Facile Synthesis of New Polyazamacrocycles by the Pd−Catalyzed Amination of 3,3'−Dibromobiphenyl

Alexei D. Averin,[a@] Alexei N. Uglov,[a] Alexei K. Buryak,[b] and Irina P. Beletskaya[a,b]

[a]*Lomonosov Moscow State University, Department of Chemistry, Leninskie Gory, Moscow, 119991 Russia.*
[b]*A. N. Frumkin Institute of Physical and Electrochemistry, 31 Leninskii prosp., Moscow, 119991, Russia.*
[@]*Corresponding author E-mail: averin@org.chem.msu.ru*

Pd-Catalyzed amination of 3,3'-dibromobiphenyl using various polyamines and oxadiamines was studied. Target macrocycles were obtained in yields from moderate to good with a variety of polyamines and oxadiamines, cyclic oligomers were isolated in the majority of cases as by-products. Synthesis of the macrocycles containing two 3,3'-disubstituted biphenyls and two polyamine fragments (cyclodimers) was elaborated using intermediate di(bromobiphenyl)substituted polaymines or bis(polyamine)substituted biphenyls.

Keywords: Macrocycles, amination, catalysis, polyamines, biphenyl.

Introduction

Macrocycles containing biphenyl units attract a constant interest of researchers due to interesting coordination possibilities arising from attaching flexible and tunable polyoxa- and polyazacycles to a rigid non-planar aryl moiety. The most of reported macrocycles based on biphenyls were synthesized using non-catalytic approaches. Cyclic polyethers were formed starting from 2,2'-dihydroxybiphenyl,[1-3] and their coordination with cations like *tert*-butylammonium was studied.[2] Transport of Li, Na, K cations[4,5] and of $Hg(CF_3)_2$[6,7] through a liquid membrane was investigated using macrocycles of similar structure, in which one or two polyoxaethylene chains were attached to one biphenyl unit. Polyoxadiaminomacrocycles were also synthesized on the basis of 2,2'-disubstituted biphenyl and their complexation of primary alkylammonium salts, including chiral ones, was studied.[8] Polyazamacrocycles with 3, 4 and 8 nitrogen atoms were investigated as complexing agents for Cu^{2+}, Zn^{2+} and $[PdCl_4]^{2-}$ ions.[9] More sophisticated macrocycles like peptide-biphenyl hybrid[10] and hemispherand macrocycle[11] with bi- and quaterphenyl moieites have been recently reported. Cyclic triamides[12] as well as cyclic Schiff bases (trianglimines)[13,14] comprise three 3,3'-disubstituted biphenyls, the latter can be aslo built on the basis of 4,4'-disubstituted biphenyls. In some cases biphenyl fragment was built using Pd-catalyzed coupling of two benzene moieties at the step of macrocyclization, as it was in the case of the compound with diazacrown, dipeptide and biphenyl fragments.[15] It is to be mentioned that biphenyls are incorporated in some biologically active macrocycles, *e.g.* tricyclic glucopeptides of vancomicine group.[16] To the moment, there are no literature data on the synthesis of biphenyl-based macrocycles which employs catalytic bond formation between aromatic and aliphatic parts of the molecule. In recent years we have accumulated experience on the application of the Buchwald-Hartwig amination[17] in the synthesis of polyazamacrocycles starting from various dihaloarenes[18-21] and we investigated this approach for the construction of biphenyl-based macrocycles.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Ultraflex spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as standards. 2-Bromonitrobenzene, oxadiamines, polyamines, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP), 2-dimethylamino-2'-dicyclohexylphosphinobiphenyl (DavePHOS), sodium *tert*-butoxide were purchased from Aldrich and Acros and used without further purification, $Pd(dba)_2$ was synthesized according to the method described earlier.[22] 3,3'-Dibromobiphenyl was synthesized in 3 steps from 2-bromonitrobenzene according to the procedure.[23] Dioxane was distilled over NaOH followed by the distillation over sodium under argon, dichloromethane and methanol were distilled.

*Typical procedure for the synthesis of macrocycles **3**.*

A two-neck flask equipped with a magnetic stirrer and a condenser, flushed with dry argon, was charged with 3,3'-dibromobiphenyl (**1**) (0.5 mmol, 156 mg), absolute dioxane (25 ml), $Pd(dba)_2$ (24 mg, 8 mol%) and BINAP (28 mg, 9 mol%). The mixture was stirred for 2 min, then appropriate polyamine **2** (0.5 mmol) and ^{t}BuONa (1.5 mmol) were added, and the reaction mixture was refluxed for 24 h. After cooling to the ambient temperature and filtration of the precipitate dioxane was evaporated *in vacuo* and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2-MeOH 500:1 – 3:1, CH_2Cl_2-MeOH-aq. NH_3 100:20:1 – 10:4:1.

*11,22,26-Tetraazapentacyclo[25.3.1.1^{2,6}.1^{12,16}.1^{17,21}] tetratriaconta-1(31),2(34),3,5,12(33),13,15,17(32),18,20,27,29-dodecaene, **4a*** (n=1). Obtained from 37 mg of propane-1,3-diamine **2a**. Eluent: CH_2Cl_2-MeOH 200:1. Yield 27 mg (24%). Pale-yellow crystals, m.p. 224-225°C (decomp.) *m/z* (MALDI-TOF) found: 448.2593. $C_{30}H_{32}N_4$ requires 448.2627 [M^+]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.94 (4H, quintet, ^3J = 6.1 Hz), 3.37 (8H, t, ^3J = 6.1 Hz), 3.91 (4H, br.s), 6.60 (4H, dd, ^3J = 7.6 Hz, ^4J = 1.8 Hz), 6.78 (4H, br.s), 6.91 (4H, d, ^3J = 7.7 Hz), 7.21 (4H, t, ^3J = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 28.6 (2C), 42.4 (4C), 111.6 (4C), 112.1 (4C), 116.5 (4C), 129.6 (4C), 142.9 (4C), 148.3 (4C).

7,10,13,24,27,30-Hexaazapentacyclo[29.3.1.1^{2,6}.1^{14,18}.1^{19,23}] octatriaconta-1(35),2(38),3,5,14(37),15,17,19(36),20,22,31,33-dodecaene, ***4b*** (n=1). Obtained from 52 mg of triamine **2b**. Eluent: CH_2Cl_2-MeOH/NH_3-aq 100:20:1. Yield 29 mg (23%). Pale-yellow glassy solid. Contains admixtures of cyclotrimer **4b** (n=2) and cyclotetramer **4b** (n=3). *m/z* (MALDI-TOF) 507.39 (**4b** (n=1) [(M+H)$^+$]), 760.44 (**4b** (n=2) [(M+H)$^+$]), 1012.72 (**4b** (n=3) [M$^+$]). ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 2.85 (8H, br.s), 3.12–3.30 (8H, m), 6.50–6.58 (4H, m), 6.82–6.94 (8H, m), 7.11–7.21 (4H, m), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.0 (4C), 48.0 (4C), 111.7 (4C), 111.8 (4C), 116.4 (4C), 129.4 (4C), 142.3 (4C), 148.4 (4C).

7,11,15-Triazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene, ***3c***. Obtained from 66 mg of triamine **2c**. Eluent: CH_2Cl_2-MeOH 3:1. Yield 35 mg (25%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 281.1930. $C_{18}H_{23}N_3$ requires 281.1892 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.82 (4H, quintet, ^3J = 6.7 Hz), 2.71 (4H, t, ^3J = 6.0 Hz), 3.37 (4H, t, ^3J = 7.3 Hz), 4.06 (2H, br.s), 6.54 (2H, dd, ^3J = 8.0 Hz, ^4J = 0.8 Hz), 7.03 (2H, d, ^3J = 7.5 Hz), 7.17 (2H, t, ^3J = 7.8 Hz), 7.29 (2H, br.s), NH proton of the dialkylamino group was not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 29.7 (2C), 41.3 (2C), 47.0 (2C), 109.6 (2C),114.0 (2C), 114.8 (2C), 129.3 (2C), 142.1 (2C), 147.9 (2C).

7,11,15,26,30,34-Hexaazapentacyclo[33.3.1.1^{2,6}.1^{16,20}.1^{21,25}] dotetraconta-1(39),2(42),3,5,16(41),17,19,21(40),22,24,35,37-dodecaene, ***4c*** (n=1). Obtained as by-product in the synthesis of macrocycle **3c**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:1. Yield 30 mg (21%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 562.3701. $C_{36}H_{46}N_6$ requires 562.3784 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.80 (8H, quintet, ^3J = 6.7 Hz), 2.68 (8H, t, ^3J = 5.9 Hz), 3.29 (8H, t, ^3J = 5.1 Hz), 3.90 (4H, br.s), 6.53 (4H, d, ^3J = 8.0), 7.02 (4H, d, ^3J = 7.4 Hz), 7.16 (4H, t, ^3J = 7.7 Hz), 7.17 (4H, br.s), NH proton of the dialkylamino group was not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 28.4 (4C), 41.1 (4C), 48.0 (4C), 109.8 (4C), 114.0 (4C), 114.8 (4C), 129.3 (4C), 142.3 (4C), 147.7 (4C).

7,10,13,16-Tetraazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene, ***3d***. Obtained from 73 mg of tetraamine **2d**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:3. Yield 23 mg (16%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 296.1959. $C_{18}H_{24}N_4$ requires 296.2001 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 2.82 (4H, s), 2.87 (4H, t, ^3J = 6.6 Hz), 3.29 (4H, t, ^3J = 6.6 Hz), 6.54 (2H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 7.02 (2H, d, ^3J = 7.7 Hz), 7.06 (2H, br.s), 7.16 (2H, t, ^3J = 7.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 44.27 (2C), 48.5 (2C), 49.3 (2C), 108.9 (2C), 114.2 (2C), 115.7 (2C), 129.3 (2C), 142.2 (2C), 148.9(2C).

7,10,13,16,27,30,33,36-Octaazapentacyclo[35.3.1.1^{2,6}.1^{17,21}. 1^{22,26}]tetratetraconta-1(41),2(44),3,5,17(43),18,20,22(42), 23,25,37,39-dodecaene, ***4d*** (n=1). Obtained as by-product in the synthesis of macrocycle **3d**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:25:5. Yield 27 mg (18%). Pale-yellow glassy solid. Contains admixture of cyclotrimer **4d** (n=2). *m/z* (MALDI-TOF) 592.33 (**4d** (n=2) [M$^+$]), 888.38 (**4d** (n=2) [M$^+$]). ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 2.74 (8H, s), 2.85 (8H, t, ^3J = 5.8 Hz), 3.21 (8H, t, ^3J = 5.2 Hz), 6.56 (4H, dd, ^3J = 7.8 Hz, ^4J = 1.9 Hz), 6.80 (4H, s), 6.89 (4H, d, ^3J = 7.2 Hz), 7.15 (4H, t, ^3J = 7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.5 (4C), 48.4 (4C), 48.8 (4C), 111.7 (4C), 111.8 (4C), 116.6 (4C), 129.5 (4C), 142.8 (4C), 148.6 (4C).

7,10,14,17-Tetraazatricyclo[16.3.1.1^{2,6}]tricosa-1(22),2(23),3,5,18,20-hexaene, ***3e***. Obtained from 80 mg of tetraamine **2e**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:2. Yield 41 mg (26%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 310.2190. $C_{19}H_{26}N_4$ requires 310.2157 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.67 (2H, quintet, ^3J = 6.4 Hz), 2.80 (4H, t, ^3J = 6.4 Hz), 2.83 (4H, t, ^3J = 6.9 Hz), 3.36 (4H, t, ^3J = 6.9 Hz), 4.10 (2H, br.s), 6.57 (2H, dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz), 6.96–7.00 (4H, m), 7.17 (2H, t, ^3J = 7.7 Hz), NH protons of the dialkylamino groups were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 29.5 (1C), 44.3 (2C), 48.0 (2C), 49.2 (2C), 110.1 (2C), 114.2 (2C), 116.1 (2C), 129.3 (2C), 142.7 (2C), 148.7 (2C).

7,10,14,17,28,31,35,38-Octaazapentacyclo[37.3.1.1^{2,6}.1^{18,22}. 1^{23,27}]hexatetraconta-1(43),2(46),3,5,18(45),19,21,23(44),24,26, 39,41-dodecaene, ***4e*** (n=1). Obtained as by-product in the synthesis of macrocycle **3e**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:3. Yield 12 mg (8%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 620.4307. $C_{38}H_{52}N_8$ requires 620.4314 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.69 (4H, quintet, ^3J = 5.6 Hz), 2.77 (8H, t, ^3J = 4.6 Hz), 2.83 (8H, t, ^3J = 6.4 Hz), 3.24 (8H, br.s), 6.57 (4H, d, ^3J = 7.8 Hz), 6.72 (4H, br.s), 6.85 (4H, d, ^3J = 7.6 Hz), 7.14 (4H, t, ^3J = 7.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 28.9–29.7 (m, 2C), 42.6–43.0 (m, 4C), 47.8–49.3 (m, 8C), 111.2–111.8 (m, 8C), 116.3+116.4 (4C), 129.5 (4C), 142.6 (4C), 148.4+148.5 (4C).

7,11,14,18-Tetraazatricyclo[17.3.1.1^{2,6}]tetracosa-1(23),2(24),3,5,19,21-hexaene, ***3f***. Obtained from 87 mg of tetraamine **2f**. Eluent: CH_2Cl_2-MeOH 3:1 - CH_2Cl_2-MeOH-NH_3-aq 100:20:2. Yield 71 mg (44%). Pale-yellow crystals, m.p. 115-116°C. *m/z* (MALDI-TOF) found: 324.2264. $C_{20}H_{28}N_4$ requires 324.2314 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.92 (4H, quintet, ^3J = 6.6 Hz), 2.82 (4H, t, ^3J = 6.0 Hz), 2.88 (4H, s), 3.32 (4H, t, ^3J = 7.2 Hz), 3.72 (2H, br.s), 6.53 (2H, d, ^3J = 7.6 Hz), 6.93 (2H, s), 6.94 (2H, d, ^3J = 7.8 Hz), 7.15 (2H, t, ^3J = 7.7 Hz), NH protons of the dialkylamino groups were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 28.1 (2C), 42.4 (2C), 47.5 (4C), 110.9 (2C), 113.3 (2C), 115.7 (2C), 129.5 (2C), 142.5 (2C), 148.3 (2C).

7,11,14,18,29,33,36,40-Octaazapentacyclo[39.3.1.1^{2,6}.1^{19,23}. 1^{24,28}]octatetraconta-1(45),2(48),3,5,19(47),20,22,24(46),25,27, 41,43-dodecaene, ***4f*** (n=1). Obtained as by-product in the synthesis of macrocycle **3f**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:3. Yield 41 mg (25%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 648.4612. $C_{40}H_{56}N_8$ requires 648.4628 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.73 (8H, quintet, ^3J = 6.3 Hz), 2.71 (8H, t, ^3J = 6.3 Hz), 2.72 (8H, s), 3.15 (8H, t, ^3J = 6.3 Hz), 6.53 (4H, dd, ^3J = 7.8 Hz, ^3J = 1.7 Hz), 6.76 (4H, t, ^4J = 1.7 Hz), 6.87 (4H, d, ^3J =7.5 Hz), 7.17 (4H, t, ^3J = 7.7 Hz), NH protons of the dialkylamino groups were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 29.1 (4C), 42.9 (4C), 48.1 (4C), 48.9 (4C), 111.3 (4C), 111.9 (4C), 116.2 (4C), 129.3 (4C), 142.9 (4C), 148.8 (4C).

7,11,15,19-Tetraazatricyclo[18.3.1.1^{2,6}]pentacosa-1(24),2(25),3,5,20,22-hexaene, ***3g***. Obtained from 94 mg of tetraamine **2g**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:1. Yield 69 mg (41%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 338.2410. $C_{21}H_{30}N_4$ requires 338.2470 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.70 (2H, quintet, ^3J = 6.2 Hz), 1.83 (4H, quintet, ^3J = 6.6 Hz), 2.74 (8H, t, ^3J = 6.4 Hz), 3.22 (4H, t, ^3J = 6.9 Hz), 6.53 (2H, d, ^3J = 8.0 Hz), 6.85 (2H, br.s), 6.94 (2H, d, ^3J = 7.6 Hz), 7.19 (2H, t, ^3J = 7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 28.5 (2C), 29.8 (1C), 43.1 (2C), 48.4 (2C), 48.5 (2C), 110.7 (2C), 112.2 (2C), 115.4 (2C), 129.2 (2C), 142.5 (2C), 148.6 (2C).

7,11,15,19,30,34,38,42-Octaazapentacyclo[41.3.1.1^{2,6}. 1^{20,24}.1^{25,29}]pentaconta-1(47),2(50),3,5,20(49),21,23,25(48),26,28, 43,45-dodecaene, ***4g*** (n=1). Obtained as by-product in the synthesis of macrocycle **3g**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:4:1. Yield 32 mg (19%). Contains admixtures of cyclotrimer **4g** (n=2) and cyclotetramer **4g** (n=3). Pale-yellow glassy solid. *m/z* (MALDI-TOF) 676.48 (**4g** (n=1) [M$^+$]), 1014.57 (**4g** (n=2) [M$^+$]), 1362.40 (**4g** (n=3) [M$^+$]). ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.72 (12H, br.s), 2.67 (16H, br.s), 3.11 (8H, br.s), 6.51 (4H, d, ^3J = 5.4 Hz), 6.76 (4H, br.s), 6.86 (4H, d, ^3J = 6.9 Hz), 7.15 (4H, t, ^3J = 6.5 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 28.8 (4C), 29.1 (2C), 42.7 (4C), 48.0-48.6 (8C, m), 111.3-111.7 (8C, m), 116.0 (4C), 129.3 (4C), 142.7 (4C), 148.7 (4C).

7,10,13,16,19-Pentaazatricyclo[18.3.1.1^{2,6}]pentacosa-1(24),2(25),3,5,20,22-hexaene, ***3h***. Obtained from 94 mg of pentaamine **2h**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:20:3. Yield 32 mg (19%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 339.2373. $C_{20}H_{29}N_5$ requires 339.2423 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 2.74 (4H, t, ^3J = 4.7 Hz), 2.83 (4H, t, ^3J = 4.8 Hz), 2.90 (4H, t, ^3J = 6.1 Hz), 3.34 (4H, t, ^3J = 6.1 Hz), 6.60 (2H, d, ^3J = 7.3 Hz), 6.98 (2H, s), 6.99 (2H, d, ^3J = 6.7 Hz), 7.22 (2H, t, ^3J = 8.0 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.7 (2C), 48.6 (2C), 49.1 (2C), 49.5 (2C), 111.6 (2C), 112.8 (2C), 116.2 (2C), 129.5 (2C), 142.6 (2C), 148.8 (2C).

7,10,13,16,19,30,33,36,39,42-Decaazapentacyclo [41.3.1.1^{2,6}.1^{20,24}.1^{25,29}]pentaconta-1(47),2(50),3,5,20(49),21, 23,25(48),26,28,43,45-dodecaene, ***4h*** (n=1). Obtained as by-product in the synthesis of macrocycle **3g**. Eluent: CH_2Cl_2-MeOH-NH_3-aq 100:25:5. Yield 5 mg (3%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 678.58. $C_{40}H_{58}N_{10}$ requires 678.48 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 2.73 (16H, br.s), 2.86 (8H, br.s), 3.22 (8H, br.s), 6.59 (4H, d, ^3J = 7.7 Hz), 6.82 (4H, br.s), 6.90 (4H, d, ^3J = 6.7 Hz), 7.20 (4H, t, ^3J = 7.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.5 (4C), 48.6 (4C), 49.0 (4C), 49.2 (4C), 111.9 (8C), 116.5 (4C), 129.5 (4C), 142.8 (4C), 148.7 (4C).

10,13-Dioxa-7,16-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene, ***3i***. Obtained from 74 mg of dioxadiamine **2i** in the presence of $Pd(dba)_2$ (46 mg, 16 mol%) and BINAP (56 mg, 18 mol%). Eluent: CH_2Cl_2-MeOH 100:1. Yield 60 mg (40%). Pale-yellow crystals, m.p. 211-212°C. *m/z* (MALDI-TOF) found: 298.1681. $C_{18}H_{22}N_2O_2$ requires 298.1706 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 3.49 (4H, t, ^3J =5.5 Hz), 3.70 (4H, s), 3.71 (4H, t, ^3J = 5.6 Hz), 4.09 (2H, br.s), 6.59 (2H, ddd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, ^4J = 0.8 Hz), 7.06 (2H, d, ^3J = 7.7 Hz), 7.19 (2H, t, ^3J = 7.7 Hz), 7.39 (2H, t, ^4J = 1.9 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 45.2 (2C), 70.9 (2C), 72.6 (2C), 110.9 (2C), 114.2 (2C), 116.3 (2C), 128.9 (2C), 142.7 (2C), 148.9 (2C).

10,13,30,33-Tetraoxa-7,16,27,36-tetraazapentacyclo[35.3.1.1^{2,6}.1^{17,21}.1^{22,26}]tetratetraconta-1(41),2(44),3,5,17(43), 18,20,22(42),23,25,37,39-dodecaene, ***4i*** (n=1). Obtained as by-product in the synthesis of macrocycle **3i**. Eluent: CH_2Cl_2-MeOH 75:1. Yield 22 mg (15%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 596.3409. $C_{36}H_{44}N_4O_4$ requires 596.3362 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 3.34 (8H, t, ^3J = 4.7 Hz), 3.68 (8H, s), 3.73 (8H, t, ^3J = 4.8 Hz), 4.23 (4H, br.s), 6.60 (4H, d, ^3J = 7.7 Hz), 6.79 (4H, br.s), 6.91 (4H, d, ^3J = 7.1 Hz), 7.18 (4H, t, ^3J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.7 (4C), 69.6 (4C), 70.3 (4C), 111.8 (4C), 112.5 (4C), 116.8 (4C), 129.5 (4C), 142.9 (4C), 148.5 (4C).

10,13,30,33,50,53-Hexaoxa-7,16,27,36,47,56-hexaazaheptacyclo[55.3.1.1^{2,6}.1^{17,21}.1^{22,26}.1^{37,41}.1^{42,46}] hexahexaconta-1(61),2(66),3,5,17(65),18,20,22(64), 23,25,37(63),38,40,42(62),43,45,57,59-octadecaene, ***4i*** (n=2). Obtained as by-product in the synthesis of macrocycle **3i**. Eluent: CH_2Cl_2-MeOH 20:1. Yield 24 mg (16%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 894.56. $C_{54}H_{66}N_6O_6$ requires 894.50 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 3.36 (12H, br.s), 3.67 (12H, s), 3.72 (12H, br.s), 4.06 (6H, br.s), 6.62 (6H, d, ^3J = 7.5 Hz), 6.84 (6H, br.s), 6.94 (6H, d, ^3J = 6.8 Hz), 7.22 (6H, t, ^3J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.6 (6C), 69.7 (6C), 70.3 (6C), 112.0 (6C), 112.1 (6C), 116.8 (6C), 129.5 (6C), 142.9 (6C), 148.5 (6C).

11,16-Dioxa-7,20-diazatricyclo[19.3.1.1^{2,6}]hexacosa-1(25),2(26),3,5,21,23-hexaene, ***3j***. Obtained from 102 mg of dioxadiamine **2j**. Eluent: CH_2Cl_2-MeOH 100:1. Yield 78 mg (44%). Pale-yellow crystals, m.p. 111-112°C. *m/z* (MALDI-TOF) found: 354.2279. $C_{22}H_{30}N_2O_2$ requires 354.2307 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.76 (4H, quintet, ^3J = 2.8 Hz), 1.90 (4H, quintet, ^3J = 5.8 Hz), 3.36 (4H, t, ^3J = 6.5 Hz), 3.47 (4H, br.s), 3.61 (4H, t, ^3J = 5.3 Hz), 6.57 (2H, ddd, ^3J = 8.0 Hz, ^4J = 2.2 Hz, ^4J = 0.7 Hz), 6.99 (2H, t, ^4J = 2.1 Hz), 7.01 (2H, d, ^3J = 7.7 Hz), 7.24 (2H, t, ^3J = 7.8 Hz).^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 27.2 (2C), 29.3 (2C), 43.2 (2C), 70.3 (2C), 71.2 (2C), 111.5 (4C), 115.8 (2C), 129.3 (2C), 142.2 (2C), 149.1 (2C).

11,16,35,40-Tetraoxa-7,20,31,44-tetraazapentacyclo[43.3.1.1^{2,6}.1^{21,25}.1^{26,30}]dopentaconta-1(49),2(52),3,5,21(51), 22,24,26(50),27,29,45,47-dodecaene, ***4j*** (n=1). Obtained as by-product in the synthesis of macrocycle **3j**. Eluent: CH_2Cl_2-MeOH 75:1. Yield 20 mg (12%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 708.42. $C_{44}H_{60}N_4O_4$ requires 708.46 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.66 (8H, quintet, ^3J = 2.1 Hz), 1.85 (8H, quintet, ^3J = 6.1 Hz), 3.23 (8H, t, ^3J = 6.4 Hz), 3.43 (8H, quintet, ^3J = 2.1 Hz), 3.52 (8H, t, ^3J = 5.7 Hz), 4.13 (4H, br.s), 6.54 (4H, dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz), 6.77 (4H, t, ^4J = 1.8 Hz), 6.87 (4H, d, ^3J = 7.6 Hz), 7.18 (4H, t, ^3J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 26.6 (4C), 29.3 (4C), 42.2 (4C), 69.5 (4C), 70.8 (4C), 111.4 (4C), 111.7 (4C), 116.3 (4C), 129.3 (4C), 143.0 (4C), 148.8 (4C).

11,14,17-Trioxa-7,21-diazatricyclo[20.3.1.1^{2,6}]heptacosa-1(26),2(27),3,5,22,24-hexaene, ***3k***. Obtained from 110 mg of trioxadiamine **2k**. Eluent CH_2Cl_2-MeOH 100:1. Yield 71 mg (38%). Pale-yellow crystals, m.p. 74-75°C. *m/z* (MALDI-TOF) found: 370.2240. $C_{22}H_{30}N_2O_3$ requires 370.2256 [M$^+$]. δ_H ($CDCl_3$, 297 K) 1.91 (4H, quintet, ^3J = 5.9 Hz), 3.35 (4H, t, ^3J = 6.5 Hz), 3.60–3.66 (8H, m), 3.73–3.77 (4H, m), 4.26 (2H, br.s), 6.57 (2H, d, ^3J = 7.9 Hz), 6.94 (2H, br.s), 6.97 (2H, d, ^3J = 7.7 Hz), 7.21 (2H, t, ^3J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 29.3 (2C), 42.5 (2C), 70.1 (2C), 70.7 (2C), 71.0 (2C), 111.1 (2C), 111.9 (2C), 115.9 (2C), 129.2 (2C), 142.5 (2C), 149.0 (2C).

11,14,17,36,39,42-Hexaoxa-7,21,32,46-tetraazapentacyclo[45.3.1.1^{2,6}.1^{22,26}.1^{27,31}]tetrapentaconta-1(51),2(54), 3,5,22(53),23,25,27(52),28,30,47,49-dodecaene, ***4k*** (n=1). Obtained as by-product in the synthesis of macrocycle **3k**. Eluent: CH_2Cl_2-MeOH 50:1. Yield 22 mg (12%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 740.4473. $C_{44}H_{60}N_4O_6$ requires 740.4512 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 1.84 (8H, quintet, ^3J = 6.0 Hz), 3.23 (8H, t, ^3J = 6.4 Hz), 3.55 (8H, t, ^3J = 5.8 Hz), 3.55–3.60 (8H, m), 3.63–3.67 (8H, m), 4.18 (4H, br.s), 6.54 (4H, dd, ^3J = 7.7 Hz, ^4J = 1.9 Hz), 6.73 (4H, br.s), 6.85 (4H, d, ^3J = 7.4 Hz), 7.17 (4H, t, ^3J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 29.0 (4C), 41.7 (4C), 69.7 (4C), 70.2 (4C), 70.6 (4C), 111.3 (4C), 111.8 (4C), 116.1 (4C), 129.3 (4C), 143.0 (4C), 148.8 (4C).

Synthesis of *N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5'-bromobiphenyl-3-amine),* ***5i***, is analogous to the procedure described for the preparation of macrocycles **3**, from 3,3'-dibromobiphenyl (**1**) (1.5 mmol, 468 mg) and dioxadiamine **2i** (0.5 mmol, 74 mg), in absolute dioxane (5 ml), in the presence of $Pd(dba)_2$ (12 mg, 4 mol%), Xanthphos (13 mg, 5 mol%) and ^{t}BuONa (1.5 mmol). Reflux time: 8 h. Eluent; CH_2Cl_2-MeOH 200:1. Yield 82 mg (27%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 608.0713. $C_{30}H_{30}Br_2N_2O_2$ requires 608.0674 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 3.36 (4H, t, ^3J = 5.2 Hz), 3.68 (4H, s), 3.74 (4H, t, ^3J = 5.2 Hz), 4.20 (2H, br.s), 6.63 (2H, dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz), 6.77 (2H, t, ^4J = 1.4 Hz), 6.88 (2H, d, ^3J = 7.7 Hz), 7.22 (2H, t, ^3J = 7.9 Hz), 7.25 (2H, d, ^3J = 7.8 Hz), 7.42-7.47 (4H, m), 7.69 (2H, t, ^4J = 1.6 Hz). ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 43.5 (2C), 69.6 (2C), 70.2 (2C), 111.6 (2C), 112.6 (2C), 116.6 (2C), 122.7 (2C), 125.7 (2C), 129.7 (2C), 129.9 (2C), 130.0 (2C), 130.1 (2C), 140.8 (2C), 143.8 (2C), 148.6 (2C).

Synthesis of *N^3,N$^{3'}$-bis(2-(2-(2-aminoethoxy)ethoxy)ethyl) biphenyl-3,3'-diamine,* ***6i***, is analogous to the procedure described for the preparation of compound **5i**, from 3,3'-dibromobiphenyl **1** (0.5 mmol, 156 mg) and dioxadiamine **2i** (2 mmol, 296 mg), in absolute dioxane (5 ml), in the presence of $Pd(dba)_2$ (12 mg, 4 mol%), BINAP (14 mg, 4.5 mol%) and ^{t}BuONa (1.5 mmol). Reflux time: 8 h. *m/z* (MALDI-TOF) found: 446.42. $C_{24}H_{38}N_4O_4$ requires 446.29 [M$^+$]. ^{1}H NMR ($CDCl_3$, 297 K) δ_H ppm: 2.83 (4H, t, ^3J =

5.3 Hz), 3.32 (4H, t, ^3J = 5.3 Hz), 3.49 (4H, t, ^3J = 5.2 Hz), 3.60-3.66 (8H, m), 3.71 (4H, t, ^3J = 5.2 Hz), 6.59 (2H, ddd, ^3J = 8.1 Hz, ^4J = 2.4 Hz, ^4J = 0.7 Hz), 6.80 (2H, t, ^4J = 2.1 Hz), 6.89 (2H, d, ^3J = 7.6 Hz), 7.19 (2H, t, ^3J = 7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 297 K) δ_c ppm: 41.5 (2C), 43.4 (2C), 69.6 (2C), 70.2 (4C), 73.4 (2C), 112.0 (4C), 116.7 (2C), 129.3 (2C), 142.8 (2C), 148.4 (2C).

Synthesis of cyclodimer **4i** (n=1) from compound **5i** is analogous to the procedure described for the preparation of macrocycles **3**, from compound **5i** (0.135 mmol, 82 mg) and dioxadiamine **2i** (0.135 mmol, 20 mg), in absolute dioxane (7 ml), in the presence of $Pd(dba)_2$ (6.5 mg, 8 mol%), BINAP (7.5 mg, 9 mol%) and ^{t}BuONa (0.4 mmol, 39 mg). Reflux time: 24 h. Eluent; CH_2Cl_2-MeOH 20:1. Yield 33 mg (27%).

Synthesis of cyclodimer **4i** (n=1) from compound **6i** is analogous to the procedure described for the preparation of macrocycles **3**, from the mixture of compound **6i** (*ca* 0.25 mmol) with dioxadiamine **2i** (ca 0.5 mmol) and 3,3'-dibromobiphenyl (**1**) (0.75 mmol, 234 mg), in absolute dioxane (12 ml), in the presence of $Pd(dba)_2$ (36 mg, 8 mol%), BINAP (42 mg, 9 mol%) and ^{t}BuONa (2.25 mmol, 216 mg). Reflux time: 24 h. Eluent; CH_2Cl_2-MeOH 20:1. Yield 98 mg (44%).

Results and Discussion

The reactions of equimolar amounts of 3,3'-dibromobiphenyl **1** with a variety of di- and polyamines **2a-k** (Figure 1) were run in enough dilute dioxane solutions (c = 0.02 M) using $Pd(dba)_2$/BINAP (8/9 mol%) catalytic system[24] which was found to be almost universal for the synthesis of polyazamacrocycles, the products were isolated by column chromatography on silica gel. The results are given in Table 1.

As expected, propane-1,3-diamine **2a** was too short to give a desired mono-cycle **3**, and it produced cyclodimer **4a** (n=1) in 24% yield as well as a mixture of higher mass oligomers **4a** (n=2-7) (37%) (Table 1, entry 1). Diethylenetriamine **2b** (7 atoms in the chain) also gave only cyclooligomers **4b** (n=1-5) (entry 2), but beginning from triamine **2c** (9 atoms) target macrocycles **6** were formed successfully in yields from moderate to good (entries 3-13). The best yields (44%, entries 6, 11) were achieved with tetraamine **2f** and dioxadiamine **2j**, also enough high yields for the macrocyclization reaction (*ca* 40%) were afforded by tetraamine **2g** and trioxadiamine **2k** (entries 7, 12). We increased the yield of the macrocycle **3k** to 45% by the application of 2-dicyclohexylphosphino-2'-dimethylamino-biphenyl (DavePHOS) ligand instead of BINAP (entry 13), however, this approach did not work in the case of dioxadiamine **2i**, but the use of 16% mol catalyst gave corresponding macrocycle **3i** in 40% yield (entry 10). In many cases cyclodimers **4** (n=1) were isolated from oligomeric mixtures in 8-25% yields, and in the reactions with dioxadiamine **2i** even cyclotrimer **4i** (n=2) was obtained separately in 16% yield. It is to be mentioned that 40% yields of polyazamacrocycles are among the highest ever achieved by the Pd-catalyzed amination of dihaloarenes, *e.g.* they notably surpass those obtained recently with 2,7-dibromonaphthalene.[25] Mono-cycles **3** contain from 15 (**3c**) to 21 atoms (**3k**) in the cycle, cyclodimers **4** possess from 22 (**4a**, n=1) to 42 atoms (**4k**, n=1), while cyclotrimer **4i** (n=2) has a cavity formed by 48 atoms.

Cyclodimers which possess two biphenyl units and two polyamine chains and thus have a larger cavity size are of interest for the coordination studies with big cations and anions and organic molecules. We elaborated two approaches to such compounds. According to the first route, we synthesized *N,N'*-di(bromobiphenyl) substituted dioxadiamine **5i** which was

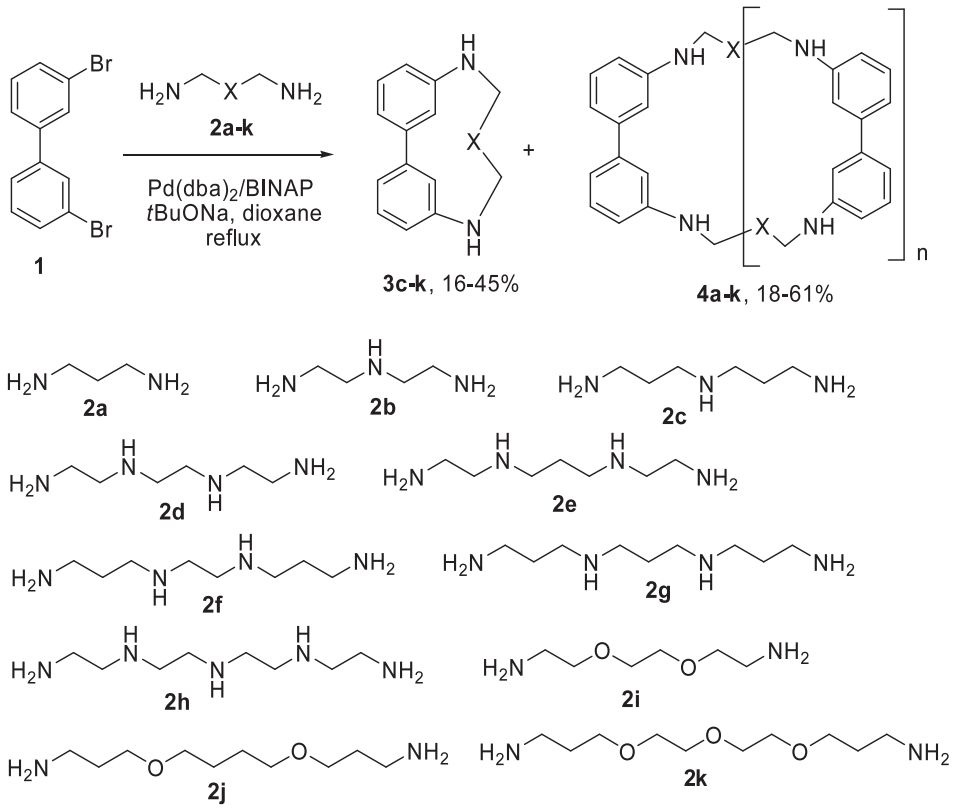

Figure 1.

Table 1. Pd-Catalyzed amination of 3,3'-dibromobiphenyl (**1**).

Entry	Amine	$Pd(dba)_2$/BINAP, mol%	Isolated yields of **3**, %	Yields of **4**, %
1	**2a**	8/9	**3a**, 0	**4a** (n=1), 24 **4a** (n=2-7), 37 (mixture)
2	**2b**	8/9	**3b**, 0	**4b** (n=1), 23 **4b** (n=2-5), 38 (mixture)
3	**2c**	8/9	**3c**, 25	**4c** (n=1), 21 **4c** (n=2-5), 23 (mixture)
4	**2d**	8/9	**3d**, 16	**4d** (n=1,2), 18 (mixture)
5	**2e**	8/9	**3e**, 26	**4e** (n=1), 8 **4e** (n=1-3), 27 (mixture)
6	**2f**	8/9	**3f**, 44	**4f** (n=1), 25 **4f** (n=1,2), 17 (mixture)
7	**2g**	8/9	**3g**, 41	**4g** (n=1-3), 19 (mixture)
8	**2h**	8/9	**3h**, 19	**4h** (n=1), 3 **4h** (n=1,2), 12 (mixture)
9	**2i**	8/9	**3i**, 19	**4i** (n=1), 12
10	**2i**	16/18	**3i**, 40	**4i** (n=1), 15 **4i** (n=2), 16
11	**2j**	8/9	**3j**, 44	**4j** (n=1), 12 **4j** (n=1-4), 18 (mixture)
12	**2k**	8/9	**3k**, 38	**4k** (n=1), 12 **4k** (n=1-4), 17 (mixture)
13[a)]	**2k**	8/10	**3k**, 45	**4k** (n=1), 21 **4k** (n=1-3), 9 (mixture)

[a)] DavePHOS was used instead of BINAP

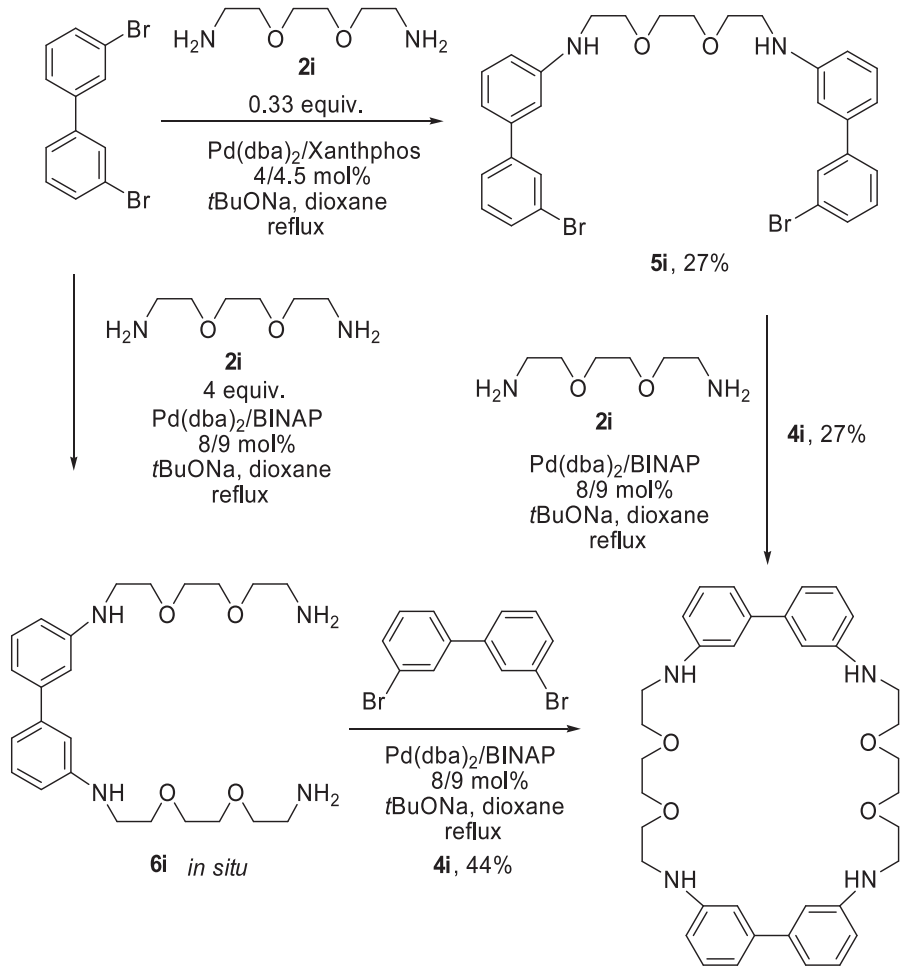

Figure 2.

taken as an exemplary amine (Figure 2). Three equivalents of 3,3'-dibromobiphenyl **1** were employed in the presence of 4 mol% catalyst to give **5i** in 27% yield. The reaction was severely complicated by *N,N*-diarylation and diamination processes, thus the application of Xanthphos ligand instead of BINAP was helpful. The cyclization into cyclodimers with dioxadiamine **2i** was carried out under the conditions similar to those used for the macrocycles **3**. As a result, **4i** (n=1) was isolated in 27% yield. The attempts to introduce diaryl derivative **5i** *in situ* were totally unsuccessful. Alternative approach included the synthesis of bis(dioxadiamine) substituted biphenyl **6i** using 4 equivalents of dioxadiamine **2i**. The yield of this compounds in the reaction mixtures was very high according to NMR data, and **6i** was used *in situ* in the further reaction with 3,3'-dibromobiphenyl (Scheme 2). Target macrocycle **4i** (n=1) was obtained in 44% yield. This approach to cyclodimers was found to be much more efficient because it is carried out as a one-pot procedure and provides higher overall yield of the target compound.

Conclusions

To sum up, we have investigated 3,3'-dibromobiphenyl in the Pd-catalyzed amination reactions with polyamines and oxadiamines, demonstrated the possibilitites to obtain polyazamacrocycles in enough high yields, elaborated two approaches to the corresponding cyclodimers and found out the advantage of the route through bis(polyamine) derivatives.

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References

1. Kohama H., Yoshinaga M., Ishizu K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3707-3708.
2. Reinhoudt D.N., de Jong F., van de Vondervoort E.M. *Tetrahedron* **1981**, *37*, 1753-1762.
3. Reinhoudt D.N., de Jong F., van de Vondervoort E.M. *Tetrahedron* **1981**, *37*, 1985-1990.
4. Rebek Jr. J. *Acc. Chem. Res.* **1984**, *17*, 258-264.
5. Rebek Jr.J. Costello T., Marshall L., Wattley R., Gadwood R.C., Onan K. *J. Am. Chem. Soc.* **1985**, *107*, 7481-7487.
6. Rebek Jr.J., Wattley R.V., Costello T., Gadwood R., Marshall L. *J. Am. Chem. Soc.* **1980**, *102*, 7398-7400.
7. Gaviña F., Luis S.V., Costero A.M., Burguete M.I., Rebek Jr., J. *J. Am. Chem. Soc.* **1988**, *110*, 7140-7143.
8. Burguete M.I., Diaz P., Garcia-España E., Luis S.V., Miravet J.F., Querol M., Ramirez J.A. *Chem. Commun.* **1999**, 649-650.
9. Pearson D.P.J., Leigh S.J., Sutherland I.O. *J. Chem. Soc., Perkin Trans.* **1979**, *1*, 3113-3126.
10. Montero A., Albericio F., Royo M., Herradón B. *Eur. J. Org. Chem.* **2007**, 1301-1308.
11. Artz S.P., Cram D.J. *J. Am. Chem. Soc.* **1984**, *106*, 2160-2171.
12. Choi K., Hamilton A.D. *J. Am. Chem. Soc.* **2003**, *125*, 10241-10249.
13. Kuhnert N., Straßnig K., Lopez-Periago A.M. *Tetrahedron: Asymmetry* **2002**, *13*, 123-128.
14. Kuhnert N., Rossignolo G.M., Lopez-Periago A.M. *Org. Biomol. Chem.*, **2003**, *1*, 1157-1170.
15. Patel H.K., Kilburn J.D., Langley G.J., Edwards P.D., Mitchell T., Southgate R. *Tetrahedron Lett.* **1994**, *35*, 481-484.
16. Lloyd-Williams P., Giralt E. *Chem. Soc. Rev.* **2001**, *30*, 145-157.
17. Yang B.H., Buchwald S.L. *J. Organomet. Chem.* **1999**, *576*, 125-146.
18. Beletskaya I.P., Bessmertnykh A.G., Averin A.D., Denat F., Guilard R. *Eur. J. Org. Chem.* **2005**, 281-305.
19. Averin A.D., Ulanovskaya O.A., Fedotenko I.A., Borisenko A.A., Serebryakova M.V., Beletskaya I.P. *Helv. Chim. Acta* **2005**, *88*, 1983-2002.
20. Averin A.D., Ulanovskaya O.A., Pleshkova N.A., Borisenko A.A., Beletskaya I.P. *Coll. Czech. Chem. Comm.* **2007**, *72*, 785-819.
21. Averin A.D., Shukhaev A.V., Golub S.L., Buryak A.K., Beletskaya I.P. *Synthesis* **2007**, 2995-3012.
22. Ukai T., Kawazura H., Ishii Y., Bonnet J.J., Ibers J.A. *J. Organomet. Chem.* **1974**, *65*, 253-266.
23. Snyder H.R., Weaver C., Marshall C.D. *J. Am. Chem. Soc.* **1949**, *71*, 289-291.
24. Wolfe J.P., Buchwald S.L. *J. Org. Chem.* **2000**, *65*, 1147-1157.
25. Averin A.D., Uglov A. N., Beletskaya I.P. *Chem. Lett.* **2008**, *37*, 1074-1075.

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