was found that the product yield was consistently twice as many in the presence of the 2-chloro analogue than in the presence of phenothiazine.[16] We speculated some subtle electron effect was operating through the chloro substituent of the phenothiazine inhibitor that deterred the rate of polymerization, but were unable to provide any conclusive evidence at presence. After the reaction, the mixture was filtered to remove the insoluble polymer by-products. The filtrate was then concentrated under reduced pressure to give the target PCPs **14** as solids.

For the dimerization of the 2-substituted xylylenes **13b–d** (entries 2–4), only the 4,16-disubstituted isomers **14b–d** were obtained in about 20% yield. This value was comparable to the reaction yield obtained from the direct electrophilic aromatic substitution of the parent [2.2]paracyclophane. However, no chromatographic purification was required in our improved synthetic procedure. The structures of the products were confirmed by ^{1}H NMR and ^{13}C NMR spectral analysis, and the data also matched well

Table 1 Synthesis of [2.2]Paracyclophanes **14** from Precursors **13**

Entry	Starting material(s)	Product	Yield (%)[a]
1	 **13a**	 **14a**	10 (20)
2	 **13b**	 **14b**	10 (22)
3	 **13c**	 **14c**	10 (20)
4	 **13d**	 **14d**	9 (19)
5	 **13e**	 **14e**	9 (21)
6	 **13f**	 **14f**	9 (20)
7	 **13g**	 **14g**	9 (21)
8	 **13h**	 **14h**	9 (20)

[a] In the presence of phenothiazine. Figures in parenthesis are yields in the presence of 2-chlorophenothiazine.

with those reported in the literature.[17] Hence, the mode of dimerization was exactly as predicted previously, i.e. the two substituents were oriented in a *pseudo-para* fashion in the cyclization transition state. We could not isolate any other regioisomers from the soluble fraction.

Similarly, dimerization of 2,5-dihaloxylylenes **13e** and **13f** took place in a highly regiospecific manner to produce the 4,7,12,15-tetrasubstituted derivatives **14e** and **14f**, respectively, in 20% yield (entries 5 and 6). For the 4,7,12,15-tetrabromo PCP derivative **14e**, its ^{1}H NMR and ^{13}C NMR spectral data matched well with those reported in the literature,[18] thus confirming its 4,7,12,15-substitution pattern. The structure of the tetrachloro analogue **14f** was also consistent with its NMR spectral data. On the other hand, dimerization of the 2,6-dibromoxylylene **13g** (entry 7) afforded the previously unknown 4,8,12,16-tetrabromo[2.2]paracyclophane **14g** in 21% yield. It should be pointed out that this compound could not be obtained from the tetrabromination of the parent [2.2]paracyclophane, as the electronic inductive effect would direct the reaction towards the production of the 4,7,12,15- or the 4,5,15,16-regioisomer. The ^{1}H NMR data of the 4,8,12,16-isomer **14g** were different from those of the 4,7,12,15-isomer **14e**, and the structure of the former was also confirmed by X-ray crystallography.[19]

Dimerization of the tetrabromoxylylene produced the highly insoluble 4,5,7,8,12,13,15,16-octabromide **14h** (entry 8). Therefore the reaction had to be carried out in large volume of solvents to ensure the product remained in solution. Despite the large steric repulsions among the eight bromine atoms in the octabromide **14h**, the yield of the cyclization was still 20%. We reasoned that such steric repulsion was also operative in the polymerization reaction and hence both the cyclization and polymerization rate were retarded to the same extent, and so the yields of the PCP product **14h** were unaffected by the substitution pattern. The ^{1}H NMR spectrum of the product **14h** in nitrobenzene-d_5 showed a singlet at δ = 3.39 ppm. In addition, mass spectrometric analysis showed the presence of the most abundant molecular ion at m/z = 839 with the expected isotopic distribution pattern. A single crystal of the octabromide **14h** was obtained and its structure was thus ascertained.[20] It should be noted that the octabromide **14h** could not be obtained from exhaustive bromination of [2.2]paracyclophane.

In summary, we report a regiospecific and high yielding synthesis of polysubstituted PCPs using the Winberg 1,6-elimination–dimerization reaction from substituted (4-methylbenzyl)trimethylammonium hydroxides. The use of 2-chlorophenothiazine as an inhibitor greatly improved the yields of the dimerization products. The ammonium salts could be conveniently prepared in large quantities (10 g scale) from commercially materials in not more than three steps. No chromatographic purification was needed and the resulting substituted PCPs could be readily obtained in gram quantities and high purity. Finally, this method also allows the preparation of substituted PCPs such as the 4,8,12,16-tetrabromo- and 4,5,7,8,12,13,15,16-octabromo derivatives that are not obtainable from direct electrophilic substitutions.[5b] Such PCP compounds, especially the bromo and chloro derivatives, are extremely important building blocks in material science and catalysis applications.

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(12) **Typical Procedure for the Preparation of Substituted (4-Methylbenzyl)trimethylammonium Bromides 13.**
In a 250-mL three-necked flask equipped with a stirrer, a gas outlet connected to an acid trap, and a gas inlet tube directed to about 1 cm above the surface of the liquid was placed a solution of the substituted benzyl bromide **12** (ca. 10 g) in Et_2O (100 mL). The flask was cooled in an ice-water bath with stirring. Et_3N was generated by heating an aqueous solution of Et_3N (45% w/w, 50 mL) and passed into the inlet tube for 2 h. The product began to precipitate as a white solid. The resulting mixture was then allowed to stand overnight at r.t. and the ammonium salt **13** was collected on a Büchner funnel and dried under reduced pressure.
Data for compounds **13b**: highly hygroscopic solid. ^{1}H NMR (D_2O): δ = 2.33 (3 H, s, ArCH_3), 3.11 and 3.16 [total 9 H, s, N(CH_3)$_3$], 4.46 and 4.62 (total 2 H, s, ArCH_2), 7.30–7.72 (total 3 H, m, ArH). ^{13}C NMR (D_2O): δ = 21.4, 23.3, 53.3, 53.8, 68.4, 68.6, 124.9, 125.6, 127.5, 127.7, 130.0, 132.3, 132.8, 135.0, 135.8, 136.7, 141.3, 144.3. MS (FAB): *m/z* (%) = 242 (100) [M – Br]$^+$. HRMS: *m/z* calcd for $C_{11}H_{17}N^{79}Br$: 242.0539; found: 242.0540.
Data for compound **13e**: mp >230 °C (dec.). ^{1}H NMR (D_2O): δ = 2.37 (3 H, s, ArCH_3), 3.18 [9 H, s, N(CH_3)$_3$], 4.63 (2 H, s, ArCH_2), 7.68 (1 H, s, ArH), 7.81 (1 H, s, ArH). ^{13}C NMR (D_2O): δ = 22.7, 53.6, 67.8, 124.5, 126.3, 126.9, 136.3, 138.3, 144.0. MS (FAB) *m/z* (%) = 322 (80) [M – Br]$^+$. HRMS: *m/z* calcd for $C_{11}H_{16}N^{79}Br_2$: 319.9644; found: 319.9636.
Data for compound **13g**: mp >230 °C (dec.). ^{1}H NMR (D_2O): δ = 2.52 (3 H, s, ArCH_3), 3.10 [9 H, s, N(CH_3)$_3$], 4.44 (2 H, s, ArCH_2), 7.74 (2 H, s, ArH). ^{13}C NMR (D_2O): δ = 23.8, 53.1, 60.2, 68.3, 125.8, 128.2, 136.2, 141.2. MS (FAB): *m/z* (%) = 322 (70) [M – Br]$^+$. HRMS: *m/z* calcd for $C_{11}H_{16}N^{79}Br_2$: 319.9644; found: 319.9652.
Data for compound **13h**: mp >210 °C (dec.). ^{1}H NMR (DMSO-d_6): δ = 2.85 (3 H, s, ArCH_3), 3.26 [9 H, s, N(CH_3)$_3$], 5.15 (2 H, s, ArCH_2). ^{13}C NMR (DMSO-d_6): δ = 29.8, 54.1, 71.3, 129.3, 130.1, 131.4, 144.3. MS (FAB) *m/z* (%) = 480 (100) [M – Br]$^+$. HRMS: *m/z* calcd for $C_{11}H_{14}N^{79}Br_4$: 475.7854; found: 475.7848.
(13) **Synthesis of Substituted 4-Methylbenzyl Bromides 12 from Substituted *p*-Xylenes.**
A mixture of the substituted *p*-xylenes (ca. 10 g), *N*-bromosuccinimide (1 equiv) and benzoyl peroxide (0.01 g) in CCl_4 (100 mL) was heated to reflux. After 3 h, the reaction mixture was cooled to 0 °C and the precipitated succinimide was removed by filtration and washed with $CHCl_3$. The combined filtrates were evaporated under reduced pressure to give an oil that was purified by flash chromatography on silica gel (eluent: hexane) to afford the bromides **12** as a single compound or a regioisomeric mixture.
Data for **12b**: colorless oil; R_f = 0.68 (hexane). ^{1}H NMR ($CDCl_3$): δ = 2.32 and 2.38 (total 3 H, s, ArCH_3), 4.41 and 4.58, (total 2 H, s, ArCH_2Br), 7.07–7.56 (total 3 H, m, ArH). ^{13}C NMR ($CDCl_3$): δ = 20.8, 22.6, 32.1, 33.5, 124.2, 124.8, 127.8, 128.7, 130.9, 131.0, 132.6, 133.7, 133.9, 137.0, 138.1, 140.5. MS (EI): *m/z* (%) = 264 (23) [M$^+$]. HRMS: *m/z* calcd for $C_8H_8{}^{79}Br_2$: 261.8987; found: 261.8990. Anal. Calcd for $C_8H_8Br_2$: C, 36.40; H, 3.05. Found: C, 36.16; H, 2.97.
Data for **12f**: colorless oil; R_f = 0.65 (hexane). ^{1}H NMR ($CDCl_3$): δ = 2.35 (3 H, s, ArCH_3), 4.51 (2 H, s, ArCH_2), 7.26 (1 H, s, ArH), 7.41 (1 H, s, ArH). ^{13}C NMR ($CDCl_3$): δ = 19.7, 29.5, 131.2, 131.9, 132.1, 133.0, 134.2, 138.3. MS (EI): *m/z* (%) = 254 (50) [M$^+$]. HRMS: *m/z* calcd for $C_8H_7{}^{79}Br^{35}Cl_2$: 251.9103; found: 251.9110. Anal. Calcd for $C_8H_7BrCl_2$: C, 37.84; H, 2.78. Found: C, 37.78; H, 2.91.
(14) **Synthesis of Substituted 4-Methylbenzyl Bromides 12 from Substituted 4-Methylbenzyl Alcohols.**
A mixture of the substituted 4-methylbenzyl alcohol (30 mmol), CBr_4 (14.92 g, 45 mmol) and PPh_3 (11.80 g, 45 mmol) was stirred in THF at r.t. for 4 h. The reaction mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator. The crude product was purified by flash chromatography on silica gel (eluent: hexane) to give the target bromide.
Data for **12d**: white solid, mp 43–45 °C; R_f = 0.75 (hexane). ^{1}H NMR ($CDCl_3$): δ = 2.25 (6 H, s, ArCH_3), 4.47 (2 H, s, ArCH_2Br), 7.11–7.17 (3 H, m, ArH). ^{13}C NMR ($CDCl_3$): δ = 19.5, 19.7, 33.9, 126.4, 130.0, 130.3, 135.2, 137.1. MS (CI): *m/z* (%) = 198 (23) [M$^+$]. HRMS: *m/z* calcd for $C_9H_{11}{}^{79}Br$:

198.0039; found: 198.0039. Anal. Calcd for $C_8H_{11}Br$: C, 54.30; H, 5.57. Found: C, 54.11; H, 5.61.
Data for **12g**: white solid, mp 99–100 °C; R_f = 0.75 (hexane). ^{1}H NMR ($CDCl_3$): δ = 2.54 (3 H, s, ArCH_3), 4.33 (2 H, s, ArCH_2Br), 7.52 (2 H, s, ArH). ^{13}C NMR ($CDCl_3$): δ = 23.5, 30.7, 125.2, 132.2, 137.7, 138.0. MS (EI): *m/z* (%) = 342 (15) [M^+]. HRMS: *m/z* calcd for $C_8H_7{}^{79}Br_3$: 339.8092; found: 339.8090. Anal. Calcd for $C_8H_7Br_3$: C, 28.03; H, 2.06. Found: C, 27.88; H, 2.12.

(15) **General Procedure for the Synthesis of Substituted [2.2]Paracyclophanes.**
Ag_2O (23.0 g, 0.10 mol) was added to an aqueous solution (75 mL) of the substituted ammonium bromide(s) **13** (0.10 mol) and the mixture was stirred at r.t. for 1.5 h. The mixture was filtered and the solid was washed with H_2O (40 mL). The combined aqueous layers were placed in a 500-mL three-necked round-bottom flask equipped with a stirrer and a Dean–Stark water separator attached to a reflux condenser. Toluene (300 mL) and phenothiazine (0.50 g, 2.5 mmol) or 2-chlorophenothiazine (0.59 g, 2.5 mmol) was then added to the solution and the mixture was heated under reflux for 3 h. When all the water had been removed, Et_3N began to evolve and a pale yellow solid (*p*-phenyleneethylene polymer) began to precipitate. Heating and stirring were continued for another 1.5 h, after which time the evolution of Et_3N had ceased. The mixture was cooled and the solid was filtered and washed with toluene (10 mL × 3). The filtrates were combined and concentrated under reduced pressure to give the target compound as a solid that was further washed with acetone (10 mL × 3). Analytically pure samples were obtained from recrystallization from an organic solvent.
Data for **14e**: white solid, mp >280 °C (dec.). ^{1}H NMR ($CDCl_3$): δ = 2.92–3.07 (4 H, m, CH_2), 3.15–3.35 (4 H, m, CH_2), 7.20 (4 H, s, ArH). ^{13}C NMR ($CDCl_3$): δ = 32.6, 125.2, 134.3, 140.2. MS (EI): *m/z* (%) = 524 (1) [M^+]. HRMS: *m/z* calcd for $C_{16}H_{14}{}^{79}Br_4$: 523.7628; found: 523.7634.
Data for **14g**: white solid, mp >280 °C (dec.). ^{1}H NMR ($CDCl_3$): δ = 2.93–2.98 (4 H, m, CH_2), 3.40–3.45 (4 H, m, CH_2), 7.17 (4 H, s, ArH). ^{13}C NMR ($CDCl_3$): δ = 31.0, 34.8, 127.2, 132.8, 137.5, 141.7. MS (EI): *m/z* (%) = 523 (54) [M^+]. HRMS: *m/z* calcd for $C_{16}H_{12}{}^{79}Br_4$: 523.7667; found: 523.7658. Anal. Calcd for $C_{16}H_{12}Br_4$: C, 36.68; H, 2.31. Found: C, 36.59; H, 2.37.
Data for **14h**: white powder, mp >280 °C (dec.). ^{1}H NMR ($PhNO_2$-d_5): 3.39 (8 H, s, ArCH_2). MS (EI): *m/z* (%) = 839 (22) [M^+]. HRMS: *m/z* calcd for $C_{16}H_8{}^{79}Br_8$: 831.4088; found: 831.4078.

(16) The yields reported were the average of two or more runs.
(17) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3534.
(18) We wish to point out that there were only two aromatic ^{13}C signals instead of three for this compound in the paper reported by de Meijere (see ref. 7d). We also noted that the atom numbering system used in de Meijere's paper was different from ours.
(19) CCDC-274514 contains the crystallographic data of compound **14g**. The data can be obtained via www.ccdc.cam.ac.uk/conts/retrieving.html.
(20) CCDC-274513 contains the crystallographic data of compound **14h**. The data can be obtained via www.ccdc.cam.ac.uk/conts/retrieving.html.