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Planar–Chiral Macrobicycles Comprising Cyclam Moiety

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Dedicated to Academician Aslan Yusupovich Tsivadze on the occasion of his 70th Anniversary

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Macrobicycles derived from 1,8-disubstituted cyclam in principle may be planar-chiral provided that the second chain cannot rotate around the cyclam fragment. Hindered rotation is enabled by the introduction of two additional substituents at nitrogen atoms and by enough short chain which forms the second cycle. N,N',N'',N'''-tetrasubstituted cyclams bearing two 3-bromobenzyl and two arylmethyl substituents were synthesized starting from protected bis-formaldehyde-cyclam. These compounds were introduced in the Pd-catalyzed amination reactions with 1,3-diaminopropane, 1,2-diaminoethane and 1,2-diphenyl-1,2-diaminoethane to form corresponding macrobicycles. Various chiral diphosphine ligands were tested in these reactions and asymmetric induction was noted in some cases. The pronounced dependence of the chemical yields and enantiomeric excess on the nature of the starting compounds and chiral phosphine ligand was observed. The highest chemical yields of macrobicycles reached 50 %, the best enantiomeric excess was 13 % when using Josiphos-type ferrocene-based ligand.

Keywords: Macrocycles, palladium-catalized amination, planar chirality, enantioselectivity.

Планарно–хиральные макробициклы с фрагментом циклама

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Посвящается академику Аслану Юсуповичу Цивадзе по случаю его 70–летнего юбилея

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Макробициклы, содержащие в своем составе фрагмент 1,8-дизамещенного циклама, в принципе могут быть планарно-хиральными при условии, что цепь атомов, образующих второй макроцикл, не может свободно прокручиваться вокруг фрагмента циклама. Затрудненное вращение может быть обеспечено двумя дополнительными заместителями при атомах азота при условии небольшой длины цепи второго цикла. N,N',N'',N'''-тетразамещенные цикламы, содержащие два 3-бромбензильных и два арилметильных заместителя, были синтезированы из бис-формальдегид-циклама. Данные соединения ввели в реакции палладий-катализируемого аминирования с 1,3-диаминопропаном, 1,2-диаминоэтаном и 1,2-дифенил-1,2-диаминоэтаном, при этом были получены соответствующие макробициклы. В данных реакциях исследовали различные хиральные дифосфиновые лиганды и в некоторых случаях была отмечена асимметрическая

индукция. Наблюдалась сильная зависимость химических выходов и энантиомерных избытков от природы исходных соединений и хиральных лигандов. Наибольшие химические выходы макробициклов составили 40-50 %, а наилучший энантиомерный избыток составил 13 % в реакции с 1,3-диаминопропаном при использовании лиганда типа Josiphos на основе 1,2-дизамещенного ферроцена.

Ключевые слова: Макроциклы, палладий-катализируемое аминирование, планарная хиральность, энантиоселективность.

Introduction

In recent years much attention is paid to the design, synthesis and use of various macrocyclic receptors, since their cavity size and shape can be finely tuned. This useful feature led to the development of many applications of these compounds, including catalysis, transport of ions and molecules, development of molecular sensors, molecular machines, and applications in pharmacology.[1] Chiral macrocyclic ligands are of special interest because they may be used as host molecules for asymmetric catalysis[2] and chiral recognition.[3] For example, lanthanide complexes, that catalyze asymmetric aldol reactions, were synthesized on the basis of chiral *N,O*-macrocycles,[4] they were also used as catalysts in the enantioselective Michael addition reactions.[5] Chiral carbohydrate-based crown ethers were employed as ligands in asymmetric hydrogenation.[6] The catalysts for C-C coupling reactions may contain the complexes of chiral macrocycles with the transition metals.[7] Macrocycles with planar chirality occupy a special position among other chiral macrocycles, and yet no general and convenient synthetic procedures has been developed for their synthesis. The simplest bicyclic compounds based on tetraazamacrocycles are various so-called cross-bridged cyclen and cyclam.[8-10] The introduction of aromatic and heteroaromatic fragments in polymacrocyclic compounds often increases the conformational rigidity of the molecule thus fixing the cavity size. Also, these fragments are crucial in the creation of chemosensors because (hetero)aromatic moieties play the role of chromophores or fluorophores being responsible for the physical response to coordination. Usually macrobicycles possessing cross-bridged cyclen and cyclam moieties do not contain many donor atoms like nitrogen, oxygen or sulfur in the second cycle,[11-15] however, described are macrobicycles with several donor atoms.[16] Our own interest is drawn to the synthesis of macrobicyclic compounds derived from *trans*-disubstituted cyclen and cyclam and we proposed simple routes to macrobicycles using Pd-catalyzed amination of bis(bromobenzyl) derivatives of tetraazamacrocycles.[17-20] Also we were first to show the possibility to use Pd-catalyzed amination with chiral ligands for the synthesis of planar-chiral macrocycles based on 1,5-disubstituted anthracene and anthraquinone.[21] In this work we decided to combine our approaches to macrobicyclic cryptands with asymmetric induction in the amination reaction in order to try the synthesis of planar-chiral macrobicycles.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Autoflex II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. Enantiomeric excess was determined by means of HPLC with Bischoff liquid chromatograph using Chiralcel OD-H, Chiralpak IA, Kromasil 5-TBB, Welk O1 columns and various eluents containing combinations of hexane (heptane), *i*-PrOH (MeOH), THF, $CHCl_3$, Et_3N and $HNEt_2$ (0.7-1 ml/min, 230, 254, 260 nm UV detector), X-ray analysis of the compound 9 was done using CAD-4 Enraf-Nonius apparatus, the structure is deposited at Cambridge Structural Database (*http://www.ccdc.cam.ac.uk)*, deposit number CCDC 912600. Benzyl bromide, 3-bromobenzyl bromide, 2-(bromomethyl)naphthalene, 4-methylbiphenyl, propane-1,2-diamine, ethane-1,2-diamine, 1,2-diphenylethane-1,2-diamine, *rac*-BINAP, *(R)*-BINAP and other ferrocene-based chiral phosphine ligands, sodium *tert*-butoxide were purchased from Aldrich and Acros and used without further purification, $Pd(dba)_2$ was synthesized according to the method described.[22] 4-(Bromomethyl)biphenyl was synthesized from 4-methylbiphenyl by a standard procedure using NBS in CCl_4 with AIBN as radical initiator. Bis-formaldehide cyclam and 1,8-dibenzyl cyclam were provided by the CheMatech Co, Dijon, France. Dioxane was distilled over NaOH followed by the distillation over sodium under argon, dichloromethane and methanol were used freshly distilled.

*Typical procedure for the synthesis of 1,8-bis(arylmethyl) derivatives of cyclam **5**, **6**.*

In a one-neck flask (100 ml) bis-formaldehyde-cyclam (**1**) (2.50 g, 11.2 mmol) was dissolved in 52 ml CH_3CN, corresponding bromomethyl substituted arene (2-(bromomethyl)naphthalene or 4-(bromomethyl)bipehenyl, 22.4 mmol) was added and the reaction mixture was stirred at room temperature for 72 h. The residue was filtered off, washed with CH_3CN (3×40 ml) and dried *in vacuo* to obtain di-salts 2 and 3. The deprotection was carried out as follows: di-salt (2 or 3, 5 mmol) was mixed with the aqueous solution of NaOH (8 g in 60 ml) and stirred at 80-90 °C for 48 h. The resulting compound (**5** or **6**) was taken with CH_2Cl_2, dried over anhydrous Na_2SO_4, the solvent was evaporated *in vacuo* to give pure product.

*1,8-Bis(2-naphthylmethyl)-4,11-diaza-1,8-diazonia-tricyclo[9.3.1.1^{4,8}]hexadecane dibromide (**2**)*. Yield 5.80 g (78 %), white crystalline powder, m.p. >200 °C. ^{1}H NMR (DMSO-d_6, 298 K) δ_H ppm: 1.72-1.82 (2H, m), 2.32-2.43 (4H, m), 2.84 (2H, d, ^2J = 14.7 Hz), 2.92 (2H, d, ^2J = 16.4 Hz), 3.17 (2H, br.s), 3.37 (4H, br.s), 3.53 (2H, d, J = 10.0 Hz), 3.70 (2H, t, J = 14.6 Hz), 4.45 (2H, t, J = 13.4 Hz), 4.87 (4H, s), 5.48 (2H, d, ^3J = 9.1 Hz), 7.60-7.67 (4H, m), 7.72 (2H, d, ^3J = 8.4 Hz), 8.02 (4H, d, ^3J = 7.3 Hz), 8.06 (2H, d, ^3J = 8.0 Hz), 8.21 (2H, br.s).

*1,8-Bis(biphenyl-4-ylmethyl)-4,11-diaza-1,8-diazonia-tricyclo[9.3.1.1^{4,8}]hexadecane dibromide (**3**)*. Yield 3.20 g (64 %). white crystalline powder, m.p. >200 °C. ^{1}H NMR (DMSO-d_6, 298 K) δ_H ppm: 1.72-1.82 (2H, m), 2.28-2.42 (4H, m), 2.83 (4H, t, J = 15.7 Hz), 3.17 (2H, br.s), 3.49 (2H, d, ^3J = 9.7 Hz), 3.65 (2H, t, J = 13.3 Hz), 4.42 (2H, t, J = 12.6 Hz), 4.72-4.80 (4H, m), 5.43 (2H, d, ^3J = 8.6 Hz), 7.42 (2H, t, ^3J = 7.0 Hz), 7.51 (4H, t, ^3J = 7.0 Hz), 7.73 (8H, d, ^3J = 7.2 Hz), 7.83 (4H, d, ^3J = 7.7 Hz), four protons are overlapped by the signal of CHD_2.

*1,8-Bis(2-naphthylmethyl)-1,4,8,11-tetraazacyclo-tetradecane (**5**)*. Yield 2.16 g (90 %), white crystalline powder, m.p.

127-129 °C. (MALDI-TOF) found: 481.3367. $C_{32}H_{41}N_4$ requires 481.3331 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.88 (4H, quintet, ^3J = 4.3 Hz), 2.58 (4H, t, ^3J = 5.5 Hz), 2.65-2.70 (4H, m), 2.72-2.79 (8H, m), 3.87 (4H, s), 7.38-7.46 (4H, m), 7.51 (2H, dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz), 7.70 (2H, br.s), 7.73-7.79 (6H, m), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 25.9 (2C), 47.7 (2C), 49.9 (2C), 51.9 (2C), 53.9 (2C), 58.2 (2C), 125.6 (2C), 125.9 (2C), 127.6 (6C), 127.7 (2C), 128.3 (2C), 132.6 (2C), 133.2 (2C), 135.2 (2C).

*1,8-Bis(biphenyl-4-ylmethyl)-1,4,8,11-tetraazacyclotetradecane (**6**)*. Yield 2.56 g (96 %), white crystalline powder, m.p. 129-131 °C. (MALDI-TOF) found: 533.3627. $C_{36}H_{45}N_4$ requires 533.3644 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.88 (4H, br.s), 2.57 (4H, t, ^3J = 5.2 Hz), 2.62-2.67 (4H, m), 2.73-2.80 (8H, m), 3.09 (2H, br.s), 3.79 (4H, s), 7.30 (2H, t, ^3J = 7.3 Hz), 7.36-7.42 (8H, m), 7.50-7.56 (8H, m). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 25.8 (2C), 47.6 (2C), 50.0 (2C), 51.6 (2C), 53.9 (2C), 57.5 (2C), 126.9 (4C), 127.0 (4C), 127.0 (2C), 128.6 (4C), 129.9 (4C), 136.4 (2C), 139.9 (2C), 140.8 (2C).

T*ypical procedure for the synthesis of N,N'N'',N'''-tetrabenzyl derivatives of cyclam **7-9***.

A one-neck flask (100 ml) was charged with a solution of *trans*-disubstituted cyclam (**4, 5** or **6**) (1 mmol in 10 ml CH_2Cl_2), then aqueous solution of NaOH was added (160 mg (4 mmol) in 10 ml H_2O), and to a stirred mixture the solution of 3-bromobenzyl bromide (500 mg (2 mmol) in 10 ml CH_2Cl_2) was added dropwise in 1 h. The reaction mixture was stirred for 48 h, organic phase was separated, dried over anhydrous Na_2SO_4, solvent was evaporated *in vacuo*¸ and the pure product was obtained.

*1,8-Dibenzyl-4,11-bis(3-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane (**7**)*. Obtained from 380 mg (1 mmol) of *trans*-dibenzylcyclam (**4**). Yield 680 mg (95 %), white crystalline powder, m.p. 129-131 °C. (MALDI-TOF) found: 717.2120. $C_{38}H_{47}Br_2N_4$ requires 717.2167 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.80 (4H, quintet, ^3J = 6.6 Hz), 2.53 (4H, t, ^3J = 6.6 Hz), 2.56 (4H, t, ^3J = 7.1 Hz), 2.60-2.64 (4H, m), 2.65-2.69 (4H, m), 3.38 (4H, s), 3.49 (4H, s), 7.15 (2H, t, ^3J = 7.8 Hz), 7.22-7.33 (12H, m), 7.38 (2H, d, ^3J = 8.0 Hz), 7.61 (2H, br.s). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 24.3 (2C), 50.2 (2C), 50.6 (2C), 51.2 (2C), 51.6 (2C), 58.1 (2C), 59.3 (2C), 122.2 (2C), 126.6 (2C), 127.3 (2C), 128.0 (4C), 128.8 (4C), 129.5 (2C), 129.6 (2C), 131.9 (2C), 139.8 (2C), 142.8 (2C).

*1,8-Bis(3-bromobenzyl)-4,11-bis(2-naphthylmethyl)-1,4,8,11-tetraazacyclotetradecane (**8**)*. Obtained from 480 mg (1 mmol) of compound 5. Yield 326 mg (40 %), yellowish crystalline powder, m.p. 138-140 °C. (MALDI-TOF) found: 817.2425. $C_{46}H_{51}Br_2N_4$ requires 817.2480 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.82 (4H, br.s), 2.46 (4H, t ^3J = 6.1 Hz), 2.53-2.68 (12H, m), 3.29 (4H, s), 3.59 (4H, s), 7.07 (2H, t, ^3J = 7.7 Hz), 7.17 (2H, d, ^3J = 7.3 Hz), 7.33 (2H, d, ^3J = 7.7 Hz), 7.38-7.43 (4H, m), 7.46 (2H, d, ^3J = 8.2 Hz), 7.60 (2H, br.s), 7.62-7.70 (6H, m), 7.75-7.80 (2H, m). δ_c ($CDCl_3$, 298 K) 24.6 (2C), 50.1 (2C), 50.7 (2C), 51.3 (2C), 51.8 (2C), 57.9 (2C), 60.0 (2C), 122.2 (2C), 125.3 (2C), 125.7 (2C), 127.2 (2C), 127.3 (2C), 127.4 (2C), 127.6 (6C), 129.5 (2C), 129.6 (2C), 132.0 (2C), 132.6 (2C), 133.3 (2C), 137.8 (2C), 143.0 (2C).

*1,8-Bis(biphenyl-4-ylmethyl)-4,11-bis(3-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane (**9**)*. Obtained from 532 mg (1 mmol) of compound 6. Yield 443 mg (51 %), beige crystalline powder, m.p. 128-130 °C. (MALDI-TOF) found: 869.2865. $C_{50}H_{55}Br_2N_4$ requires 869.2793 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.79 (4H, br.s), 2.50 (4H, t, ^3J = 6.4 Hz), 2.55 (4H, br.s), 2.60-2.68 (8H, m), 3.35 (4H, s), 3.48 (4H, s), 7.11 (2H, t, ^3J = 7.8 Hz), 7.20 (2H, d, ^3J = 7.6 Hz), 7.29-7.35 (8H, m), 7.42 (4H, t, ^3J = 7.6 Hz), 7.46 (4H, d, ^3J = 8.1 Hz), 7.53-7.59 (6H, m). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 24.4 (2C), 50.3 (2C), 50.7 (2C), 51.3 (2C), 51.8 (2C), 58.2 (2C), 59.0 (2C), 122.2 (2C), 126.8 (4C), 126.9 (4C), 127.0 (2C), 127.3 (2C), 128.7 (4C), 129.3 (4C), 129.5 (2C), 129.7 (2C), 131.9 (2C), 139.1 (2C), 139.6 (2C), 141.0 (2C), 142.9 (2C).

*Typical procedure for the synthesis of macrobicycles **11-13***.

A two-neck flask (25 ml) equipped with a condenser, flushed with argon, was charged with corresponding tetrasubstituted cyclam **7-9** (0.1-0.2 mmol), $Pd(dba)_2$ (9-18 mg, 16 mol%), diphosphine ligand (0.036 mmol, 18 mol%), and absolute dioxane (5-10 ml). The mixture was stirred for several min, then appropriate diamine **10a-c** (0.1-0.2 mmol) and *t*BuONa (30-58 mg, 0.6 mmol) were added, and the reaction mixture was refluxed for 24-30 h. After the reaction was complete, the mixture was cooled, filtered, the residue was washed with CH_2Cl_2, the combined organic solvents were evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2-MeOH 25:1 – 3:1, CH_2Cl_2-MeOH-NH_3(aq) 100:20:1 – 10:4:1.

*22,28-Dibenzyl-1,8,12,19,22,28-hexaazatetracyclo[17.6.6.1^{3,7}.1^{13,17}]tritriaconta-3(33),4,6,13(32),14,16-hexaene (**11a**)*. Obtained from 144 mg (0.20 mmol) of compound **7**, 15 mg (0.20 mmol) of propanediamine-1,3 (**10a**), in the presence of the ligand L4 (18 mol%, 20 mg). Eluent: CH_2Cl_2:MeOH 10:1. Yield 63 mg (50 %), *ee* = 11 %, light-beige crystalline powder, m.p. 147-149 ºC. (MALDI-TOF) found: 631.4465. $C_{41}H_{55}N_6$ requires 631.4488 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.70 (2H, br.s), 1.85 (4H, quintet, ^3J = 5.5 Hz), 2.29-2.50 (6H, m), 2.52-2.72 (8H, m), 3.12 (2H, br.s), 3.21-3.28 (2H, m), 3.32 (4H, t ^3J = 5.6 Hz), 3.41-3.48 (2H, m), 3.52 (4H, s), 3.90 (2H, br.s), 6.48 (2H, br.d $^3J_{obs}$ = 6.6 Hz), 6.52 (2H, d, ^3J = 7.8 Hz), 7.04 (2H, br.s), 7.06 (2H, t, ^3J = 7.6 Hz), 7.16-7.27 (10H, m). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 24.5 (2C), 28.5 (1C), 42.0 (2C), 52.0 (4C), 52.8 (2C), 53.0 (2C), 59.5 (4C), 111.4 (2C), 113.8 (2C), 118.0 (2C), 126.7 (2C), 128.0 (4C), 128.8 (2C), 129.0 (4C), 139.5 (2C), 141.9 (2C), 148.4 (2C).

*22,47,53,61-Tetrabenzyl-1,8,12,19,22,26,33,37,44,47,53,61-dodecaazaheptacyclo-[42.6.6.6^{19,26}.1^{3,7}.1^{13,17}.1^{28,32}.1^{38,42}]hexaconta-3(66),4,6,13(65),14,16,28(58),29,31,38(57),39,41-dodecaene (**14**)*. Obtained as the second product in the synthesis of macrobicycle **7** using BINAP as a ligand. Eluent: CH_2Cl_2-MeOH-NH_3(aq) 100:20:1. Yield 24 mg (19 %), yellowish solid. (MALDI-TOF) found: 1261.8814. $C_{82}H_{109}N_{12}$ requires 1261.8898 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.70-1.82 (12H, m), 2.44-2.58 (16H, m), 2.62 (16H, br.s), 3.12 (8H, t, ^3J = 6.6 Hz), 3.38 (8H, s), 3.46 (8H, s), 6.44 (4H, d, ^3J = 8.6 Hz), 6.59 (4H, br.d $^3J_{obs}$ = 6.4 Hz), 6.65 (4H, br.s), 7.05 (4H, t, ^3J = 7.6 Hz), 7.16-7.36 (20H, m), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 24.1 (4C), 29.2 (2C), 41.9 (4C), 50.0-51.6 м (16H), 59.3 (4C), 59.6 (4C), 111.3 (4C), 113.1 (4C), 118.0 (4C), 126.6 (4C), 128.0 (8C), 128.8 (4C), 128.9 (8C), 140.1 (4C), 141.3 (4C), 148.2 (4C).

*N-(3-{[4,11-dibenzyl-8-(3-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane-1-yl]methyl}phenyl)-propane-1,3-diamine (**15**)* was obtained as the by-product in the synthesis of compound **7** using ligand L7. Yield 53 mg (37 %) yellowish solid. (MALDI-TOF) found: 711.3787. $C_{41}H_{56}BrN_6$ requires 711.3750 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.68-1.79 (6H, m), 2.43-2.66 (16H, m), 2.80 (2H, br.s), 3.11 (2H, br.s), 3.37 (2H, s), 3.38 (2H, s), 3.44 (2H, s), 3.45 (2H, s), 6.46 (1H, br.d $^3J_{obs}$ = 7.1 Hz), 6.58-6.63 (2H, m), 7.06 (1H, t, ^3J = 7.6 Hz), 7.09 (1H, t, ^3J = 7.7 Hz), 7.17-7.36 (12H, m), 7.50 (1H, br.s), three NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 23.9 (1C), 24.0 (1C), 32.9 (1C), 40.2 (1C), 42.0 (1C), 50.2-51.5 м (8C), 58.6 (1C), 59.2 (2C), 59.5 (1C), 110.9 (1C), 113.2 (1C), 117.9 (1C), 122.2 (1C), 126.6 (2C), 127.3 (1C), 128.0 (4C), 128.8 (1C), 128.9 (4C), 129.5 (1C), 129.7 (1C), 131.7 (1C), 139.9 (1C), 140.2 (1C), 141.1 (1C), 142.8 (1C), 148.4 (1C).

*21,27-Dibenzyl-1,8,11,18,21,27-hexaazatetracyclo[16.6.6.6.1^{3,7}.1^{12,16}]-dotriaconta-3(32),4,6,12(31),13,15-hexaene (**11b**)*. Obtained from 144 mg (0.20 mmol) of compound **7**, 12 mg (0.20 mmol) of ethanediamine-1,2 (**10b**) in the presence of the ligand L3 (18 mol%, 20 mg). Eluent: CH_2Cl_2:MeOH 10:1. Yield 39 mg (32 %), *ee* = 2 %, slightly beige crystalline powder, m.p. 147-149 °C. (MALDI-TOF) found: 617.4351. $C_{40}H_{53}N_6$ requires 617.4332

$[M+H]^+$. ^{1}H NMR ($CDCl_3$, 328 K) δ_H ppm: 1.72 (2H, br.s), 1.91 (2H, br.s), 2.43 (4H, br.s), 2.54-2.81 (12H, m), 3.37-3.56 (12H, m), 6.39 (2H, br.s), 6.47 (2H, br.d, $^3J_{obs}$ = 6.6 Hz), 6.92 (2H, br.s), 7.12 (2H, br.s), 7.18-7.28 (10H, m), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 328 K) δ_C ppm: 24.5 (2C, br.s, $\Delta\nu_{1/2}$ = 50 Hz), 45.0 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 51.8 (2C, br.s, $\Delta\nu_{1/2}$ = 50 Hz), 52.1 (4C), 52.8 (2C, br.s, $\Delta\nu_{1/2}$ = 20 Hz), 59.3 (2C, br.s, $\Delta\nu_{1/2}$ = 20 Hz), 60.0 (2C), 113.6 (4C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 118.7 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 127.4 (2C, br.s, $\Delta\nu_{1/2}$ = 12 Hz), 128.3 (4C), 128.7 (2C), 129.5 (4C), 137.0 (2C), 144.1 (2C), 149.1 (2C).

*22,28-Bis(2-naphthylmethyl)-1,8,12,19,22,28-hexaazatetracyclo[17,6.6.1^{3,7}.1^{13,17}]-tritriaconta-3(33),4,6,13(32),14,16-hexaene (**12a**)*. Obtained from 82 mg (0.10 mmol) of compound **8**, 7.5 mg (0.10 mmol) of propanediamine-1,3 (10a) in the presence of ligand L3 (18 mol%, 10 mg). Eluent: CH_2Cl_2:MeOH 10:1. Yield 19 mg (25 %), *ee* = 9 %, slightly beige crystalline powder, m.p. 141-143ºC. (MALDI-TOF) found: 731.4765. $C_{49}H_{59}N_6$ requires 731.4801 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 328 K) δ_H ppm: 1.83 (2H, quintet, ^3J = 5.9 Hz), 1.91 (4H, br.s), 2.40-2.85 (16H, m), 3.29 (4H, t, ^3J = 5.9 Hz), 3.39 (4H, br.s), 3.70 (4H, br.s), 6.39 (4H, br.s), 6.94 (2H, br.s), 7.02 (2H, br.s), 7.32 (2H, br.s), 7.44 (4H, br.s), 7.61 (2H, br.s), 7.67-7.82 (6H, m), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 328 K) δ_C ppm: 24.6 (2C, br.s, $\Delta\nu_{1/2}$ = 60 Hz), 29.5 (1C, br.s, $\Delta\nu_{1/2}$ = 50 Hz), 42.0 (2C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 52.4 (8C, br.s, $\Delta\nu_{1/2}$ = 100 Hz), 59.6 (2C, br.s, $\Delta\nu_{1/2}$ = 70 Hz), 60.0 (2C), 112.2 (2C, br.s, $\Delta\nu_{1/2}$ = 20 Hz), 114.3 (2C), 118.4 (2C, br.s, $\Delta\nu_{1/2}$ = 25 Hz), 125.2 (2C), 126.0 (2C, br.s, $\Delta\nu_{1/2}$ = 25 Hz), 127.6 (2C), 127.7 (2C), 127.9 (2C), 128.9 (2C), 133.1 (2C), 133.5 (2C), 142.6 (2C), 148.9 (2C), six quaternary carbon atoms were not assigned.

21,27-Bis(2-naphthylmethyl)-1,8,11,18,21,27-hexaazatetracyclo-[16.6.6.1^{3,7}.1^{12,16}]dotriaconta-3(32),4,6,12(31),13,15-hexaene (***12b***). Obtained from 123 mg (0.15 mmol) of compound **8**, 9 mg (0.15 mmol) of ethanediamine-1,2 (**10b**) in the presence of the ligand L7 (18 mol%, 23 mg). Eluent: CH_2Cl_2:MeOH 10:1. Yield 20 mg (19 %), *ee* = 1 %, slightly beige crystalline powder, m.p. 107-109 ºC. (MALDI-TOF) found: 717.4687. $C_{48}H_{57}N_6$ requires 717.4645 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 328 K) δ_H ppm: 1.80 (2H, br.s), 1.90 (4H, br.s), 2.45-2.87 (16H, m), 3.33-3.55 (6H, m), 3.58-3.74 (4H, m), 6.25-6.50 (4H, m), 6.85 (2H, br.s), 6.90-7.17 (2H, m), 7.37-7.50 (6H, m), 7.57 (2H, br.s), 7.66-7.81 (6H, m), two NH protons were not assigned.

*22,28-Bis(biphenyl-4-ylmethyl)-1,8,12,19,22,28-hexaazatetracyclo-[17,6.6.1^{3,7}.1^{13,17}]tritriaconta-3(33),4,6,13(32),14,16-hexaene (**13a**)*. Obtained from 130 mg (0.15 mmol) of compound **9**, 11 mg (0.15 mmol) of propanediamine-1,3 (**10a**) in the presence of the ligand L3 (18 mol%, 15 mg). Eluent: CH_2Cl_2:MeOH 10:1. Yield 32 mg (27 %), *ee* = 9 %, slightly beige crystalline powder, m.p. 130-132 ºC. (MALDI-TOF) found: 783.5038. $C_{53}H_{63}N_6$ requires 783.5114 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.84 (4H, quintet, ^3J = 5.6 Hz), 1.96 (2H, br.s), 2.45-3.03 (16H, m), 3.31 (4H, t, ^3J = 5.6 Hz), 3.42 (4H, s), 3.59 (4H, s), 4.62 (2H, br.s), 6.44 (2H, br.d $^3J_{obs}$ = 6.8 Hz), 6.46 (2H, br.d, $^3J_{obs}$ = 7.8 Hz), 6.97-7.04 (4H, m), 7.27-7.57 (18H, m). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 24.7 (2C, br.s, $\Delta\nu_{1/2}$ = 20 Hz), 29.4 (1C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 42.1 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 52.3 (8C, br.s, $\Delta\nu_{1/2}$ = 80 Hz), 58.9 (2C, br.s, $\Delta\nu_{1/2}$ = 20 Hz), 59.9 (2C), 112.0 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 114.2 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 118.4 (2C), 127.0 (8C), 127.3 (2C), 128.8 (4C), 129.0 (2C), 130.0 (2C, br.s, $\Delta\nu_{1/2}$ = 12 Hz), 132.6 (2C), 140.4 (6C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 140.9 (2C), 148.8 (2C).

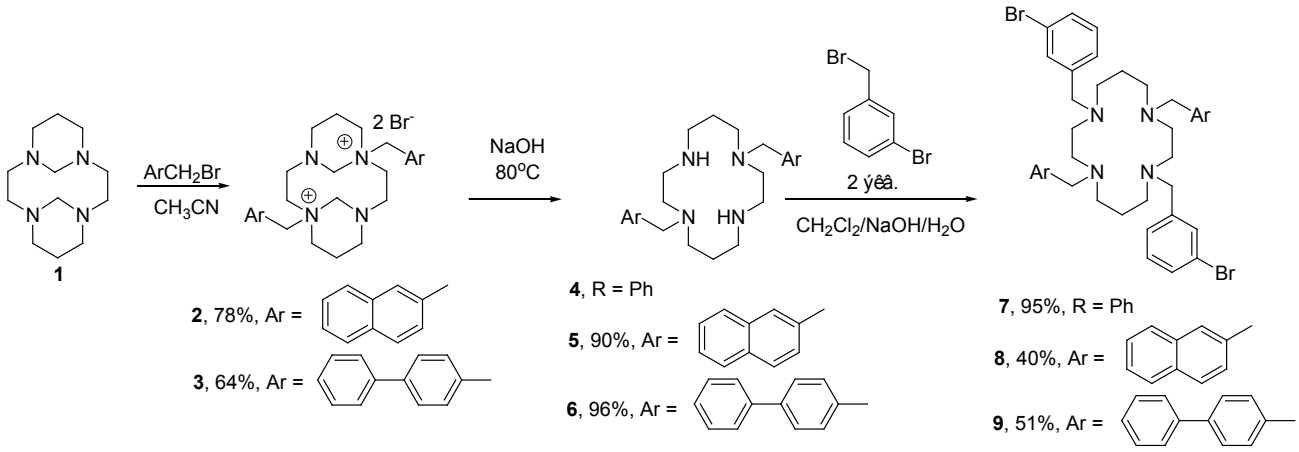
*21,27-Bis(biphenyl-4-ylmethyl)-1,8,11,18,21,27-hexaazatetracyclo-[16.6.6.1^{3,7}.1^{12,16}]dotriaconta-3(32),4,6,12(31),13,15-hexaene (**13b**)*. Obtained from 130 mg (0.15 mmol) of compound **9**, 9 mg (0.15 mmol) of ethanediamine-1,2 (**10b**), in the presence of the ligand L3 (18 mol%, 15 mg). Eluent: CH_2Cl_2:MeOH 10:1. Yield 22 mg (19 %), *ee* = 0 %, slightly beige crystalline powder, m.p. 135-137 ºC. (MALDI-TOF) found: 783.5038. $C_{52}H_{61}N_6$ requires 769.4958 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.69 (2H, br.s), 1.93 (2H, br.s), 2.40-2.75 (16H, m), 3.40 (4H, br.s), 3.47 (8H, br.s), 6.45 (4H, br.s), 6.97 (4H, br.s), 7.34 (4H, t, ^3J = 7.1 Hz), 7.32-7.38 (10H, m), 7.59 (4H, br.d, $^3J_{obs}$ = 6.8 Hz), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 328 K) δ_C ppm: 24.6 (2C, br.s, $\Delta\nu_{1/2}$ = 50 Hz), 44.9 (2C), 51.9 (8C, br.s, $\Delta\nu_{1/2}$ = 35 Hz), 59.1 (2C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 60.0 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 113.5 (4C, br.s, $\Delta\nu_{1/2}$ = 100 Hz), 118.6 (2C, br.s, $\Delta\nu_{1/2}$ = 20 Hz), 125.2 (2C), 127.0 (8C), 127.2 (2C), 128.8 (4C), 129.8 (4C), 132.1 (2C), 135.2 (2C), 140.1 (2C), 141.0 (2C), 149.0 (2C).

*21,27-Bis(biphenyl-4-ylmethyl)-9,10-diphenyl-1,8,11,18,21,27-hexaazatetracyclo-[16.6.6.1^{3,7}.1^{12,16}]dotriaconta-3(32),4,6,12(31),13,15-hexaene (**13c**)*. Synthesizd from 130 mg (0.15 mmol) of compound **9**, 32 mg (0.15 mmol) of the diamine (**10c**) in the presence of the ligand L3 (18 mol%, 15 mg). Elunet: CH_2Cl_2:MeOH 10:1. Yield 31 mg (22 %), *ee* = 5 %, slightly beige crystalline powder, m.p. 145-147 ºC. (MALDI-TOF) found: 921.5536. $C_{64}H_{69}N_6$ requires 921.5584 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.78 (4H, br.s), 2.57 (16H, br.s), 3.33 (4H, br.s), 3.48 (4H, br.s), 4.54 (2H, br.s), 6.35 (2H, br.s), 6.49 (2H, br.s), 6.85-7.65 (32H, m), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 328 K) δ_C ppm: 24.4 (2C, br.s, $\Delta\nu_{1/2}$ = 15 Hz), 51.0 (2C, br.s, $\Delta\nu_{1/2}$ = 80 Hz), 51.9 (4C, br.s, $\Delta\nu_{1/2}$ = 50 Hz), 52.5 (2C, br.s, $\Delta\nu_{1/2}$ = 60 Hz), 58.9 (4C, br.s, $\Delta\nu_{1/2}$ = 80 Hz), 64.0 (2C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 113.3 (2C, br.s, $\Delta\nu_{1/2}$ = 40 Hz), 115.5 (2C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 119.0 (2C, br.s, $\Delta\nu_{1/2}$ = 50 Hz), 125.2 (2C), 127.0 (8C), 127.3 (4C), 127.7-128.2 (8C, m), 128.8 (4C), 129.8 (4C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 132.1 (2C), 140.4 (4C, br.s, $\Delta\nu_{1/2}$ = 40 Hz), 140.9 (4C, br.s, $\Delta\nu_{1/2}$ = 30 Hz), 148.2 (2C, br.s, $\Delta\nu_{1/2}$ = 70 Hz).

Results and Discussion

Macrobicycles comprising the cyclam fragments can be planar-chiral provided that the chain that forms the second cycle does not rotate around the cyclam moiety. We established that the derivatives of the *trans*-dibenzylcyclam which do not contain additional substituents at two other nitrogen atoms cannot be planar-chiral because even a short diaminotrimethylene chain easily rotates around the cyclam moiety at room temperature. In this connection we synthesized a series of *N,N',N'',N'''*-tetrasubstitued cyclams bearing two bromine atoms in aromatic substituents, in which additional groups could hinder the rotation of the chain around the cyclam moiety. The reaction of bis-formaldehyde-cyclam (**1**) with bromomethylarenes (2 equiv.) in CH_3CN led to corresponding di-salts **2** and **3** which were deprotected using aqueous solutions of NaOH at 80-90 ºC. As a result, *trans*-disubstituted cyclams **5** and **6** were obtained in good overall yields (70 % for the compound **5** bearing two naphthylmethyl substituents and 61 % for the compound **6** containing two biphenylmethyl substitutents). The compounds **4-6** were modified with two *m*-bromobenzyl substituents using 2 equiv. of *m*-bromobenzyl bromide in a two-phase H_2O-CH_2Cl_2 system with NaOH as a base to give tetrasubstituted derivatives **7-9** in yields 40-95 % (Scheme 1). It is noteworthy that the application of other solvents like CH_3CN and other bases like K_2CO_3 as well as the attempts to introduce first *m*-bromobenzyl substituents followed by the introduction of arylmethyl groups were all unsuccessful due to the formation of numerous by-products caused by the quaternization of the nitrogen atoms of cyclam.

We obtained monocrystals of the compound **9** and its molecular structure was studied by X-ray analysis (Figure 1). In the crystalline form two bromine atoms are oriented in the opposite directions but in the solution due to easy rotations around C(sp^2)-C(sp^3) and C(sp^3)-N bonds these bromine



Scheme 1.

atoms can be oriented in the same direction to favor the formation of the second macrocycle; this was further verified experimentally.

We studied the Pd-catalyzed amination of the compounds **7-9** with diamines **10a-c** using racemic BINAP in order to check the possibility of the macrocyclization reactions leading to the formation of macrobicycles **11-13**, and then a series of different chiral ligands ((*R*)- and (*S*)-BINAP, **L1-L8**) were tested to study the asymmetric induction (Scheme 2). The results are given in the Table 1. Enantiomeric excess was determined using HPLC with a chiral stationary phase. At first the reactions of tetrabenzyl substituted cyclam **7** were studied. The best chemical yields of macrobicycle **11a** (40-50 %) were achieved using ligands **L1**, **L2**, **L4**, **L6**, **L7** (entries 3, 4, 6, 8, 9), while traditional BINAP provided 22-28 % yields (entries 1, 2). As for enantiomeric excess, only ligands **L3**, **L4**, **L7** were to some extent efficient providing 9, 11 and 13 % *ee*, respectively (entries 5, 6, 9). For the synthesis of **11b**, ligand **L3** was

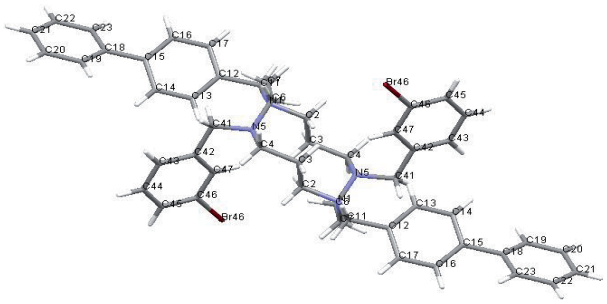
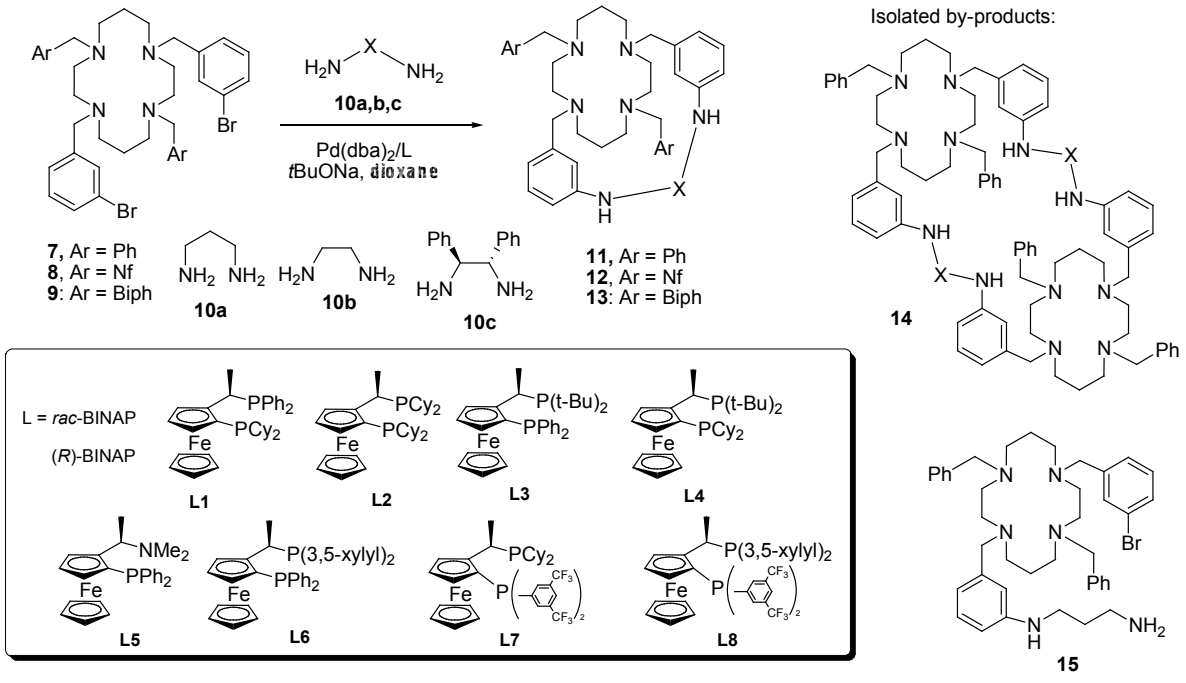


Figure 1. Molecular structure of the cyclam derivative **9**.

better than BINAP considering its chemical yield (entries 11 and 12), however, the asymmetric induction was too small though the chain of the corresponding amine was shorter (4 atoms in **10b** *vs* 5 atoms in **10a**). Ligand **L3** afforded equal



Scheme 2.

Table 1. Pd-catalyzed amination of tetrasubstituted cyclams **7-9**.

Entry	Substitutent in cyclam	Diamine	Ligand	Yield of macrobicycle, %	*ee*, %	Yield of by-products, %
1	Bn	$NH_2(CH_2)_3NH_2$ **10a**	*rac*-BINAP	**11a**, 28	-	**14**, 19
2	Bn	$NH_2(CH_2)_3NH_2$ **10a**	(*S*)-BINAP	**11a**, 22	0	-
3	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L1	**11a**, 46	1	-
4	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L2	**11a**, 40	2	**14**, 33
5	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L3	**11a**, 16	9	**14**, 16
6	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L4	**11a**, 50	11	**14**, 42
7	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L5	**11a**, 32	5	**15**, 30
8	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L6	**11a**, 44	2	**14**, 51
9	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L7	**11a**, 41	13	**15**, 37
10	Bn	$NH_2(CH_2)_3NH_2$ **10a**	L8	**11a**, 18	6	-
11	Bn	$NH_2(CH_2)_2NH_2$ **10b**	*rac*-BINAP	**11b**, 18	-	-
12	Bn	$NH_2(CH_2)_2NH_2$ **10b**	L3	**11b**, 32	2	-
13	Nf	$NH_2(CH_2)_2NH_2$ **10a**	*rac*-BINAP	**12a**, 15	-	-
14	Nf	$NH_2(CH_2)_3NH_2$ **10a**	(*R*)-BINAP	**12a**, 25	1	-
15	Nf	$NH_2(CH_2)_3NH_2$ **10a**	L3	**12a**, 25	9	-
16	Nf	$NH_2(CH_2)_3NH_2$ **10a**	*rac*-BINAP	**12b**, 17	-	-
17	Nf	$NH_2(CH_2)_2NH_2$ **10b**	L7	**12b**, 19	1	-
18	Biph	$NH_2(CH_2)_3NH_2$ **10a**	*rac*-BINAP	**13a**, 21	-	-
19	Biph	$NH_2(CH_2)_3NH_2$ **10a**	L3	**13a**, 27	9	-
20	Biph	$NH_2(CH_2)_2NH_2$ **10b**	*rac*-BINAP	**13b**, 23	-	-
21	Biph	$NH_2(CH_2)_2NH_2$ **10b**	L3	**13b**, 19	0	-
22	Biph	$NH_2CH(Ph)CH(Ph)NH_2$ **10c**	*rac*-BINAP	**13c**, 29	-	-
23	Biph	$NH_2CH(Ph)CH(Ph)NH_2$ **10c**	L3	**13c**, 22	5	_

enantiomeric excess (9 %) in the reactions of bisnaphthyl and bisbiphenyl derivatives **8** and **9** with diamine **10a** (entries 15, 19), and it was again inefficient in the reaction with 1,2-ethanediamine (**10b**) (entry 21). The use of a more sterically hindered 1,2-diphenyl-1,2-ethanediamine (**10c**) provided a better result regarding chemical yield of the corresponding macrobicycle **13c** and the possibility of asymmetric induction (entries 22, 23). The general feature of all studied reactions was the fact that enantiomeric induction was better for a longer diamine **10a** and almost was not dependent on the nature of arylmethyl substitutents introduced in the cyclam moiety to ensure planar chirality.

The formation of macrotricyclic by-product **14** was observed in some reactions of compound **7** with diamine **10a** (entries 1, 4-6, 8). The yields reached 50 % and were comparable with those of the target macrobicycle **11a**. In two cases (entries 7, 9) the product of monoamination **15** was isolated. NMR spectra of many macrobicycles (**11b**, **12a**,**b**, **13a-c**) are characterized by the signal broadening due to hindered conformational dynamics resulting from the presence of bulky substitutents and short linkers. In many cases satisfactory ^{13}C NMR spectra could be recorded only at elevated temperature (328 K), though many signals were still enough broad ($\Delta\nu 1/2$ up to 100 Hz).

Conclusions

To sum up, we investigated the synthesis of the planar-chiral macrobicycles using Pd-catalyzed amination of tetrasubstituted cyclams, bearing two 3-bromobenzyl and two arylmethyl substituents, in the presence of various chiral diphosphine ligands, target macrobicyclic compounds were obtained in yields up to 50 %, we demonstrated the possibility of enantiomeric induction up to 13 % *ee* and found out that the best enantiomeric excess was achieved with propanediamine-1,3 notwithstanding the bulkiness of the substituents.

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