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Synthesis of tethered bis-macrocycles by cross-coupling of *N*-(3,5-dibromobenzyl)azacrowns with α,ω-diamino compounds

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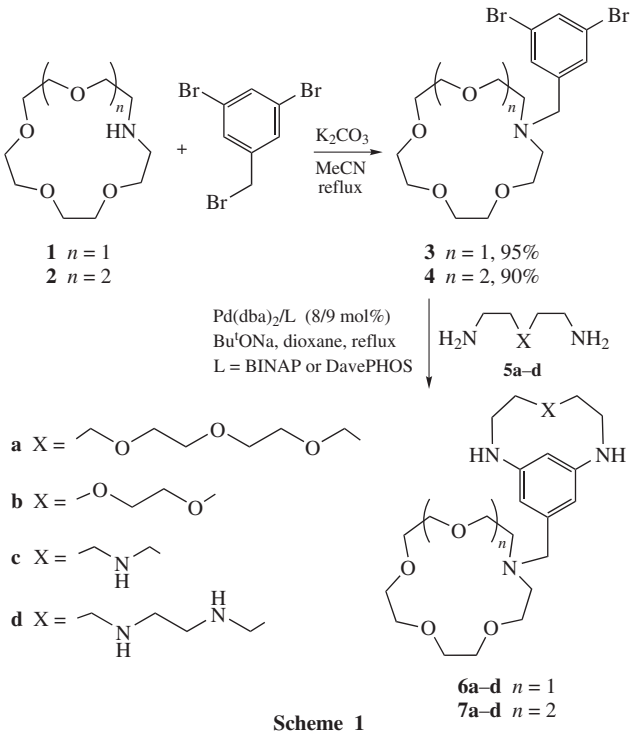
Palladium-catalyzed cross-coupling of *N*-(3,5-dibromobenzyl) derivatives of 1-aza-15-crown-5 and 1-aza-18-crown-6 with α,ω-diamino compounds afforded macrocyclization products comprising two tethered different azacrowns.

Macrocyclic compounds containing two azacrown moieties are known for about 20 years and they are of constant interest due to unique coordination properties. General approaches to various bicyclic cryptands and more sophisticated polycyclic supercryptands and macropolycycles with isolated rings comprising azacrown ethers were developed by Krakowiak *et al.*[1–3] using simple nucleophilic substitution reactions. Many valuable compounds contain two symmetrically arranged azacrown moieties attached to various linkers, such as aromatic backbone,[4,5] metallocenes,[6] porphyrin,[7] or simple functionalized alkane.[8] Azacrown ethers can be attached to calixarenes as substituents[9] or form calixcrowns.[10–12] To create fluorescent sensors on the basis of such macrobicyclic compounds, fluorophores like coronene,[10] perylene,[11] anthracene,[12] coumarin,[13] or BODIPY[14] were introduced as substituents *via* linkers or were incorporated in the macrocycle. Bis(azacrown) ethers were tested as photosensors for K^+, Cs^+, Ag^+ and Ba^{2+} ions.[11,12,14] According to literature data, in the majority of cases two identical azacrown moieties are present in the polycyclic molecules.

As cyclen and cyclam can be regarded as tetraazacrown ethers, it is worth noting that König[15] synthesized bis(triBOCcyclen)-substituted benzene and pyridine using Pd-catalyzed amination. In the meantime, we proposed the Pd-catalyzed amination of 1,8-dichloroanthracene with 1-aza-15-crown-5 and trimethylcyclam for the synthesis of face-to-face arranged bis-macrocycles.[16] Recently, we have also accessed 1,3-bis(trimethylcyclen)- and 1,3-bis(trimethylcyclam)-substituted benzenes.[17] Here we report a simple and enough general route to bis(azacrown) ethers with two different isolated azacrown fragments.

1-Aza-15-crown-5 **1** and 1-aza-18-crown-6 **2** were reacted with 1 equiv. of 3,5-dibromobenzyl bromide in boiling acetonitrile using K_2CO_3 as base to produce corresponding *N*-(3,5-dibromobenzyl) derivatives **3** and **4** in 95% and 90% yields, respectively (Scheme 1).† These compounds were subjected to Pd-catalyzed amination with equimolar amounts of trioxadiamine **5a**, dioxadiamine **5b**, triamine **5c** and tetraamine **5d** to afford the corresponding bis-macrocyclic compounds **6a–d** and **7a–d**. The reactions were run in refluxing dioxane (*c* 0.02 M) for 24 h using 8 mol% $Pd(dba)_2$ and Bu^tONa as base (Scheme 1, Table 1).‡ DavePHOS (2-dicyclohexylphosphino-2′-dimethylaminobiphenyl)



Scheme 1

† *7-(3,5-Dibromobenzyl)-1,4,10,13-tetraoxa-7-azacyclopentadecane* **3**. A flask equipped with a condenser and a magnetic stirrer was charged with 1-aza-15-crown-5 **1** (3 mmol, 657 mg) and 3,5-dibromobenzyl bromide (3.04 mmol, 1 g) dissolved in dry acetonitrile (10 ml). Potassium carbonate (7.68 mmol, 1.06 g) was added and the reaction mixture was refluxed for 24 h. After cooling to ambient temperature the precipitate was filtered off, acetonitrile evaporated *in vacuo*, the residue was taken with dichloromethane (10 ml), filtered, washed with water (10 ml), organic phase was dried over $MgSO_4$, solvent was evaporated *in vacuo* to give product **3** as a yellowish oil. Yield 1.33 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75 (t, 4H, *J* 5.9 Hz), 3.61 (t, 4H, *J* 6.5 Hz), 3.61–3.64 (m, 6H), 3.67 (s, 4H), 3.66–3.69 (m, 4H), 7.44 (d, 2H, *J* 1.4 Hz), 7.50 (t, 1H, *J* 1.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 54.4 (2C), 59.6 (1C), 69.8 (2C), 70.2 (2C), 70.5 (2C), 71.0 (2C), 122.7 (2C), 130.3 (2C), 132.4 (1C), 144.3 (1C). MALDI-TOF, *m/z*: 465.0146 (M^+); calcd for $C_{17}H_{25}Br_2NO_4$: 465.0150.

7-(3,5-Dibromobenzyl)-1,4,10,13,16-pentaoxa-7-azacyclooctadecane **4** was synthesized analogously to compound **3**, starting from 1-aza-18-crown-6 **2** (3.8 mmol, 1 g), 3,5-dibromobenzyl bromide (3.8 mmol, 1.25 g) in dry acetonitrile (12 ml) and potassium carbonate (10.4 mmol, 1.44 g). A yellowish oil. Yield 1.75 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.73 (t, 4H, *J* 5.2 Hz), 3.50–3.60 (m, 16H), 3.61 (s, 4H), 3.63 (s, 2H), 7.30 (br. s, 2H), 7.46 (t, 1H, *J* 1.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 54.4 (2C), 56.5 (1C, line width 15 Hz), 68.3 (2C, line width 10 Hz), 69.9 (2C), 70.0 (2C), 70.1 (2C), 70.2 (2C), 122.6 (2C), 130.4 (2C), 132.3 (1C), 143.1 (1C); MALDI-TOF, *m/z*: 509.0429 (M^+); calc. for $C_{19}H_{29}Br_2NO_5$: 509.0412.

Table 1 Synthesis of bis-macrocycles **6** and **7**.

Entry	Dibromide	Diamine	Ligand[a]	Yields of **6** and **7**[b]
1	**3**	**5a**	DavePHOS	**6a**, 53%
2	**3**	**5b**	DavePHOS	**6b**, 41%
3	**3**	**5c**	DavePHOS	**6c**, 29%
4	**3**	**5d**	DavePHOS	**6d**, 28%
5	**3**	**5a**	BINAP	**6a**, 5%
6	**3**	**5d**	BINAP	**6d**, 28%
7	**4**	**5a**	BINAP	**7a**, 32%[c]
8	**4**	**5a**	DavePHOS	
9	**4**	**5b**	BINAP	**7b**, 14%
10	**4**	**5b**	DavePHOS	**7c**, 8%
11	**4**	**5c**	BINAP	**7c**, 27%
12	**4**	**5d**	BINAP	**7d**, 20%
13	**4**	**5d**	DavePHOS	**7b**, 0%

[a] $Pd(dba)_2$/L 8/9 mol%. [b] Yields after column chromatography on silica gel. [c] Chromatography of combined reaction mixtures (entries 7 and 8).

was suitable for the reactions with the 1-aza-15-crown-5 derivative **3** (entries 1–4). The highest yield was achieved by the longest trioxadiamine **5a** (53%, entry 1). Dioxadiamine **5b** with a shorter chain also gave macrocycle **6b** in a good yield (41%, entry 2). These yields are among the highest ever observed for the synthesis of nitrogen- and oxygen-containing macrocycles *via* Pd-catalyzed amination. The application of 16 mol% catalyst did not improve the yields. The use of triamine **5c** and tetraamine **5d** resulted in somewhat lower yields (29%, entry 3; 28%, entry 4). We also tried more common BINAP as ligand in these processes, however, in the case of oxadiamines it turned to be inefficient (5% yield with trioxadiamine **5a**, entry 5). In the meantime, with tetraamine **5d**, BINAP was of the same efficiency as DavePHOS providing 28% yield of bis-macrocycle **6d** (entries 4, 6).

The reactions of another substituted azacrown ether **4** with the same α,ω-diamines **5a–d** gave lower yields of the target bis-macrocycles **7a–d**, the use of BINAP being preferable. Only with trioxadiamine **5a**, BINAP and DavePHOS were of the similar efficiency (entries 7, 8), while with dioxadiamine **5b** BINAP performed better (entries 9, 10). The reaction with triamine **5c** catalyzed by Pd^0/BINAP system provided 27% yield of the target macrobicycle **7c** (entry 11). As for tetraamine **5d**, only BINAP catalyzed the reaction (entries 12, 13). We may explain poorer yields of the macrocycles **7a–d** by the difference in the ability of 1-aza-15-crown-5 and 1-aza-18-crown-6 to coordinate Na^+ what changes substantially the efficacy of Bu^tONa as base which is crucial for the intramolecular diamination process.

In the NMR spectra of bis-macrocycles **6a–c** and **7a–c** some signals are broad (line widths up to 100 Hz in ^1H NMR and 200 Hz in ^{13}C NMR). This fact can be explained by a hindered rotation of the benzyl group due to its fusion with the second azamacrocycle and possibly by through-the-space interactions of closely arranged macrorings. In previous investigations we often obtained cyclic dimers and oligomers as by-products in the macrocycles synthesis by the Pd-catalyzed amination of dihaloarenes. However, in the described reactions with compounds **3** and **4** we did not observe formation of such cyclooligomers. As no unreacted stating compounds were found in the reaction mixtures after the completion of reactions, it is likely that linear oligomers were formed as side products.

In conclusion, we worked out a simple and efficient access to bis-macrocycles consisting of two different azacrown moieties using Pd-catalyzed amination, demonstrated the possibility to vary the size of the second macrocycle and the number of N and O atoms in it, and revealed the substrate dependence of the yields of the target products. Synthesized bis-macrocycles may provide cooperative effect of two azacrown moieties in coordinating metal cations and these investigations are underway now.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.04.005.

‡ *Typical procedure for the synthesis of bis-macrocycles* **6** *and* **7**. A two-neck flask equipped with a magnetic stirrer and a condenser was flushed with dry argon, charged with dibromobenzyl derivative of azacrown ethers **3** or **4** (0.25 mmol, 116 or 128 mg, respectively), absolute dioxane (12 ml), $Pd(dba)_2$ (12 mg, 8 mol%) and BINAP or DavePHOS (14 or 9 mg respectively, 9 mol%). The mixture was stirred for 2 min, then appropriate α,ω-diamine **5a–d** (0.25 mmol) and Bu^tONa (0.75 mmol, 72 mg) were added, and the reaction mixture was refluxed for 24 h. After cooling to 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 (50:1–3:1), CH_2Cl_2–MeOH–$NH_{3(aq)}$ (100:20:1–10:4:1) to obtain the target bis-macrocycles as pale-yellow glassy compounds.

19-[(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-yl)methyl]-6,9,12-trioxa-2,16-diazabicyclo[15.3.1]henicosa-1(21),17,19-triene **6a** was synthesized in the first experiment from 55 mg of trioxadiamine **5a** in the presence of DavePHOS (9 mg, 9 mol%) and in the second experiment from 55 mg of trioxadiamine **5a** in the presence of DavePHOS (18 mg, 18 mol%). Chromatography of combined reaction mixtures was carried out. Eluent CH_2Cl_2–MeOH (10:1). Yield 140 mg (53%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.77 (quint., 4H, *J* 5.6 Hz), 2.93 (br. s, 4H, line width 30 Hz), 3.24 (t, 4H, *J* 6.3 Hz), 3.53 (t, 4H, *J* 5.2 Hz), 3.55–3.67 (m, 26H), 5.97 (br. s, 2H), 6.05 (br. s, 1H) (NH protons were not unambiguously assigned). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.5 (2C), 41.7 (2C), 54.1 (2C), 60.1 (1C), 67.2 (2C, line width 10 Hz), 69.3 (2C, line width 10 Hz), 69.4 (2C), 69.5 (2C, line width 10 Hz), 69.6 (2C, line width 10 Hz), 69.9 (2C), 70.7 (2C), 95.9 (1C), 103.6 (2C), 128.1 (1C, line width 20 Hz), 150.4 (2C). MALDI-TOF, *m/z*: 525.3334 (M^+); calc. for $C_{27}H_{47}N_3O_7$: 525.3414.

For characteristics of compounds **6b–d** and **7a–d**, see Online Supplementary Materials.

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