Pd(0)–Catalyzed Amination in the Synthesis of Planar–Chiral Macrobicyclic Compounds Comprising 1,5–Disubstituted Anthraquinone Moiety

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Planar-chiral N- and O-containing macrocycles were obtained via enantioselective Pd(0)-catalyzed amination of 1,5-dichloroanthraquinone and converted into corresponding di(bromobenzyl) substituted derivatives. The latter compounds were introduced in the Pd(0)-catalyzed macrocyclization reactions with several linear oxadiamines and certain pairs of reagents gave macrobicyclic compounds with a central planar-chiral structural fragment.

Keywords: Macrocycles, Pd catalysis, chirality, polyamines, amination.

Pd(0)–Катализируемое аминирование в синтезе планарно–хиральных макробициклических соединений, содержащих фрагмент 1,5–дихлорантрахинона

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Планарно-хиральные N- и O-содержащие макроциклы получены энантиоселективным Pd(0)-катализируемым аминированием 1,5-дихлорантрахинона и превращены далее в соответствующие ди(бромбензил) производные. Данные соединения были введены в Pd(0)-катализируемую макроциклизацию с несколькими линейными оксадиаминами, и некоторые пары реагентов привели к образованию макробициклических соединений, содержащих центральный планарно-хиральный структурный фрагмент.

Ключевые слова: Макроциклы, Pd катализ, хиральность, полиамины, аминирование.
Introduction

Macrocyclic compounds containing endocyclic chiral fragments are of substantial interest due to their ability for selective binding of optical isomers of small organic molecules thus acting as molecular chemosensors. Also they are useful as chiral ligands for the preparation of the complexes with metals, especially with those active in transition metal catalysis, in order to ensure enantioselective version of the catalytic processes. From the early days of the macrocycles era, a number of such compounds which contain one or several identical chiral elements in the structure of the macrocycle are known. In 1984 the first micro-review on the chiral macrocycles was published,[1,3] and in 1991 an unprecedented review on the hundreds of the macrocycles synthesized to that date also contained several macrocycles with various elements of chirality.[4] During last two decades many macrocyclic compounds differing by the nature of chiral fragments, cavity size and heteroatoms present in their structure were reported. They include the compounds which are based on chiral diamines and Schiff bases,[5,6] contain amino acid fragments,[7] or in other molecules macrocycles are cyclocondensed with chiral skeletons,[7] usually such molecules comprise oxygen and nitrogen donor atoms, and also phosphorus-containing chiral macrocycles have been described.[8,9] Planar-chiral macrocycles are still quite rare.[10–12] Until last time macrocycles with BINOL C2-chiral moiety have been of constant interest.[13] Almost all these reactions were accomplished using non-catalytic methods, and a rare exception is the synthesis of several planar-chiral macrocycles using metathesis reaction at the macrocyclization step.[15]

Several years ago we have proposed a direct route to planar-chiral macrocycles using Pd(0)-catalyzed macrocyclization in the presence of chiral phosphine ligands,[16] and further the possibility to synthesize planar-chiral macrobicycles comprising cyclam central moiety was also shown.[17] In this connection the present research is aimed at the synthesis of macrobicycles based on the central planar-chiral macrocycle formed around 1,5-disubstituted anthracnine. Such compounds may be of interest not only due to their chirality but also due to their properties as chromophores and possibility to form chiral complexes with metal cations.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer in CDCl3 at 298 K, MALDI-TOF spectra were obtained with Bruker Autoflex II spectrometer using 1,8,9-trihydropyranthacene as matrix and PEGs as internal standards. HPLC for the determination of enantiomeric excess was performed with Bischoff liquid chromatography using OJ-H and OD-H Chiralcel columns or Chiralpak AD columns and hexane/i-PrOH 7:3 v/v or hexane/i-PrOH/ Et3N 70:30:0.2 v/v eluents (1 ml/min, 219 nm and 254 nm UV detectors). X-Ray study was carried out on STOE STADI VARI PILATUS-100K single crystal diffractometer (focusing mirrors, rotation method, 3493 frames, detector distance=60 mm) using microfocus Cu GenIX 3D radiation source. Structure was solved by direct methods and refined by full-matrix Least Squares procedure using SHELXTL program complex. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and assigned to the following deposition number: CCDC 949468. Preparative column chromatography was performed using silica gel 40–60 mesh purchased from Fluka. 1,5-Dichloroanthraquinone (1), dioxadiamines 2a,e, trioxadiamines 2b,c, tetraoxadiamine 2d, rac-BINAP, DavCyPhos and Josiphos SL-J002-2 and SL-J009-2 ligands, cesium carbonate, potassium carbonate, were purchased from Aldrich and used without further purification, Pd(dba)2, was synthesized according to the method described.[18] 1-(bromomethyl)-3-iodobenzene and 1-(bromomethyl)-4-iodobenzene were obtained from commercially available m-iodotoluene by a standard bromination with NBS in CCl4. Dioxane was distilled over NaOH followed by the distillation over sodium under argon, acetonitrile was distilled over CaH2, dichloromethane and methanol were used freshly distilled.

Typical procedure for the synthesis of macrocycles 3a–d. A flask equipped with a condenser and magnetic stirrer was charged with 1,5-dichloroanthraquinone (0.2–3 mmol, 55–831 mg), Pd(dba)2, (8 or 16 mol %) and rac-BINAP (9 or 18 mol %) or Josiphos SL-J002-2, Josiphos SL-J009-2 (9 or 18 mol %). Then absolute dioxane (10–150 ml) and cesium carbonate (0.8–12 mmol, 261–3192 mg, 4 equiv.) were added and the reaction mixture was refluxed for 30–40 h. After cooling the reaction mixture down to room temperature the precipitate was filtered off, washed with CH2Cl2, combined organic phases were evaporated in vacuo, and the solid residue was chromatographed on silica gel using a sequence of eluents: CH2Cl2, CH2Cl2/MeOH (500:1–50:1). Corresponding experimental details with yields and spectra are described below only for racemic macrocycles as enantiomerically enriched mixtures were isolated with the same eluents and possess essentially the same spectra. Their yields, type of chiral catalyst, their loadings and enantiomeric excess are given in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Macrocycle</th>
<th>Yield (mol %)</th>
<th>NMR data</th>
<th>HPLC data</th>
</tr>
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<tbody>
<tr>
<td>1a-r</td>
<td>93</td>
<td></td>
<td>93%</td>
</tr>
<tr>
<td>2a-r</td>
<td>91</td>
<td></td>
<td>91%</td>
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<td>3a-r</td>
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<td></td>
<td>90%</td>
</tr>
<tr>
<td>4a-r</td>
<td>90</td>
<td></td>
<td>90%</td>
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</table>

1,5-(Epimino)propanoxybutanoxypropanoiminooanthracene-9,10-dione (3a–r). Obtained from 1,5-dichloroanthraquinone (1) (0.5 mmol, 139 mg) and dioxadiamine 2a (0.5 mmol, 102 mg) in the presence of Pd(dba)2 (8 mol %, 23 mg), rac-BINAP (9 mol %, 28 mg) and Cs2CO3 (2 mmol, 672 mg) in 25 ml absolute dioxane. Eluent: CH2Cl2/MeOH (200:1). Yield 93 mg (45 %). NMR data are consistent with those described in literature.[16,19]
5.5'-2,2'-2-(2'-Oxybis(ethane-2,1-diyli)b(isoxyli)
(bisethane-2,1-diyli))bis(azanediyl)bis(1-chloroanthraquen-9,10-
dione) (4d). Obtained as the second product in the synthesis of compound 3b from 1,5-dichloroaanthraquinone (1) (2 mmol, 554 mg) and trioxadiazine 2b (2 mmol, 384 mg) in the presence of Pd(dbpa)2 (16 mol%, 184 mg), rac-BINAP (18 mol%, 224 mg) and Cs2CO3 (8 mmol, 2,688 g) in 100 ml absolute dioxide. Eluent: CHCl3/MeOH (100:1). Yield 31 mg (5%). Deep-red solid. (MALDI-TOF) found: 673.1562. C17H11Cl2N2O4 requires 673.1508 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 3.47 (4H, q, J\textsubscript{1} = 5.0 Hz), 3.71–3.76 (8H, m), 3.79 (4H, t, J\textsubscript{2} = 5.6 Hz), 6.92–6.96 (2H, m), 7.4–7.48 (4H, m), 7.54 (2H, t, J\textsubscript{2} = 7.8 Hz), 7.63 (2H, dd, J\textsubscript{2} = 7.8 Hz, J\textsubscript{3} = 1.3 Hz), 8.19 (2H, dd, J\textsubscript{2} = 7.8 Hz, J\textsubscript{3} = 1.9 Hz), 9.65 (2H, brs). 13C NMR (CDCl3, 298 K) δ ppm: 42.7 (2C), 70.7 (2C), 70.8 (2C), 112.4 (2C), 115.1 (2C), 116.0 (2C), 116.4 (2C), 117.2 (2C), 117.2 (2C), 126.2 (2C), 126.8 (2C), 133.3 (2C), 133.4 (2C), 134.2 (2C), 135.0 (2C), 135.5 (2C), 136.1 (2C), 136.3 (2C), 137.5 (2C), 151.1 (2C), 151.3 (2C), 182.4 (2C), 183.1 (2C), 185.1 (2C).

Typical procedure for the synthesis of N,N'-difluoriobenzene substituted macrocycles 6a-c and 7a-c. A flask equipped with a condenser and magnetic stirrer was charged with racemic macrocycles 3a-c (0.2 mmol), 1-(bromomethyl)-4-iodo-benzene (0.4–0.4 mmol), potassium carbonate (0.8–0.8 mmol) and dry MeCN (1–6 ml) and the reaction mixture was refluxed for 24 h. After cooling the reaction mixture down to room temperature the precipitate was filtered off, washed with CHCl3, combined organic phases were evaporated in vacuo, and the solid residue was chromatographed on silica gel using a sequence of eluents: CHCl3, CH2Cl2/MeOH (501:1–501).

Macrocycle 6a. Obtained from 1-(bromomethyl)-4-iodo-benzene (0.5 mmol, 149 mg) and macrocycle 3a-c (0.25 mmol, 102 mg) in the presence of K2CO3 (1 mmol, 138 mg) in 1.5 ml dry acetonitrile. Eluent: CHCl3/MeOH (200:1). Yield 138 mg (66%). Deep-red crystalline powder, m. p. 125–127 °C (MALDI-TOF) found: 841.0936. C38H37I3N2O5 requires 841.0999 [M+H]+.

MACROCYCLE 6B. Obtained from 1-(bromomethyl)-4-iodo-benzene (0.24 mmol, 72 mg) and macrocycle 3b-c (0.12 mmol, 48 mg) in the presence of K2CO3 (0.5 mmol, 92 mg) in 1 ml dry acetonitrile. Eluent: CHCl3/MeOH (200:1). Yield 74 mg (74%). Deep-red crystalline powder, m. p. 97–99 °C (MALDI-TOF) found: 829.0577. C38H36I2N2O6 requires 829.0635 [M+H]+.

MACROCYCLE 6C. Obtained from 1-(bromomethyl)-4-iodobenzene (0.29 mmol, 71 ml) and macrocycle 3b-c (0.46 mmol, 193 mg) in the presence of K2CO3 (1.8 mmol, 248 mg) in 3 ml dry acetonitrile. Eluent: CHCl3/MeOH (200:1). Yield 204 mg (54%). Deep-red solid. (MALDI-TOF) found: 857.0882. C38H36I2N2O6 requires 857.0948 [M+H]+.

MACROCYCLE 7A. Obtained from 1-(bromomethyl)-3-iodobenzene (2.02 mmol, 601 mg) and macrocycle 3a-c (1.01 mmol, 414 mg) in the presence of K2CO3 (4.05 mmol, 559 mg) in 6 ml of dry acetonitrile. Eluent: CHCl3/MeOH (100:1). Yield 541 mg (64%). Deep-red solid. (MALDI-TOF) found: 841.1056. C38H36I2N2O6 requires 841.0999 [M+H]+.

MACROCYCLE 7B. Obtained from 1-(bromomethyl)-3-iodobenzene (2.02 mmol, 601 mg) and macrocycle 3a-c (1.01 mmol, 414 mg) in the presence of K2CO3 (4.05 mmol, 559 mg) in 6 ml of dry acetonitrile. Eluent: CHCl3/MeOH (100:1). Yield 541 mg (64%).
Typical procedure for the synthesis of macrobicycles 8-12. A flask equipped with a condenser and magnetic stirrer was charged with N,N'-di(diodobenzyl) derivative 7a-e (0.1–0.3 mmol), Pd(dba)2 (16 mol%) and DavePhos (18 mol%). Then absolute dioxane (2.5–8 ml) and cesium carbonate (0.4–1.2 mmol, 4 equiv.) were added and the reaction mixture was refluxed for 30–40 h. After cooling the reaction mixture down to room temperature the precipitate was filtered off, washed with CH2Cl2, combined organic phases were evaporated in vacuo, and the solid residue was chromatographed on silica gel using a sequence of eluents: CH2Cl2, CH2Cl2/MeOH (0.24:1), CH2Cl2/MeOH (0.12:1), and MeOH (5:1).

Macrocycle 8. Obtained from compound 7a (0.308 mmol, 259 mg) and trioxadiamine 2b (0.308 mmol, 59 mg) in the presence of Pd(dba)2 (16 mol%, 28 mg), DavePhos (18 mol%, 22 mg) and Cs2CO3 (1.23 mmol, 401 mg) in 8 ml absolute dioxane. Eluent: CH2Cl2/MeOH (50:1). Yield 12 mg (3%). Deep-red solid. (MALDI-TOF) found: 821.4436, CH2H7N9O4 requires 821.4489 [M+H]+. 

Macrocycle 9. Obtained from compound 7a (0.241 mmol, 180 mg) and trioxadiamine 2c (0.241 mmol, 47 mg) in the presence of Pd(dba)2 (16 mol%, 20 mg), DavePhos (18 mol%, 15 mg) and Cs2CO3 (0.85 mmol, 260 mg) in 5 ml absolute dioxane. Eluent: CH2Cl2/MeOH (50:1). Yield 9 mg (5%). Deep-red solid. (MALDI-TOF) found: 805.4592, C16H11N4O5 requires 805.4540 [M+H]+. 

Macrocycle 9a. Obtained from compound 7a (0.1 mmol, 79 mg) and dioxadiamine 2e (0.1 mmol, 15 mg) in the presence of Pd(dba)2 (16 mol%, 9 mg), DavePhos (18 mol%, 7 mg) and Cs2CO3 (0.4 mmol, 131 mg) in 2.5 ml absolute dioxane. Eluent: CH2Cl2/MeOH (50:1). Yield 21 mg (29%). Deep-red crystalline powder, m.p. 121–122 °C (MALDI-TOF) found: 749.3987. C16H11N4O8 requires 749.3914 [M+H]+. 

Macrocycle 10. Obtained from compound 7e (0.1 mmol, 79 mg) and dioxadiamine 2e (0.1 mmol, 15 mg) in the presence of Pd(dba)2 (16 mol%, 9 mg), DavePhos (18 mol%, 7 mg) and Cs2CO3 (0.4 mmol, 131 mg) in 2.5 ml absolute dioxane. Eluent: CH2Cl2/MeOH (50:1). Yield 19 mg (24%). Deep-red crystalline powder, m.p. 123–124 °C (MALDI-TOF) found: 805.4540 [M+H]+. C16H11N4O8 requires 805.4540 [M+H]+. 

Macrocycle 11. Obtained from compound 7e (0.1 mmol, 79 mg) and dioxadiamine 2a (0.1 mmol, 21 mg) in the presence of Pd(dba)2 (16 mol%, 9 mg), 5 ml absolute dioxane. Eluent: CH2Cl2/MeOH (50:1). Yield 19 mg (24%). Deep-red crystalline powder, m.p. 123–124 °C (MALDI-TOF) found: 805.4540 [M+H]+. C16H11N4O8 requires 805.4540 [M+H]+. 

Macrocycle 12. Obtained from compound 7c (0.1 mmol, 79 mg) and dioxadiamines 2b (0.1 mmol, 22 mg) and 2e (0.1 mmol, 15 mg) in the presence of Pd(dba)2 (16 mol%, 9 mg), DavePhos (18 mol%, 7 mg) and Cs2CO3 (0.4 mmol, 131 mg) in 2.5 ml absolute dioxane. Eluent: CH2Cl2/MeOH (50:1). Yield 26 mg (32%). Deep-red crystalline powder, m.p. 116–118 °C (MALDI-TOF) found: 821.4436, C16H11N4O4 requires 821.4489 [M+H]+. 

Results and Discussion

At the first step we synthesized 4 planar-chiral macrocycles 3a-d by the reaction of 1,5-dichloroanthraquione (1) with dioxadiamines 2a and trioxadiamines 2b-d differing by the chain length (13–16 atoms) and the number of oxygen...
Planar-Chiral Macrobicyclic Compounds Comprising 1,5-Disubstituted Anthraquinone Moiety

![Scheme 1](image)

Table 1. Synthesis of macrocyclic compounds 3a-d.

| Entry | Amine | Ligand | [Pd/L], mol% | Product<sup>a</sup> | Yield, %<sup>b</sup> | Enantiomeric excess, %
<table>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>rac-BINAP</td>
<td>8/9</td>
<td>3a-r</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2a</td>
<td>Josiphos SL-J002-2</td>
<td>8/9</td>
<td>3a-ee</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2b</td>
<td>rac-BINAP</td>
<td>16/18</td>
<td>3b-r</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>Josiphos SL-J002-2</td>
<td>16/18</td>
<td>3b-ee</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>Josiphos SL-J009-2</td>
<td>16/18</td>
<td>3b-ee</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>2c</td>
<td>rac-BINAP</td>
<td>16/18</td>
<td>3c-r</td>
<td>38</td>
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<tr>
<td>7</td>
<td>2c</td>
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<td>8/9</td>
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<tr>
<td>8</td>
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<td>8/9</td>
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<tr>
<td>9</td>
<td>2c</td>
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<td>16/18</td>
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<td>27</td>
<td>58</td>
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<tr>
<td>10</td>
<td>2d</td>
<td>rac-BINAP</td>
<td>16/18</td>
<td>3d-r</td>
<td>36</td>
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</tr>
<tr>
<td>11</td>
<td>2d</td>
<td>Josiphos SL-J002-2</td>
<td>16/18</td>
<td>3d-ee</td>
<td>13</td>
<td>34</td>
</tr>
</tbody>
</table>

<sup>a</sup> “r” after the macrocycle’s number denotes “racemic”, “ee” denotes “enantiomerically enriched”;

<sup>b</sup> After column chromatography;

<sup>c</sup> In the scaled-up reaction with 3 mmol of 1 and 2a compound 4a was isolated in 12% yield;

<sup>d</sup> In the scaled-up reaction with 2 mmol of 1 and 2b compound 4b was isolated in 5% yield.

atoms. The macrocyclization was catalyzed by Pd(dba)/rac-BINAP to form racemic mixtures of the macrocycles 3 or by Pd(dba)/Josiphos SL-J002-2 which was found out by us previously to be the best for ensuring the enantiomeric induction in such processes. The reactions were run in boiling dioxane in the presence of Cs₂CO₃ as base for 30–40 h using 0.02 M concentration of the reagents (Scheme 1). Usually the reactions were first run with 0.2–0.25 mmol of starting compounds and in the case of success they were scaled up to 2–3 mmol of the starting reagents. The results of the experiments are summarized in Table 1.

It is clearly seen that the outcome of the macrocyclization processes in the majority of cases do not differ much for oxadiamines under investigation. The chemical yields of compounds 3a-r – 3d-r ranged from 31 to 45 % when using rac-BINAP ligand (entries 1, 3, 6, 7, 10) what is a good result for such type of the catalytic processes, with oxadiamines 2a,c the possibility of the application of 8 mol% catalytic system instead of 16 mol% was demonstrated (entries 1, 7). The macrocyclization with oxadime 2a in the presence of Josiphos SL-J002-2 ligand (8/9 mol% catalytic system) was quite successful as it produced the macrocycle 3a-ee also in
a good yield and with 60 % enantiomeric excess (entry 2). In the scaled-up reaction with 3 mmol of 1 and 2a a linear diaryl derivative 4a was isolated in 12 % yield. The macrocyclization with trioxadiamine 2b was carried out using 16/18 mol% of the catalytic systems Pd(dba)2/rac-BINAP or Pd(dba)/Josiphos SL-J002-2, the first system provided 31 % yield of the target compound 3b-ee (entry 3) while with the second one the yield was slightly smaller and enantiomeric excess reached 55 % (entry 4). Again, scaling up the synthesis allowed the isolation of a linear diaryl derivative 4b.

It is noteworthy that the application of another chiral ligand with more electron-rich substituents at the phosphorus atom, namely Josiphos SL-J009-2, provided both poorer chemical and optical yields of the macrocycle (entry 5). Note that the macrocyclization with trioxadiamine 2e in the presence of Pd(dba)/Josiphos SL-J002-2 (8/9 mol%) gave smaller yield of the product (18 %) but provided higher enantioselectivity (66 %) compared to the result with 16/18 mol% of the same catalytic system (entries 8, 9). The reaction with the longest tetraoxadiamine 2d was quite successful with rac-BINAP as a ligand (entry 10) and not only the target macrocycle 3d-r but also linear oligomers 4d and 5d were isolated, but the result with chiral ligand was more modest and enantioselectivity reached only 34 % (entry 11). Our new results notably surpass those reported in the ref.[19] where the yields of the macrocycles 3a,c were 30 and 28 %, respectively, in the presence of the same catalytic systems.

In the case of the macrocycles 3a-ee, 3c-ee it is possible to isolate individual isomers by crystallization and in the case of compound 3b-ee, on contrary, crystallization gave pure racemate and the mother liquor was enriched with the major isomer. The same was true for the macrocycle 3d-ee possessing the longest tetraoxadiamine chain.

In 1H NMR spectra of the macrocycles 3a-d protons in all CH2 groups are inequivalent what leads to complex multiplets, moreover, the protons of all methylene groups except CH2N are shifted more or less upfield due to their position above the aromatic rings. On contrary, carbon atoms have usual chemical shifts. We carried out the X-Ray analysis of the compound 3b (racemate), the molecular structure is given in Figure 1. This compound crystallizes as deep-red prisms in a triclinic symmetry space group, each cell containing two opposite enantiomers.

At the next step we modified the macrocycles 3a-r–3c-r with two iodobenzyl substituents in view of the further macrocyclization of these compounds. The reactions were conducted using 2 equiv. of para- and meta-iodobenzyl bromides in boiling MeCN with K2CO3 as a base, the target derivatives 6a-c and 7a-c were obtained after chromatographic purification in 54–74 % and 64–72 % yields, respectively (Scheme 2). Macrocycles substituted with iodobenzyl groups were synthesized in order to favor their Pd(0)-catalyzed amination in the presence of a weak base, Cs2CO3, because anthraquinone moiety does not tolerate stronger sodium tert-butoxide and iodine is more active than bromine in the catalytic amination reactions.

Catalytic transformation of compounds 6 and 7 into macrobicyclic compounds with oxadiamines 2a-c and

Figure 1. Molecular structure of the macrocycle 3b.

Scheme 2.
Planar-Chiral Macrobicyclic Compounds Comprising 1,5-Disubstituted Anthraquinone Motiey

2e was carried out using the catalytic system Pd(dba)$_2$/DavePhos, this electron-donor phosphine ligand is known to provide amination with weak bases better than rac-BINAP. It was found that only some pairs of the reagents gave target compounds: bis(4-iodobenzyl) derivatives 6a-c did not provide corresponding products of macrocyclization at all but rather produced only linear oligomers and the products of the catalytic reduction of C-I bonds and debenzylation in the starting reagents 6a-c. These compounds were not isolated in pure state but were analyzed as fractioned mixtures by $^1$H NMR and mass spectrometry. Better results were obtained with bis(3-iodobenzyl) derivatives: compound 7a gave the target macrobicycle 8 with trioxadiamine 2b, though in a very low yield (3 %), the yield of the macrobicycle 9 in the reaction with another trioxadiamine 2c was also small (5 %). The rest in both reaction mixtures was composed of the reduction products and oligomers. However, the compound 7c was much more active and gave macrobicycles 10–12 with oxadiamines 2a,c,e in yields 24–32 % which are quite good for the macrocyclization reactions especially with such a weak base as Cs$_2$CO$_3$. Unfortunately, derivative 7b did not afford macrobicycles but rather produced linear oligomers and the products of reduction. We suppose that such difference in the reactivity of bis(iodobenzyl) substituted macrocycles may be due to different orientation of the iodine atoms caused by the difference in the geometry of the substituents around nitrogen atoms. The analysis of the molecular structures of the macrocycles 3a-c demonstrates that the oxadiamino chains of various length cause different cycle strain resulting in the arrangement of the substituents at the nitrogen atoms which is probably translated to mutual orientation of two iodine atoms which favors or disfavors intramolecular cyclization. $^1$H NMR spectra of compounds 6, 7 and 8–12 are characterized by the inequivalence of CH$_2$ protons in benzyl substituents (spacers). The protons in methylene groups of the second chain in macrobicycles 8–12 are also inequivalent, thus aliphatic protons in these compounds present a complex set of multiplets.

Conclusions

To sum up, we synthesized several nitrogen- and oxygen-containing macrocycles based on 1,5-disubstituted anthraquinone in yields up to 45 % with enantioselective excess up to 66 %, and using these molecules as a platform we obtained the first representatives of the macrocycles containing planar-chiral central fragment by means of Pd(0)-catalyzed amination, and demonstrated the dramatic dependence of the result of the macrocyclization on the introduction of bis(iodobenzyl) derivatives and oxadiamines. The investigations of the binding properties of synthesized macrobicycles are underway now.

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References


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