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Palladium-catalyzed arylation of linear and cyclic polyamines*

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Abstract: Synthetic protocols for the palladium-catalyzed arylation of various linear and cyclic polyamines and polyoxapolyamines has been worked out. Pd(0) and Pd(II) complexes with such phosphine ligands as dppf, BINAP, PPF-OMe, P(*t*Bu)$_3$, 2-di*tert*-butylphosphino-1,1′-biphenyl have been explored in the catalytic amination reactions. Monoamination of chloro-, bromo-, and iodoarenes with di-, tri-, and tetraamines have been carried out, conditions for di- and polyarylation of linear polyamines have been elaborated. Successful arylation of 1,4,7,10-tetraazacyclododecane (cyclene) and 1,4,8,11-tetraazacyclotetradecane (cyclam) have been conducted. Intramolecular diamination of dihaloarenes such as 1,2-dibromobenzene, 2,6-dichlorobromobenzene, 1,3-dibromobenzene, 1,8-dichloroanthracene, 1,8-dichloroanthraquinone, 1,5-dichloroanthracene, and 1,5-dichloroanthraquinone afforded corresponding polyazamacrocycles containing arene moieties. For the first time, a convenient one-pot synthesis of the face-to-face arranged bismacrocyclic systems has been carried out.

INTRODUCTION

Polyamines attract the constant interest of chemists due to their wide use in pharmacology [1], coordination chemistry [2,3], and in the research of supramolecular systems [4]. Alkyl- and benzyl-substituted linear polyamines have been used as polydentate ligands for complexing palladium [5], copper [6], and other metals [7], and as fluorescence sensors for detecting a variety of metals such as Ni, Zn, Cd, and Pb [8]. As a result, numerous convenient approaches to *N*-alkyl- and *N*-benzyl-substituted polyamines have been proposed. We believe that direct linking of arene moieties to the nitrogen atom of polyamines will enhance interaction between the polyamine chain and the arene group with appropriate photochemical properties. This will increase the sensing properties of such molecules.

Noncatalytic methods for the synthesis of arylamines often have such drawbacks as harsh conditions, strong dependence on the substituents in the arene fragment, and necessity of protection–deprotection steps. This strictly limits the synthesis of arylated polyamines, especially nonsymmetric derivatives. Multistep syntheses were often required to prepare even simple species [9]. An indirect method comprising several steps was used for the preparation of the *N*-aryl-1,2-ethanediamines [10]. A real breakthrough in the amination of aryl halides using palladium catalysis was achieved in the late 1990s after innovative works conducted by the groups of Buchwald and Hartwig [11]. It became the most important technique due to its obvious advantages, i.e., a wide choice of amines and substrates with various substituents, high yields, and, in many cases, mild condition protocols.

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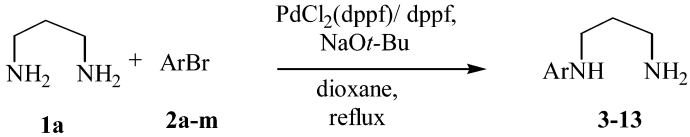
SYNTHESIS OF LINEAR ARYLATED POLYAMINES

Monoarylation of di- and polyamines

We have thoroughly investigated the possibilities of the palladium-catalyzed arylation of polyamines for the synthesis of mono- and polyarylated species [12]. At first, the amination of various aryl bromides **2a–h,k–m** and aryl iodides **2i,j** with a model 1,3-diaminopropane **1a** was carried out (Scheme 1).



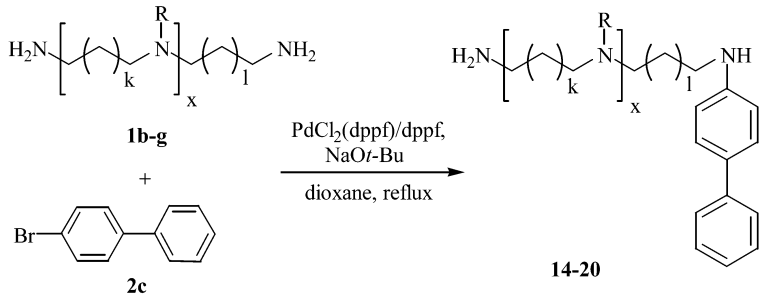
Scheme 1

The reaction employed 0.5–2 mol% of $PdCl_2$/dppf complex with a twofold excess of a free dppf ligand. Three equivalents of the diamine were taken to suppress its diarylation. Two equivalents of sodium *tert*-butoxide were used, and the reaction was run until completion in each case. The data obtained are collected in Table 1. Compared to bromobenzene, *p*-bromobiphenyl appeared to be more active, introduction of donor substituents in the benzene ring hindered the reaction and lowered the yields, electron-withdrawing benzoyl and nitrile groups afforded an excellent yield [$Pd(dba)_2$ was used instead of $PdCl_2$(dppf) complex in the last case], but some other electron-deficient groups proved to be sensitive to sodium *tert*-butoxide and this led to lower yields. The best results were achieved with active 1-bromonaphthalene and 9-bromoanthracene. Aryl iodides were not found to be advantageous to corresponding aryl bromides as they provided similar yields of arylated diamines.

Table 1 Arylation of 1,3-diaminopropane **1a**.

Aryl bromide	$PdCl_2$(dppf)/dppf, mol%	Product (yield, %)
C_6H_5Br **2a**	1/2	**3** (60)
p-MeC_6H_4Br **2b**	1/2	**4** (51)
p-$C_6H_5C_6H_4Br$ **2c**	0.5/1	**5** (75)
p-$MeOC_6H_4Br$ **2d**	5/10	**6** (19)
o-$MeOC_6H_4Br$ **2e**	1.5/3	**7** (41)
p-$CF_3C_6H_4Br$ **2f**	2/4	**8** (53)
p-$MeC(O)C_6H_4Br$ **2g**	0.5/1	**9** (21)
p-NCC_6H_4Br **2h**	4/6	**10** (95)
C_6H_5I **2i**	1/2	**3** (68)
p-MeC_6H_4I **2j**	0.5/1	**4** (49)
p-$ClC_6H_4C(O)C_6H_4Br$ **2k**	1/2	**11** (77)
1-Bromonaphthalene **2l**	0.5/1	**12** (89)
9-Bromoanthracene **2m**	1/2	**13** (85)

We investigated a model *p*-bromobiphenyl **2c** in the reactions with different polyamines. Reaction conditions mentioned above were applied in this process (Scheme 2).



Scheme 2

Corresponding arylamines **14–20** were obtained in high yields, selective arylation of primary amino groups in the presence of secondary amino groups was observed in all cases (Table 2). If the diamines branched at β-carbon atom are used, this does not affect the yield of the product. Branching at α-carbon atom results in lower yields, less regioselectivity of the process in the case of *p*-bromobiphenyl. When employing more active 1-bromonaphthalene, the reaction becomes more regioselective (Table 3, Scheme 3).

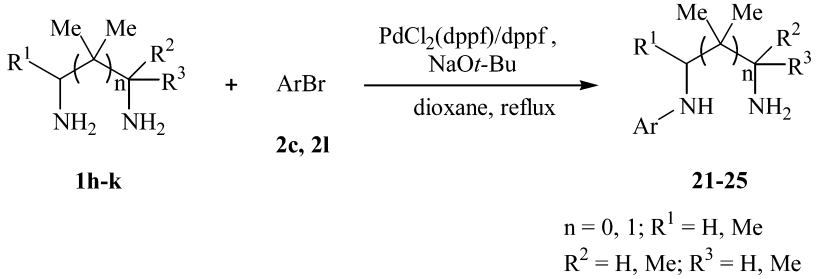
Table 2 Amination of *p*-bromobiphenyl.

Amine	$PdCl_2$(dppf)/dppf, mol%	Product (yield, %)
$NH_2CH_2CH_2NH_2$ **1b**	1/2	**14** (64)
$NH_2CH_2CH_2NHCH_2CH_2NH_2$ **1c**	1/2	**15** (65)
$NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$ **1d**	1/2	**16** (77)
$NH_2CH_2CH_2CH_2NHCH_2CH_2NH_2$ **1e**	1/2	**17** + **18** (85)[a]
$NH_2CH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ **1f**	1/2	**19** (88)
$NH_2CH_2CH_2CH_2N(Me)CH_2CH_2CH_2NH_2$ **1g**	1/2	**20** (83)

[a]A 1:1 mixture of two possible regioisomers.

Table 3 Arylation of sterically hindered diamines.

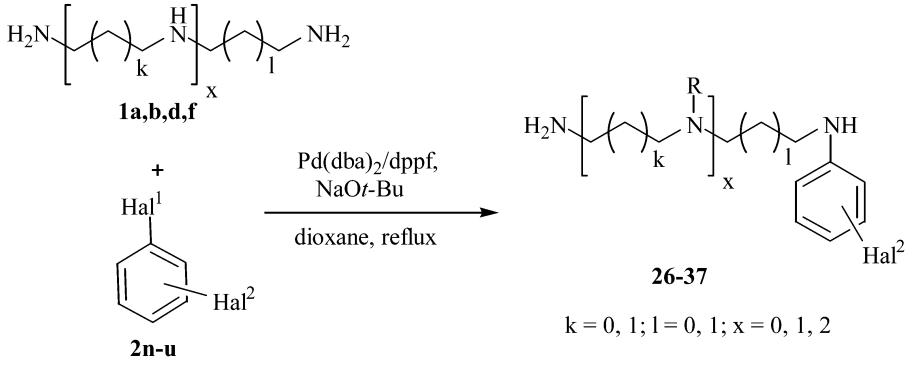
Diamine	Aryl bromide	$PdCl_2$(dppf)/dppf, mol%	Product (yield, %)
$NH_2CH_2C(Me)_2CH_2NH_2$ **1h**	*p*-$C_6H_5C_6H_4Br$ **2c**	1/1	**21** (75)
$NH_2CH_2CH(Me)NH_2$ **1i**	*p*-$C_6H_5C_6H_4Br$ **2c**	2/3	**22** (42)
$NH_2CH_2CH(Me)NH_2$ **1i**	1-bromonaphthalene **2l**	2/3	**23** (64)
$NH_2CH_2C(Me)_2NH_2$ **1j**	*p*-$C_6H_5C_6H_4Br$ **2c**	2/3	**24** (84)
1,2-diaminocyclohexane **1k**	1-bromonaphthalene **2l**	1/2	**25** (42)



Scheme 3

Monoamination of dihaloarenes

The reaction of polyamines **1a,b,d,f** with dihalobenzenes **2n–u** was conducted using $Pd(dba)_2$ (2–4 mol%) with dppf (2–6 mol%) and with polyamine to arylhalide ratio 3:1 [13]. This process afforded corresponding halosubstituted aminobenzenes **26–37** in good yields (Scheme 4, Table 4).



Scheme 4

Table 4 Monoamination of dihalobenzenes.

Amine	Aryl bromide	$Pd(dba)_2$/dppf, mol%	Product (yield, %)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*p*-BrC_6H_4Br **2n**	2/2	**26** (93)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*m*-BrC_6H_4Br **2o**	2/4	**27** (93)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*o*-BrC_6H_4Br **2p**	2/3	**28** (71)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*p*-BrC_6H_4I **2q**	4/6	**26** (72)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*p*-IC_6H_4I **2r**	4/6	**29** (57)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*o*-ClC_6H_4Br **2s**	4/6	**30** (75)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	2,4-dibromonitrobenzene **2t**	2/3	**31** (79)
$NH_2CH_2CH_2NH_2$ **1b**	*p*-BrC_6H_4Br **2n**	2/4	**32** (45)
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	*p*-BrC_6H_4Br **2n**	2/4	**33** (95)
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	*m*-BrC_6H_4Br **2o**	2/4	**34** (93)
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	*o*-BrC_6H_4Br **2p**	2/4	**35** (74)
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	*p*-IC_6H_4I **2r**	4/6	**36** (48)
$NH_2(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2$ **1f**	2,6-dichlorobromobenzene **2u**	4/6	**37** (85)

The side process of the reduction of the second halogen atom was unimportant, bromine atom was substituted in the presence of chlorine atom, and iodine atom was substituted in the presence of bromine atom. *P*-Diiodobenzene **2r** was less active than *p*-bromoiodobenzene **2q**. Like in previous experiments, only primary amino groups of the triamine **1d** and the tetraamine **1f** were selectively arylated.

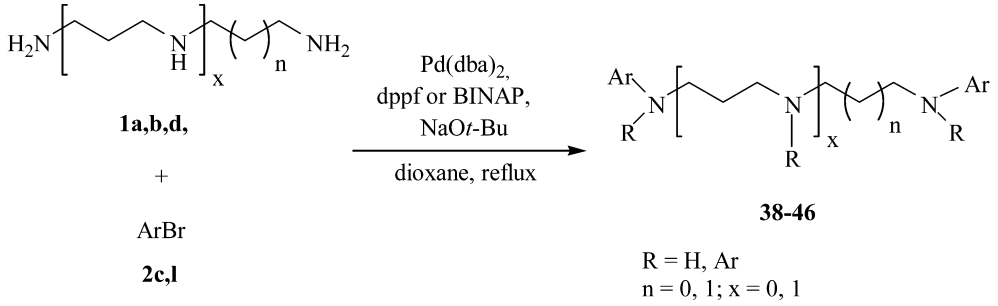
Polyarylation of polyamines

We studied the arylation of di- and triamines **1a,b,d** with aryl bromides to find out the conditions of their polyarylation. When running the reactions with equimolar amounts of starting compounds in the presence of $Pd(dba)_2$/dppf catalytic system (1–2 mol% Pd, 2–4 mol% dppf), generally the mixtures of N-arylated and N,N′-diarylated polyamines were obtained in the case of less active *p*-bromobiphenyl, while more active 1-bromonaphthalene provided selective formation of monoarylated species. When using 2:1 ratio of 1-bromonaphthalene to polyamine, corresponding N,N-diarylated compounds **38,39** were obtained in high yields. To achieve good yields of **40–42** with 1-bromonaphthalene BINAP instead

of dppf should be used. Greater excess of aryl bromides and generous loadings of the catalyst (4 mol% Pd, 8 mol% BINAP) led to exhaustive polyarylation of di- and triamines and excellent yields of tetra- and pentaaryl derivatives **43–46**. In these cases, arylation of secondary amino groups in polyamines was observed for the first time (Table 5, Scheme 5).

Table 5 Polyarylation of polyamines.

Amine	Aryl bromide	$Pd(dba)_2$/dppf or BINAP, mol%	Product (yield, %)
$NH_2CH_2CH_2CH_2NH_2$ **1a**	1-bromonaphthalene **2l**	1/2 (dppf)	**38** (88) R = H
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	1-bromonaphthalene **2l**	1/2 (dppf)	**39** (92) R = H
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*p*-$C_6H_5C_6H_4Br$ **2c**	2/4 (dppf)	**40** (36) R = H
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*p*-$C_6H_5C_6H_4Br$ **2c**	2/4 (BINAP)	**40** (85) R = H
$NH_2CH_2CH_2NH_2$ **1b**	*p*-$C_6H_5C_6H_4Br$ **2c**	2/4 (BINAP)	**41** (75) R = H
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	*p*-$C_6H_5C_6H_4Br$ **2c**	2/4 (BINAP)	**42** (89) R = H
$NH_2CH_2CH(Me)NH_2$ **1i**	1-bromonaphthalene **2l**	6/9 (dppf)	**43** (40) R = H
$NH_2CH_2CH_2CH_2NH_2$ **1a**	*p*-$C_6H_5C_6H_4Br$ **2c**	4/8 (BINAP)	**44** (95) R = Ar
$NH_2CH_2CH_2NH_2$ **1b**	*p*-$C_6H_5C_6H_4Br$ **2c**	4/8 (BINAP)	**45** (95) R = Ar
$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **1d**	*p*-$C_6H_5C_6H_4Br$ **2c**	8/16 (BINAP)	**46** (89) R = Ar



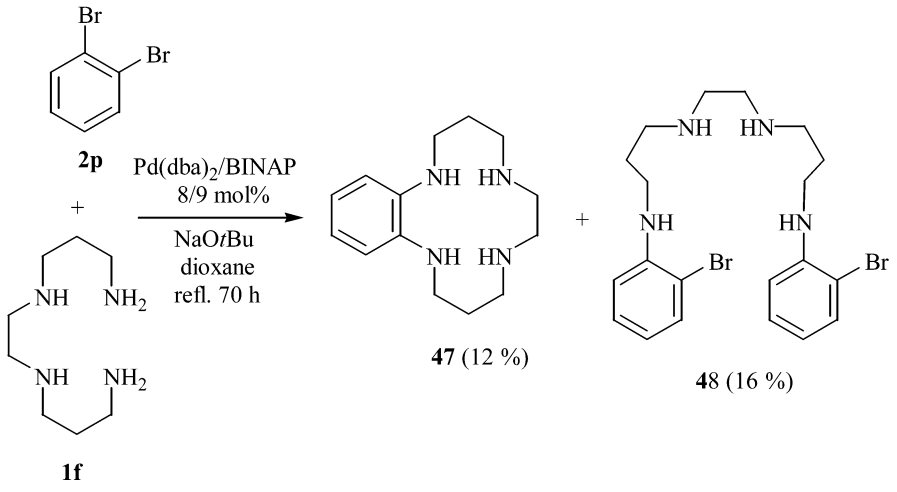
Scheme 5

FORMATION OF MACROCYCLES BY INTRAMOLECULAR CATALYTIC AMINATION REACTIONS

Amination of dihalo- and trihalobenzenes

To synthesize nitrogen-containing analogs of benzocrown ethers, we tried first the simplest *o*-dibromobenzene **2p** as a substrate in the reaction with tetraamine **1f** [14]. The reaction of equimolar amounts of **2p** and **1f** was run in the presence of 8 mol% $Pd(dba)_2$ and 9 mol% BINAP, in a diluted solution of boiling dioxane (c = 0.01 M) to avoid possible formation of oligomers, NaO*t*Bu (1.5 equiv) was employed as a base (Scheme 6).

However, the reaction was not enough successful as the desired benzocyclam **47** was formed in a low 12 % yield together with a linear product of tetraamine diarylation **48** (16 %). This can be easily explained by the fact that upon the amination of the first bromine atom, the substitution of the second bromine atom is disfavored by a strong mesomeric donor influence of the amino group in the intermediate *o*-aminobromobenzene, which readily reacts with the second molecule of *o*-dibromobenzene to form **48**.

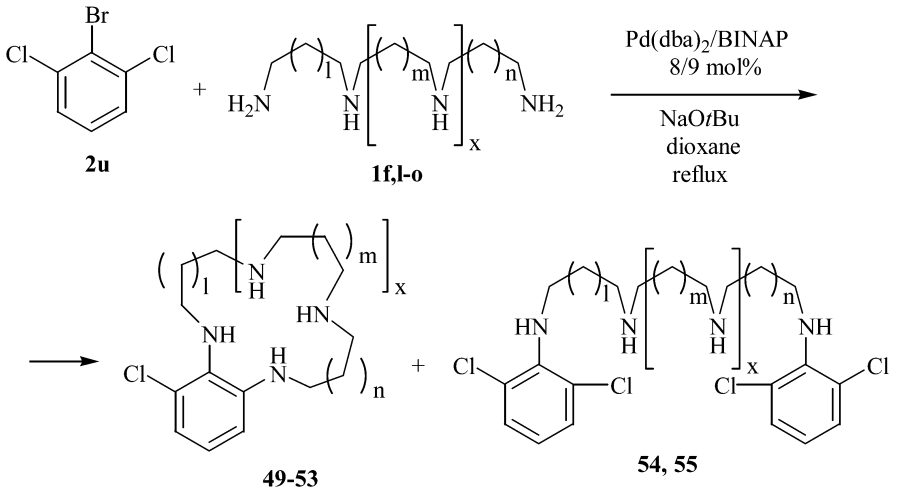


Scheme 6

In order to promote the introduction of the second amino group in the *ortho*-position to the first amino group, we decided to use 2,6-dichlorobromobenzene **2u** in which the electron-withdrawing influence of the second chlorine atom will to some extent decrease the unfavorable influence of the first introduced amino group. The same reaction conditions were used in the amination of **2u** by a variety of polyamines **1f,l–o** (Table 6, Scheme 7).

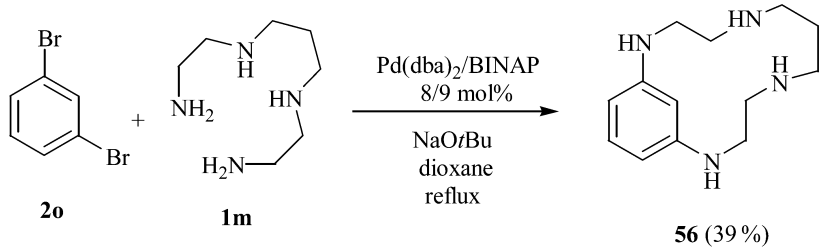
Table 6 Amination of 2,6-dichlorobromobenzene **2u**.

Amine	l	m	n	x	Product (yield, %)
$NH_2CH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ **1f**	1	0	1	1	**49** (47)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1l**	0	0	0	1	**50** (27)
$NH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2NH_2$ **1m**	0	1	0	1	**51** (17)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1n**	0	0	0	2	**52** (12)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1o**	0	0	0	3	**53** (10)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1n**	0	0	0	2	**54** (17)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1o**	0	0	0	3	**55** (21)



Scheme 7

We have also investigated the reaction of *m*-dibromobenzene **2o** in the reaction with tetraamine **1m** to obtain the benzo derivative of cyclam with an unusual configuration of the cycle. The reaction was run under the same conditions to produce the desired product **56** in 39 % yield (Scheme 8).



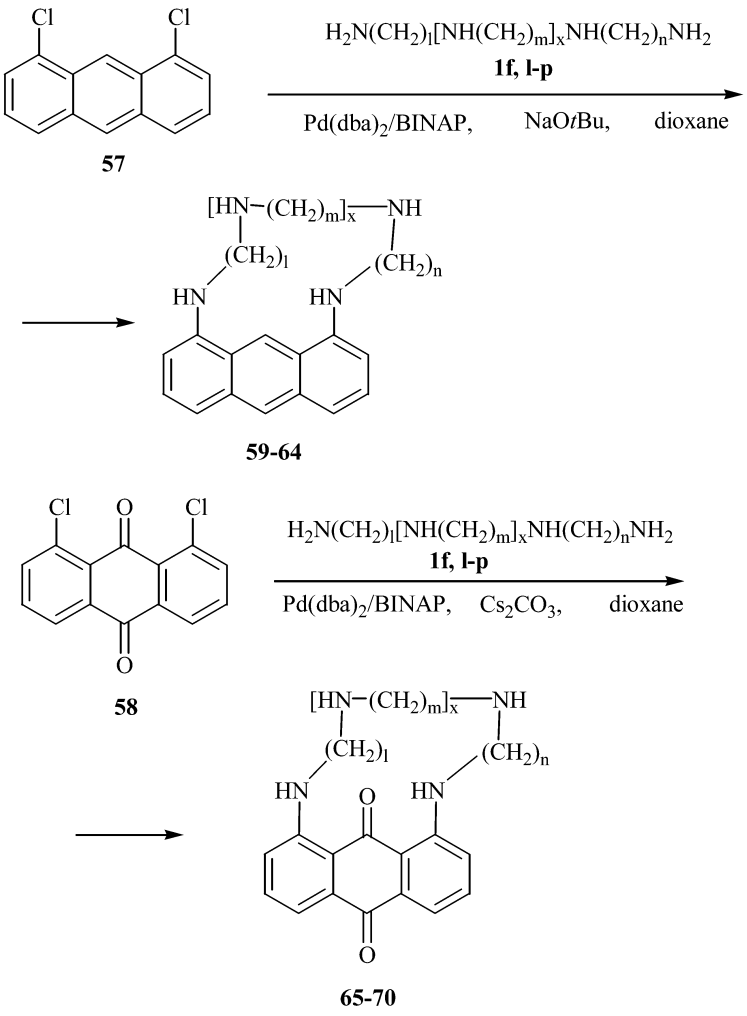
Scheme 8

Formation of polyazamacrocycles derived from 1,8-dichloroanthracene and 1,8-dichloroanthraquinone

Macrocyclic compounds containing anthracene and anthraquinone moieties were synthesized by the reaction of equimolar amounts of linear polyamines **1f,l–p** with anthracene **57** and anthraquinone **58** [15]. The $Pd(dba)_2$/BINAP catalytic system (4–8 mol% Pd, 4.5–9 mol% BINAP) was utilized with NaO*t*Bu base in the case of dichloroanthracene and Cs_2CO_3 in the reactions with dichloroanthraquinone. Diluted solutions of the reagents in dioxane were used (0.017–0.025 M) to avoid undesirable formation of oligomers (Table 7, Scheme 9).

Table 7 Amination of 1,8-dichloroanthracene **57** and 1,8-dichloroanthraquinone **58**.

Aryl dichloride	Amine	l	m	n	x	Product (yield, %)
57	$NH_2CH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ **1f**	1	0	1	1	**59** (24)
57	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1l**	0	0	0	1	**60** (33)
57	$NH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2NH_2$ **1m**	0	1	0	1	**61** (36)
57	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1n**	0	0	0	2	**62** (26)
57	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1o**	0	0	0	3	**63** (22)
57	$NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$ **1p**	1	1	1	1	**64** (21)
58	$NH_2CH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ **1f**	1	0	1	1	**65** (25)
58	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1l**	0	0	0	1	**66** (14)
58	$NH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2NH_2$ **1m**	0	1	0	1	**67** (19)
58	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1n**	0	0	0	2	**68** (27)
58	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1o**	0	0	0	3	**69** (20)
58	$NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$ **1p**	1	1	1	1	**70** (10)



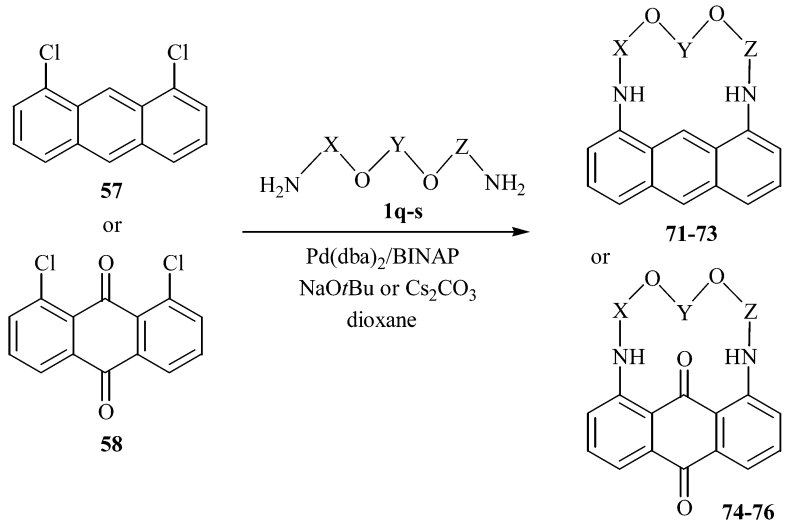
Scheme 9

The reduction of chlorine atom generally was not observed in the syntheses of the anthracene-based macrocycles. In contrast, the reactions of dichloroanthraquinone **58** with polyamines led to a substantial formation of linear compounds: a mixture of 1-amino- and 1-amino-8-chloroanthraquinones with yields up to 30 %, as well as the compounds with higher molecular weight and anthraquinone/amine ratio 2:1. While the conversion of **57** was full, the conversion of **58** was 90–95 % and some amount was reduced into anthraquinone and 1-chloroanthraquinone. In all mentioned reactions, only primary nitrogen atoms were arylated.

A new family of diazacrown ethers that incorporate anthracene or anthraquinone moiety was synthesized using the same method of Pd-catalyzed amination of 1,8-dichloroanthracene and 1,8-dichloroanthraquinone by employing 3,6-dioxa-1,8-diaminooctane **1q**, 4,9-dioxa-1,12-diaminododecane **1r**, and 4,7,10-trioxa-1,13-diaminotridecane **1s** [16]. The experimental procedure elaborated for the synthesis of tetraazamacrocycles **59–70** was successfully applied to the synthesis of diazacrown ethers **71–76** (Table 8, Scheme 10).

Table 8 Amination of 1,8-dichloroanthracene **57** and 1,8-dichloroanthraquinone **58** by di- and trioxadiamines.

Aryl dichloride	Amine	Product (yield, %)
57	$NH_2CH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$ **1q**	**71** (28)
57	$NH_2CH_2CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2CH_2NH_2$ **1s**	**72** (20)
57	$NH_2CH_2CH_2CH_2OCH_2CH_2CH_2CH_2OCH_2CH_2CH_2NH_2$ **1r**	**73** (25)
58	$NH_2CH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$ **1q**	**74** (36)
58	$NH_2CH_2CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2CH_2NH_2$ **1s**	**75** (37)
58	$NH_2CH_2CH_2CH_2OCH_2CH_2CH_2CH_2OCH_2CH_2CH_2NH_2$ **1q**	**76** (33)



Scheme 10

The anthracene-based macrocycles **71–73** were obtained in 20–29 % yields, while the yields of the anthraquinone-based crown ethers **74–76** were even higher (33–37 %). Complete conversion of starting aryl halides was observed in all cases. It should be noted that the main side-products of this reaction were the cyclic dimers and trimers (Fig. 1) which were isolated in relatively high yields (up to 18 and 8 %, respectively). Using MALDI-TOF mass spectroscopy, we revealed the formation of the cyclooligomers with higher masses, even cyclodecamers with M > 4200. The application of more diluted solutions substantially suppressed the formation of cyclic oligomers.

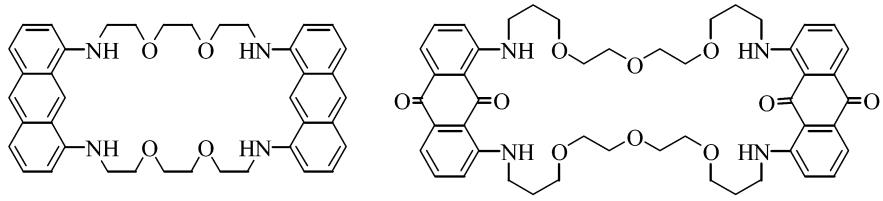


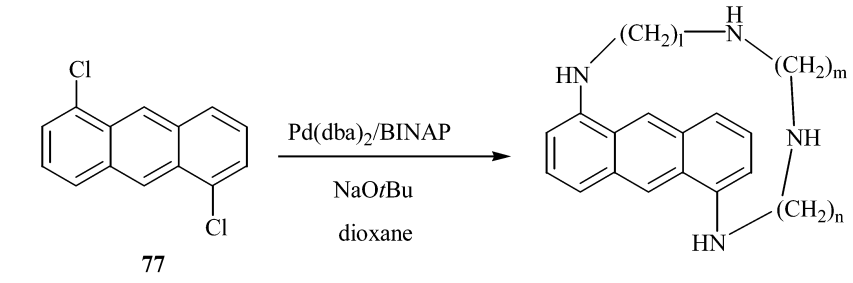
Fig. 1 Examples of cyclodimers.

Polyazamacrocycles based on 1,5-disubstituted anthracene and anthraquinone

The same conditions were employed for the synthesis of the macrocycles based on 1,5-disubstituted anthracene. The tetraamines **1f,l,m,p** were tested in this reaction with 1,5-dichloroanthracene **77**. The geometry of the starting compound **77** implies that the aliphatic chain should be long enough to accomplish cyclization. Tetraamine **1l** was too short to form the desired macrocycle **78** in a reasonable yield. Only traces of **78** were detected together with its cyclic dimer isolated in 18 % yield. Much better results were achieved with the tetraamine **1m** whose chain is only by one carbon atom longer than that of **1l**. In this case, monomeric cycle **79** was obtained in 20 % yield. Its cyclic dimer was also isolated in 10 % yield The same reaction was successfully run with tetraamines **1f** and **1p** to produce corresponding macrocycles **80** and **81** in 34 and 22 % yields, respectively (Table 9, Scheme 11). These reactions also produced substantial amounts of cyclic oligomers.

Table 9 Amination of 1,5-dichloroanthracene **77**.

Amine	Product (yield, %)
$NH_2CH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ **1f**	**80** (34)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1l**	**78** (0)
$NH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2NH_2$ **1m**	**79** (20)
$NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$ **1p**	**81** (22)
$NH_2CH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$ **1q**	**82** (0)
$NH_2CH_2CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2CH_2NH_2$ **1s**	**83** (24)
$NH_2CH_2CH_2CH_2OCH_2CH_2CH_2CH_2OCH_2CH_2CH_2NH_2$ **1r**	**84** (20)



77

\+

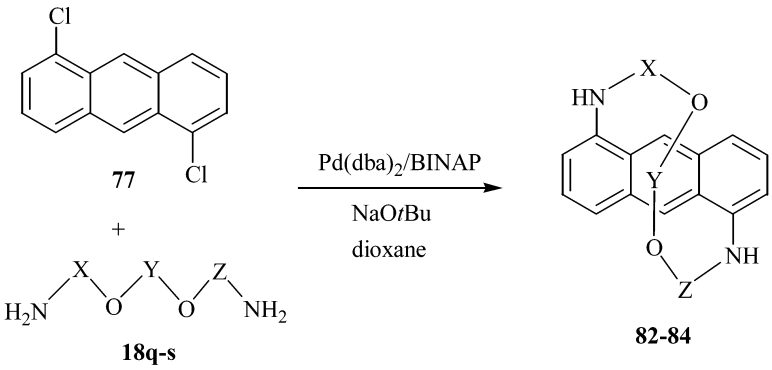
$H_2N(CH_2)_lNH(CH_2)_mNH(CH_2)_nNH_2$

1f,m,p

78-81

Scheme 11

The reaction of 1,5-dichloroanthracene **77** with dioxadiamine **1q**, which possesses the same chain length as **1l**, did not lead to the formation of the macrocycle of type **82**, but rather afforded a cyclic dimer and a mixture of linear oligomers. Both reactions with diamines **1r,s** resulted in the formation of corresponding oxaazacyclophanes **83, 84** in reasonable 24 and 20 % yields (Table 9, Scheme 12).

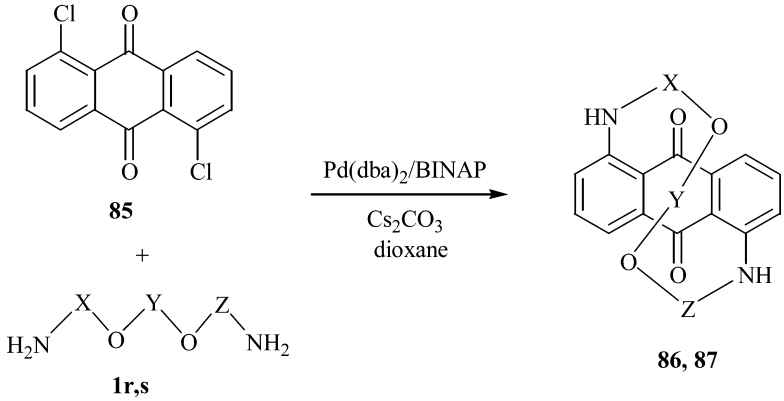


Scheme 12

The amination of 1,5-dichloroanthraquinone **85** with tetraamines **1f,l–n** and di- and trioxadiamines **1q–s** led to substantially different results in comparison with the case of 1,5-dichloroanthracene. Diazacrown ethers **86, 87** were obtained in good yields provided Cs_2CO_3 was employed as a base instead of NaO*t*Bu. Similarly, the amination of a shorter dioxadiamine **1q** did not afford the target macrocycle, but rather produced its cyclic dimer in 18 % yield. In the case of the reaction of **1r**, the target macrocycle **86** was obtained in 30 % yield and the cyclic dimer and trimer were isolated in 10 and 6 % yields, respectively. The reaction of **85** with **1s** furnished macrocycle **87** in 28 % yield (Table 10, Scheme 13).

Table 10 Amination of 1,5-dichloroanthraquinone **85**.

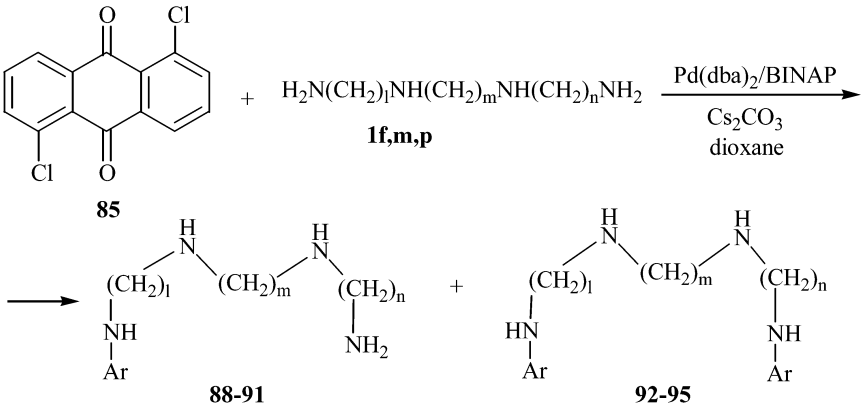
Amine	Product (yield, %)
$NH_2CH_2CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2CH_2NH_2$ **1s**	**86** (30)
$NH_2CH_2CH_2CH_2OCH_2CH_2CH_2CH_2OCH_2CH_2CH_2NH_2$ **1r**	**87** (28)
$NH_2CH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ **1f**	**88** (23) + **92** (10)
$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **1l**	**89** (28) + **93** (10)
$NH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2NH_2$ **1m**	**90** (25) + **94** (5)
$NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$ **1p**	**91** (25) + **95** (26)



Scheme 13

Surprisingly, the amination of 1,5-dichloroanthraquinone **85** by tetraamines **1f,m,p** did not lead to the formation of corresponding tetraazamacrocycles. Only 1-amino-5-chlorosubstituted anthraquinones **88–91** were built in 16–28 % yields together with bis(aryl)substituted tetraamines **92–95**,

which were formed in 5–26 % yields (Table 10, Scheme 14). The consumption of 1,5-dichloroanthraquinone was not quantitative like in the reactions of 1,8-dichloroanthraquinone with tetraamines, and partial reduction of the chlorine atom was observed. The attempts to promote the formation of



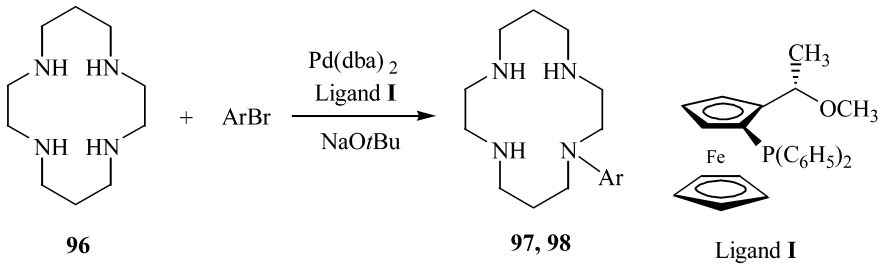
Scheme 14

macrocycles using double amount of the catalyst, the application of other phosphine ligands were not successful.

ARYLATION OF CYCLIC POLYAMINES AND AZACROWN ETHERS

Pd-catalyzed arylation of cyclam

Another approach to N-arylsubstituted polyazamacrocycles comprises direct catalytic arylation of such cyclic polyamines. Due to the fact that secondary cyclic amines are often problematic substrates in the amination reactions we tried various combinations of the catalyst precursor with supporting ligand in the reactions of 1,4,8,11-tetraazacyclotetradecane (cyclam) **96** with arylhalides (chloro-, bromo-, iodo-substituted benzenes, 1-bromonaphthaline, 4-bromobiphenyl, and 9-bromoanthracene). We tested $Pd(dba)_2$, $Pd(OAc)_2$, $PdCl_2$, in the combinations with dppf, BINAP, P*t*Bu_3, P(o-Tol)$_3$, P(Cy)$_3$, but none



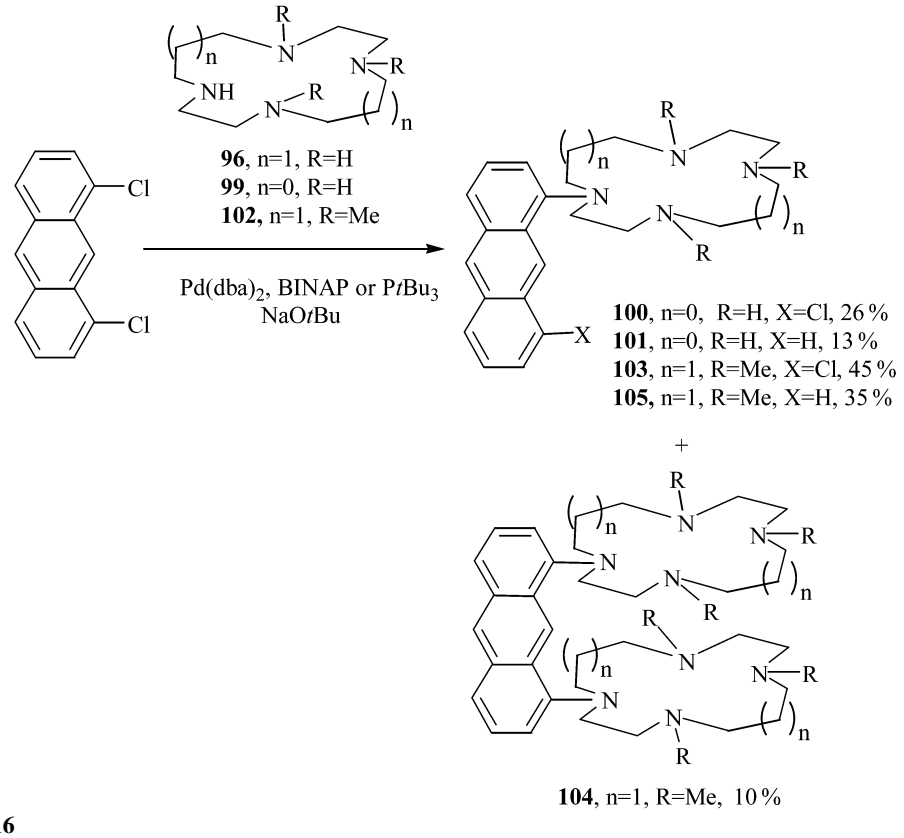
Ar = p-$C_6H_5C_6H_4$ (**97**, 20 %), *p*-NCC_6H_4 (**98**, 22 %).

Scheme 15

of them proved to be applicable to our purpose. The sole result was full or partial reduction of aryl halides into corresponding hydrocarbons by amines. At last, we managed to run the desirable reaction of cyclam with 4-bromobiphenyl and 4-bromobenzonitrile using PPF-OMe ligand, which afforded *N*-arylated cyclams **97** and **98** in 20–22 % yields (Scheme 15) [17].

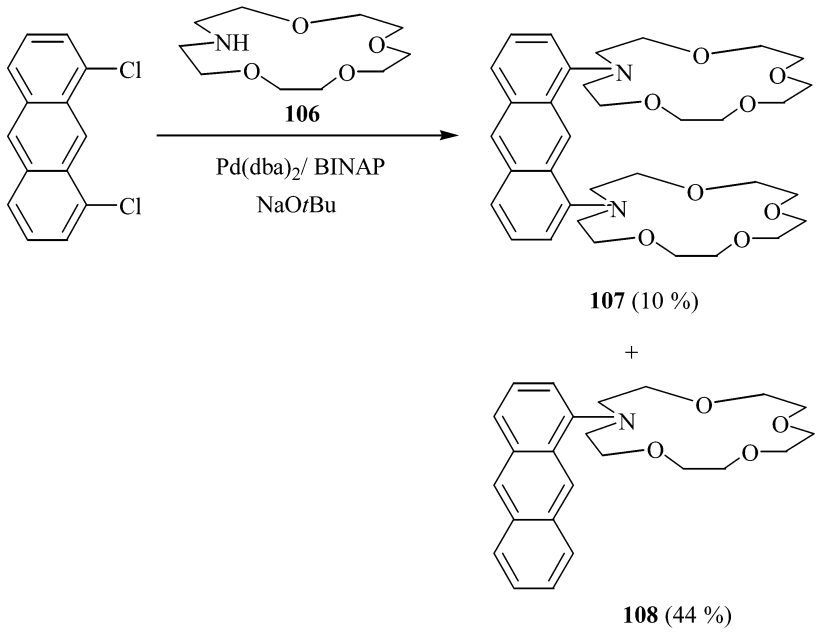
Synthesis of face-to-face arranged bismacrocyclic systems

To solve the problem of a simple one-pot synthesis of saturated analog of cofacial porphyrins [18], we chose 1,8-disubstituted anthracene as a spacer. At first, we tried a cheaper catalytic system $Pd(dba)_2$/BINAP rather than more expensive PPF-OMe. The reaction of 1,8-dichloroanthracene with cyclam in the presence of 4–8 mol% of $Pd(dba)_2$/BINAP and NaO*t*Bu led only to anthracene—the product of the reduction of the starting dichloride. The same reaction with less basic 1,4,7,10-tetraazacyclododecane (cyclen) **99** in the presence of 5 mol% $Pd(dba)_2$/BINAP proved to be more successful, generally yielding a mixture of monocyclen-substituted anthracenes **100** and **101** together with free anthracene (Scheme 16). However, disubstituted anthracene with two cyclen rings was not obtained. In order to attenuate undesirable reduction we thought to apply N,N′,N″-trisubstituted derivatives of cyclam instead of free cyclam, which contains 4 secondary amino groups capable of participating in the reduction of dichloroanthracene. BINAP and $PBut_3$ were tried as supporting ligands. Reactions of



Scheme 16

N,*N*′,*N*″-trimethylcyclam **102** promoted by Pd precursor ($Pd(dba)_2$, 16 mol%) with P*t*Bu_3 produced monocyclam derivative of anthracene **103** in 45 % yield but only traces of desirable biscyclam product **104**. Further attempts to synthesize it using $Pd(dba)_2$/BINAP catalytic system (16 mol%) resulted in the



Scheme 17

formation of the target compound **104** in 10 % yield together with monosubstituted anthracene **105** (35 %) (Scheme 16).

We have also shown the applicability of used methodology to the synthesis of bis(azacrown) substituted anthracene. We investigated the possibility to synthesize a face-to-face ring system employing two azacrown moeities. In our case, 1-aza-15-crown-5 **106** was reacted with 1,8-dichloroanthracene in the presence of $Pd(dba)_2$/BINAP catalytic system to obtain target biscrown substituted anthracene **107** in 11 % yield along with monosubstituted compound **108** (44 %) (Scheme 17).

In conclusion, the data collected in our research allows us to choose the best catalytic system, which is applicable to the amination reactions of various aryl halides that employ polyamines. This system contains $Pd(dba)_2$ as a catalyst precursor with BINAP ligand, which also proved to be a versatile tool in other amination reactions [19] where monoamines are used. In most cases, $Pd(dba)_2$/BINAP catalytic system provides the best results, first of all in intramolecular cyclizations leading to polyazamacrocycles.

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