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Palladium-Catalyzed Amination for the Synthesis of Macrocycles and Polymacrocycles: Contribution of Professor I. P. Beletskaya

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The present mini-review is dedicated to the contribution of the Full member of RAS Professor I.P. Beletskaya, a head of the Laboratory of Organoelement Compounds at the Department of Chemistry of the M.V. Lomonosov Moscow State University, to the strategy of the synthesis of versatile macrocyclic and polymacrocyclic compounds using Pd(0)-catalyzed amination reactions. Over two decades this chemistry has been steadily and very successfully developed starting from enough simple compounds, through sophisticated molecules containing several macrocycles, to recent macrocycles bearing various fluorophore and chiral moieties able to detect not only metal cations but also chiral organic molecules. Among hundreds of compounds many also include derivatives of diazacrown ethers and tetraazamacrocycles like cyclen and cyclam, structures containing different aromatic and heteroaromatic endocyclic groups, including chiral fragments. A key role of Pd(0)-catalyzed amination in the synthesis of this extremely wide range of receptors and detectors cannot be overestimated.

Keywords: Macrocycles, cryptands, polyamines, palladium catalysis, amination, chirality.

Палладий-катализируемое аминирование в синтезе макроциклов и полимакроциклов: вклад профессора И. П. Белецкой

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Данный мини-обзор посвящен вкладу Академика РАН профессора И.П. Белецкой, руководителя Лаборатории элементоорганических соединений Химического факультета МГУ имени М.В. Ломоносова, в стратегию синтеза разнообразных макроциклических и полимакроциклических соединений с использованием реакции палладий-катализируемого аминирования. На протяжении более двух десятилетий эта химия планомерно и успешно развивается, начиная с достаточно простых соединений, переходя к более усложненным молекулам, содержащим несколько макроциклов, а относительно недавно начато исследование соединений, включающих в свой состав флуорофорные и хиральные структурные фрагменты для детектирования катионов металлов и хиральных органических молекул. В результате получены многие сотни соединений – в том числе производные диазакраун-эфиров и тетраазамакроциклов (циклен и циклам), структуры с эндоциклическими ароматическими и гетероароматическими фрагментами. Роль палладий-катализируемого аминирования – ключевого процесса в синтезе всего многообразия такого рода соединений – невозможно переоценить.

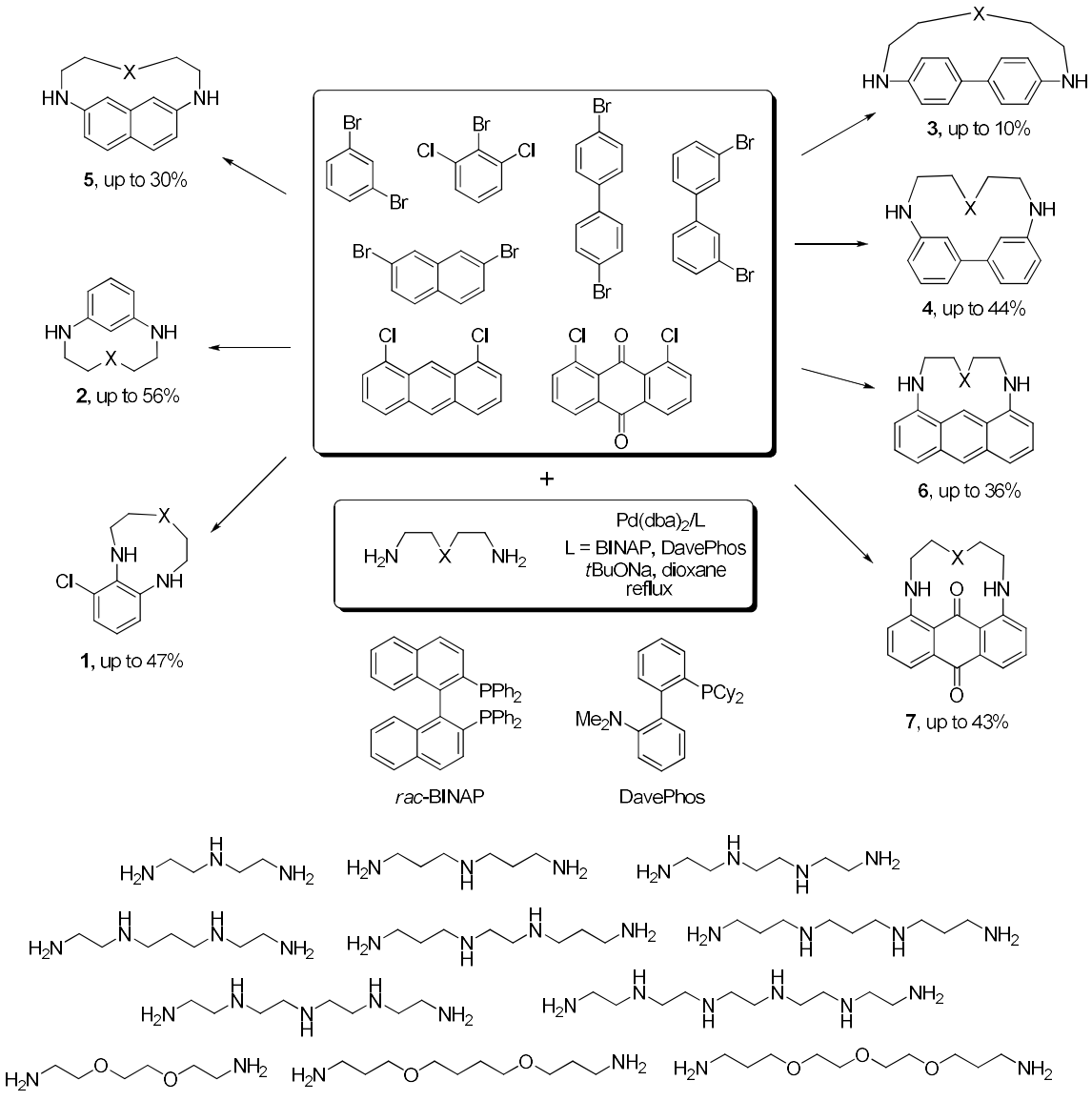
Ключевые слова: Макроциклы, криптанды, полиамины, катализ комплексами палладия, аминирование, хиральность.

Introduction

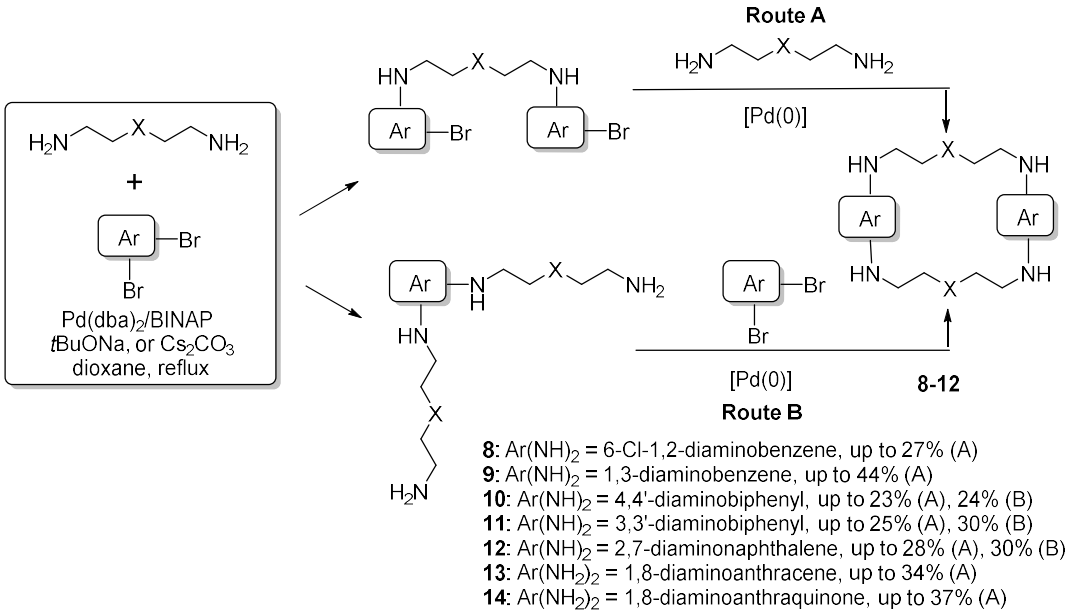
Palladium-catalyzed amination of aryl halides has become a veritable and powerful tool for constructing C(sp^2)-N bonds and its wide applications are well documented dealing with various aspects of this method.[1-3] First reported in mid-1990s,[4,5] aryl halides amination began its rapid development and after several years material was plenty enough to be summarized in the first reviews.[6,7] I. P. Beletskaya who was among the pioneers of this method,[8] has focused with coworkers on the problem of the arylation of di- and polyamines and in the first publications selective arylation of primary amino groups in the presence of secondary amino groups in linear polyamines was firmly established.[9,10] This important property was crucial for the application of linear polyamines in the Pd(0)-catalyzed intramolecular amination reaction using polyamines to form macrocyclic compounds. Also the search for the conditions of the diamination of dihaloarenes was carried out, the appropriate phosphine ligand BINAP (2,2'-bis(diphenyl-phosphino)-1,1'-binaphthalene) was shown to be most universal for this task,[11,12] and the path for the macrocycles synthesis was thus trailed.

1. Macrocycles with aryl endocyclic moieties

At the first stage of our research the synthesis of simple macrocycles based on diaminobenzene was undertaken. For this purpose a panel of polyamines and oxadiamines was used. These compounds differ in the chain length, number of internal nitrogen and oxygen atoms and by the number of methylene groups separating *N* and *O* atoms. The reactions were run using either $Pd(dba)_2$/BINAP (dba = dibenzylideneacetone) or $Pd(dba)_2$/DavePhos catalytic systems (Scheme 1).



Scheme 1. Synthesis of the macrocycles **1-7** comprising aryl endocyclic fragments.



Scheme 2. Synthesis of the cyclic dimers **8-12** comprising aryl endocyclic fragments.

Enough dilute solutions of the starting compounds in dioxane (C = 0.02 M in most cases) were needed to suppress the formation of oligomers due to intermolecular amination, *t*BuONa was employed as a base. In all cases target macrocycles were isolated using chromatography on silica gel. The reactions with the 1,2-dibromobenzene in view of forming benzoannelated azacrown ethers were not successful resulting in 12-14% yields of the desired compounds but the use of 1-bromo-2,6-dichlorobenzene was much more encouraging and it afforded macrocycles **1** in yields up to 47%.[13,14] Such result is very important for the macrocyclization reactions without any additional template. Even better yields of the macrocycles **2** (up to 56%) were achieved with 1,3-dibromobenzene, as the substitution of the first bromine did not alter seriously the reactivity of the second resting halogen atom.[15] Macrocycles **3** from 4,4'-dibromobiphenyl could be obtained only with the oxadi-amines possessing the longest chain and the result was more than modest due to geometrical reasons.[16] On contrary, an isomeric 3,3'-dibromobiphenyl gave enough high yields of the macrocycles **4**,[17] as was the case also with the compounds **5** based on 2,7-diaminonaphthalene.[18] Unexpectedly the chlorine atoms in 1,8-disubstituted anthracene and anthraquinone were found to be quite reactive, comparable with the bromine atoms, and corresponding macrocycles **6** and **7** were obtained in yields up to 36-43%.[19-21] Note that the amination of 1,8-dichloroanthraquinone demanded the use of a weaker base Cs_2CO_3. Not only linear diamines and polyamines were introduced in the described macrocyclization reactions, the ability of the diamines of the basis of 1,3-disubstituted adamantane to form macrocycles with a variety of dibromoarenes was equally shown.[22,23]

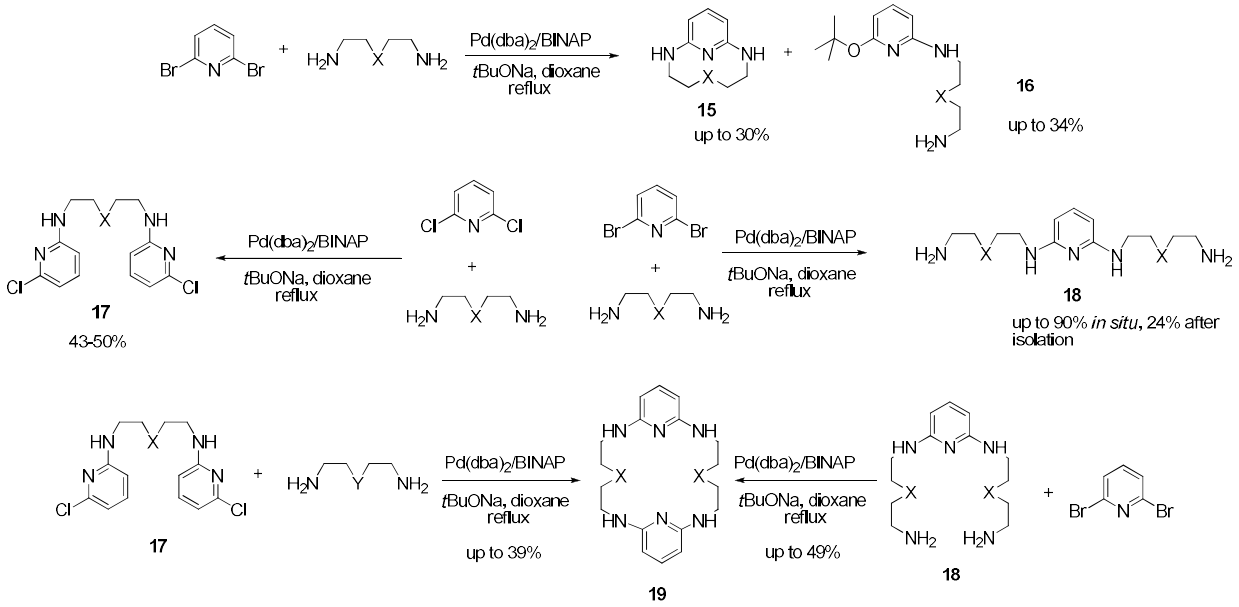
In many cases cyclic dimers and oligomers were obtained as side products. Taking into consideration that the cyclic dimers are interesting possessing larger cavities, two alternative approaches to their synthesis were elaborated (Scheme 2). Route A consists of two steps: the first is the synthesis of *N*,*N*'-bis(bromoaryl)substituted polyamines or oxadiamines, the second is the macrocyclization reaction with the polyamine (oxadiamine) compound leading to a cyclic dimer. Route B envisages the formation of bis(polyamino) substituted arene with a subsequent reaction with dibromoarene. All these steps are palladium-catalyzed; method A was shown to be more efficient when isolating intermediate *N,N'*-bis(bromoaryl)substituted polyamines while method B is more convenient as *in situ* formed bis(polyamine) derivatives can be introduced in the macrocyclization reaction. Cyclic dimers **8-14** comprising phenylenediamine,[15] diaminobiphenyl,[24] diaiminonaphthalene,[25] diaminoanthracene and diaminoanthraquinone[26,27] moieties were synthesized using this methodology, their yields were shown to reach 30% and more in the best cases, and when routes A and B were compared, no great difference in these two approaches was noted. However, in certain cases route B did not lead to desired products as it was the case with the derivatives of anthracene and anthraquinone, moreover, isolated bis(polyamino) substituted arenes often were much less reactive than obtained *in situ*.

2. Macrocycles with heteroaryl endocyclic moieties

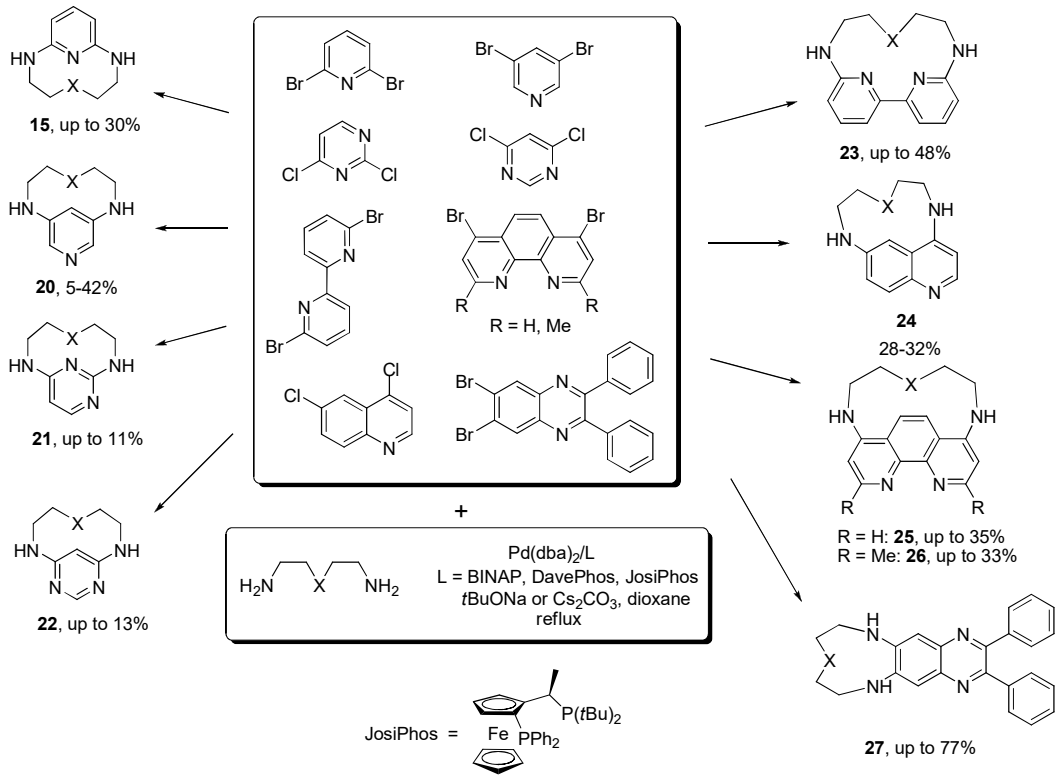
Next, the possibilities of the synthesis of macrocycles comprising *N*-heterocyclic moieties were studied. It was attractive due to the fact that these heterocyclic fragments possess nitrogen atoms which can serve as additional coordination sites. For this purpose the Pd-catalyzed macrocyclization reactions using 2,6-dihalopyridines were investigated. It was shown that 2,6-dibromopyridine was more reactive than its 2,6-dichloro analogue, the corresponding macrocycles **15** were obtained in yields up to 30%, however, due to high reactivity of C-Br bond in this compound, the target reaction proceeded along with the side process of the non-catalytic substitution of the bromine atom for *tert*-butoxy group giving rise to second non-cyclic

polyamine derivatives **16** with comparable yields (Scheme 3).[28,29] Unfortunately it was impossible to eliminate this process by changing *t*BuONa for a weaker base.

The investigation of the most reliable way to cyclic dimers included the synthesis of intermediate *N,N'*-bis(6-halogenopyridin-2-yl)substituted polyamines **17** and 2,6-bis(polyamino)substituted pyridines **18**.[29,30] While the second reaction was successful using 2,6-dibromopyridine, the first one proved to be efficient with 2,6-dichloropyridine due to less amount of undesirable side products. Two routes for cyclic dimers **19** were tried and it was found that both provided rather good yields of the target compounds (up to 39% *via* **17** and up to 49% *via* **18**) provided that diheteroaryl derivatives **17** were used after isolation by column chromatography and bis(polyamino) derivatives **18** were employed *in situ*. Though in general the yields of the cyclic dimers **19** are higher by the approach using bis(polyamino) derivatives **18**, the reaction *via* **17** can provide unsymmetrical macrocycles possessing two different polyamine chains.



Scheme 3. Synthesis of the macrocycles possessing 2,6-diaminopyridine moieties.



Scheme 4. Synthesis of the macrocycles possessing various heterocyclic moieties.

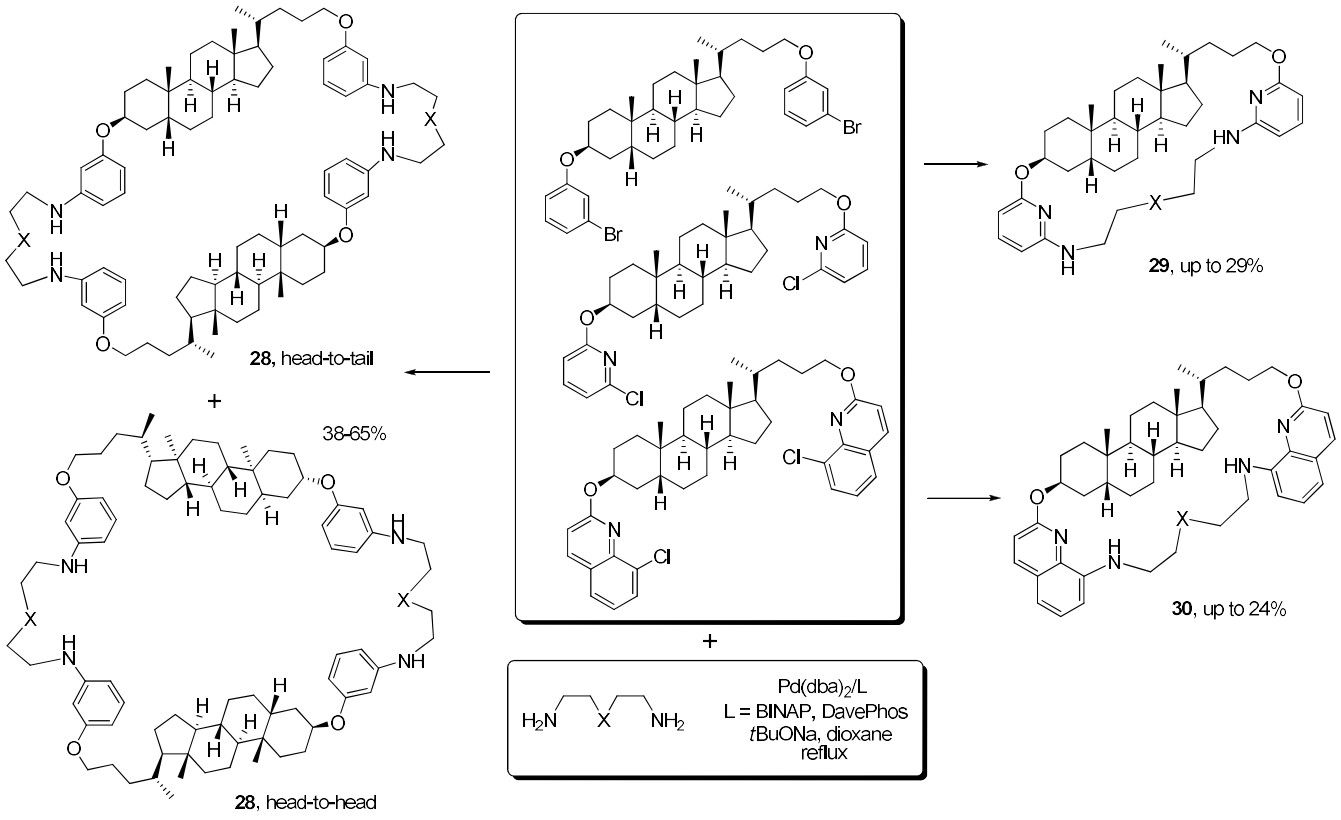
In the similar reactions with the isomeric 3,5-dibromopyridine corresponding macrocycles **20** were obtained (Scheme 4).[31,32] Their yields ranged from 5 to 42% depending on the nature of polyamines. These macrocycles are interesting due to an *exo*-orientation of the heteroaromatic nitrogen atom (in above-described macrocycles **15** they are *endo*-oriented) what can result in a different coordination mode with metal cations. Other macrocycles containing two heteroaromatic nitrogen atoms were obtained by the macrocyclization of 2,4- and 4,6-dichloropyrimidines. Though the reactivity of the chlorine atoms are high in these starting compounds, the yields of the corresponding macrocycles **21** and **22** with several oxadiamines reached only 11-13% due to the inevitable formation of linear *N,N'*-di(heteroaryl) substituted derivatives.

Involving 6,6'-dibromo-2,2'-bipyridine in the macrocyclization reaction with oxadiamines and polyamines results in the macrocycles **23** (Scheme 4).[33] The yields of the macrocycles **23** attained 48%, these compounds present interest to coordination studies as the molecules possess nitrogen atoms of different nature (aliphatic amino groups and heteroaromatic nitrogen atoms). The attempts to synthesize unsymmetrical macrocycles employing various dihalogenoquinolines were mainly unsuccessful due to different reactivity of the halogens at different positions of quinoline, and only 4,6-dichloroquinoline was found to be enough suitable for this purpose.[34] Provided DavePhos was used as a ligand, reaction with oxadiamines afforded corresponding macrocycles **24** in good 28-32% yields. These compounds were found to be interesting for spectrophotometric and fluorescent detection of Cu^{II} and Al^{III} cations.

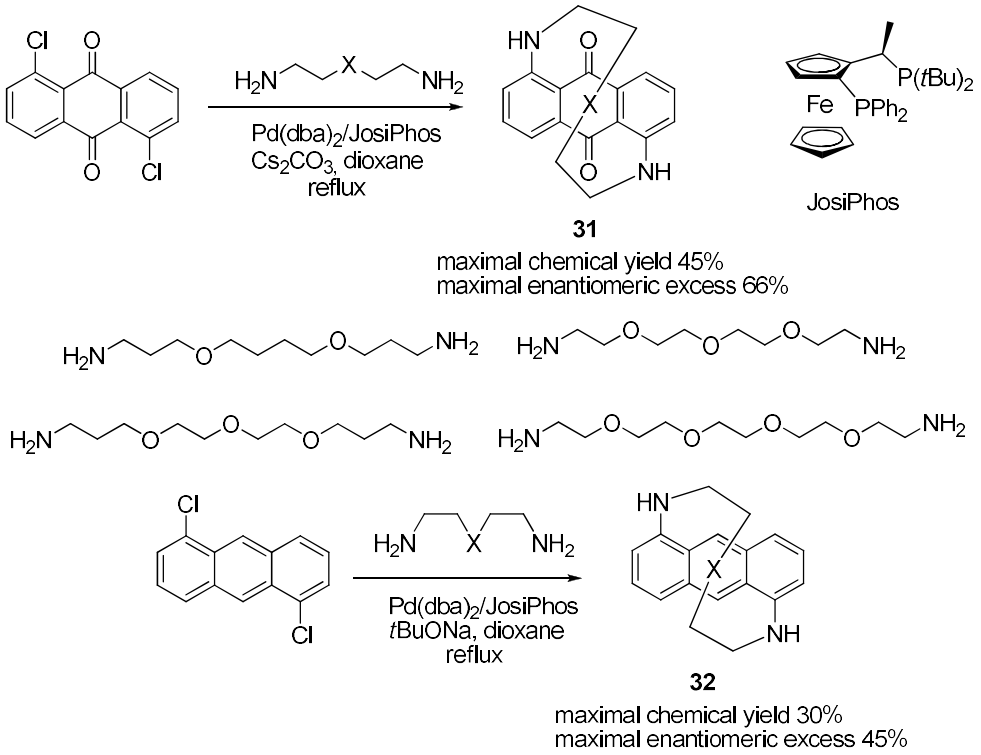
The macrocyclization reactions with more sophisticated dihaloheteroarenes demanded a tedious adjustment of the reaction conditions.[35] Thus, 4,7-dibromo-1,10-phenanthroline and its 2,9-dimethylsubstituted analogue were successfully transformed in the corresponding ditopic macrocyclic ligands **25** and **26** (in yields up to 35%) by using a special ligand JosiPhos, a 1,2-derivative of ferrocene, for the majority of polyamines, in the presence of a weaker base Cs_2CO_3. The reactions of 6,7-dibromo-2,3-diphenylquinoxaline with the oxadiamines could be carried out in the presence of BINAP ligand, but the reactions with polyamines again demanded the application of JosiPhos. It provided high yields of the macrocycles **27** (up to 77%).[36]

3. Macrocycles with chiral structural fragments

A series of macrocyclic compounds with a chiral backbone was synthesized employing 3,24-di(halogenoaryl) substituted cholane-3,24-diol (Scheme 5). Depending on the nature of halogeno(hetero)aryl spacers different products were obtained. Macrocycles **28** synthesized from 3,24-di(3-bromophenyl) derivative were formed as mixtures of cyclic dimers (head-to-tail and head-to-head regioisomers), their yields ranged from 38 to 65%.[37,38] The reactions with di(6-bromopyridin-2-yl) derivatives favoured the formation of macrocycles **29** of 1:1 composition though their yields were lower and did not surpass 29%.[39] At the same time, the yields of the mixtures of cyclic oligomers attained 71%. To involve 8-chloroquinolin-2-yl derivatives in the reactions with polyamines one need to use DavePhos ligand, the yields of the target macrocycles **30** ranged from 8 to 24%, and corresponding cyclic dimers were isolated in comparable 9-20% yields.[40]



Scheme 5. Synthesis of the macrocycles comprising steroidal fragments.

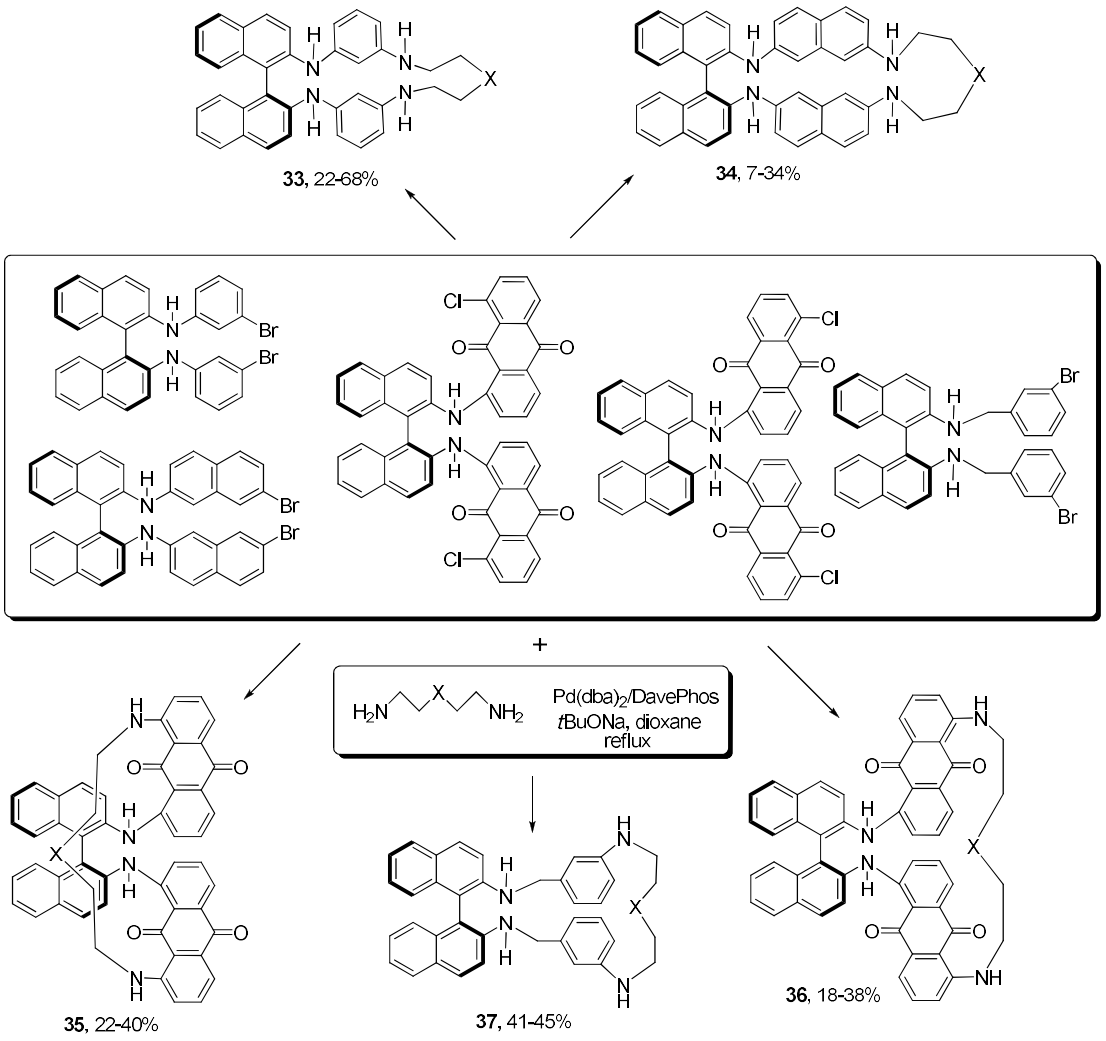


Scheme 6. Synthesis of the planar-chiral macrocycles on the basis of 1,5-disubstituted anthraquinone and anthracene.

Planar-chiral macrocycles occupy a special place in a wide panel of macrocyclic compounds. It was found to be possible to obtain a series of such macrocycles starting from 1,5-dichloroanthrquinone.[41,42] A great variety of chiral phosphine ligands were tried in this process, and the JosiPhos ligand was found to be most efficient providing best chemical yields and enantiomeric excesses of the target macrocycles **31** which reached 66% *ee* (Scheme 6). However, this reaction was limited only to oxadiamines of appropriate length. Similar reaction with 1,5-dichloroanthracene produced corresponding planar-chiral macrocycles **32**, though the yields and enantiomeric excesses were somewhat lower.

Another type of chiral macrocycles comprises various macrocyclic derivatives of (*S*)-BINAM (2,2'-diamino-1,1'-binaphthalene) possessing *C*2 chirality (Scheme 7). *N,N'*-di(halogenoaryl) derivatives of (*S*)-BINAM were obtained from a free diamine also using Pd(0)-catalyzed amination reactions, and these compounds were introduced in the catalytic macrocyclization reactions. The optimized catalytic system employed DavePhos ligand, and the best results were obtained with *N,N'*-di(3-bromopehnyl) substituted BINAM providing the yields of macrocycles **33** up to 68%.[43,44] Other chiral macrocyclic compounds contain 2,7-disubstituted naphthalene (**34**), 1,8- and 1,5-disubstituted anthraquinones (**35** and **36**) and benzyl spacers (**37**). For all structural types of stated compounds good yields in the macrocyclization reactions were observed. The obtained macrocycles were thoroughly studied as fluorescent enantioselective detectors of amino alcohols and also for metal cations sensing. The ability to distinguish between enantiomers of amino alcohols was shown to be strongly dependent on the nature of oxadiamine linkers and aryl spacers in the structure of the detectors.

Some of the (*S*)-BINAM-containing macrocycles were further modified with exocyclic fluorophore groups.[45] Thus, dansyl fluorophores (dansylamide = 5-dimethylaminonaphthalene-1-sulfonamide) were introduced at alkylarylamino groups to give macrocycles **38** and **39** (Figure 1). The yields of the dansylated derivatives ranged from rather low to almost quantitative depending on the size of the macrocyclic cavity. Also 7-methoxycoumarin fluorophore groups were added to macrocycles providing compounds **40**. The decoration of the macrocycles with quinoline moieties was carried out *via* Pd(0)-catalyzed amination reactions using 6- or 3-bromoquinolines, and corresponding derivatives **41**-**43** were synthesized in yields up to 73%. Additional modifications of the (*S*)-BINAM based macrocycles featured the introduction of exocyclic chiral groups with central chirality (Figure 2). All these compounds were obtained using intermediate *N,N'*-di(3-bromobenzyl) derivatives of corresponding macrocycles which were then catalytically aminated with chiral amines. As a result, macrocycles **44**, **45**, **48** combining axial and central chirality in the structure were synthesized. Some of them were additionally decorated with fluorophore groups (**46**, **47**, **49**). It was interesting to compare detection abilities of the initial macrocycles with those possessing additional fluorophore and chiral groups as the latter have more coordination sites, their fluorescence is shifted to the red region and also they possess more chiral elements which can favor sensing of the chiral analytes. Equally it was important to investigate the possibilities of the Pd(0)-catalyzed amination in such sophisticated and sterically hindered compounds which was found to proceed with certain difficulties though in all cases target compounds were obtained.



Scheme 7. Synthesis of BINAM-containing macrocycles with phenylene, benzyl, napththalene and anthraquinone spacers.

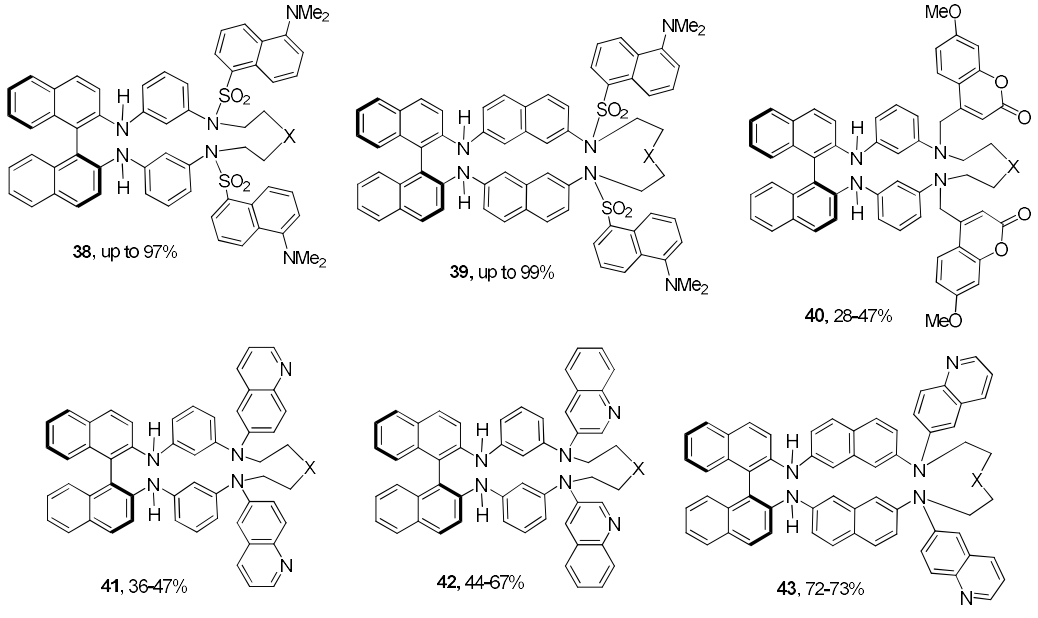


Figure 1. Derivatives of (*S*)-BINAM-containing macrocycles with additional exocyclic fluorophore groups.

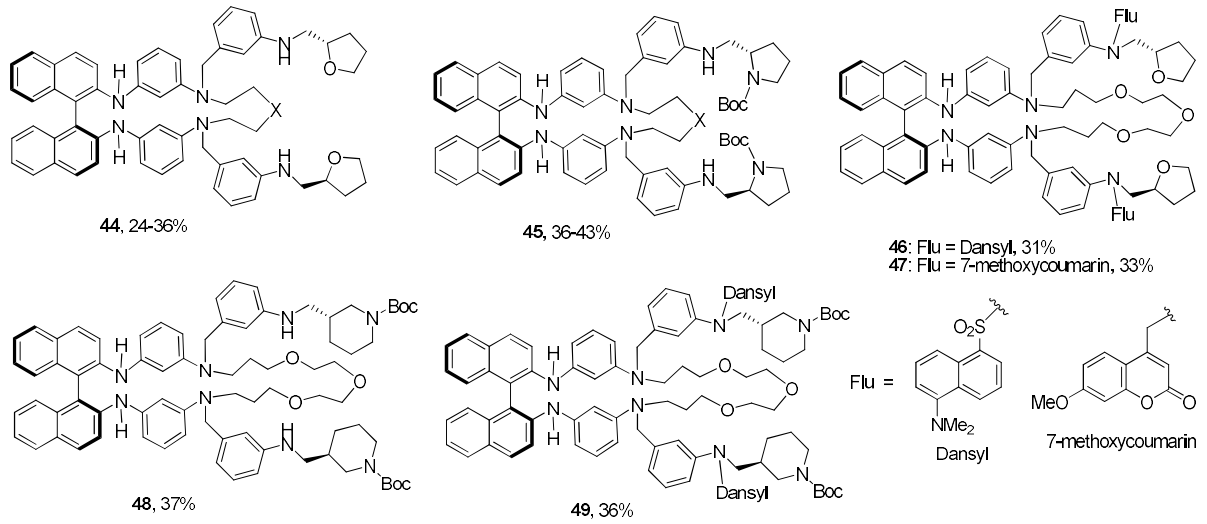
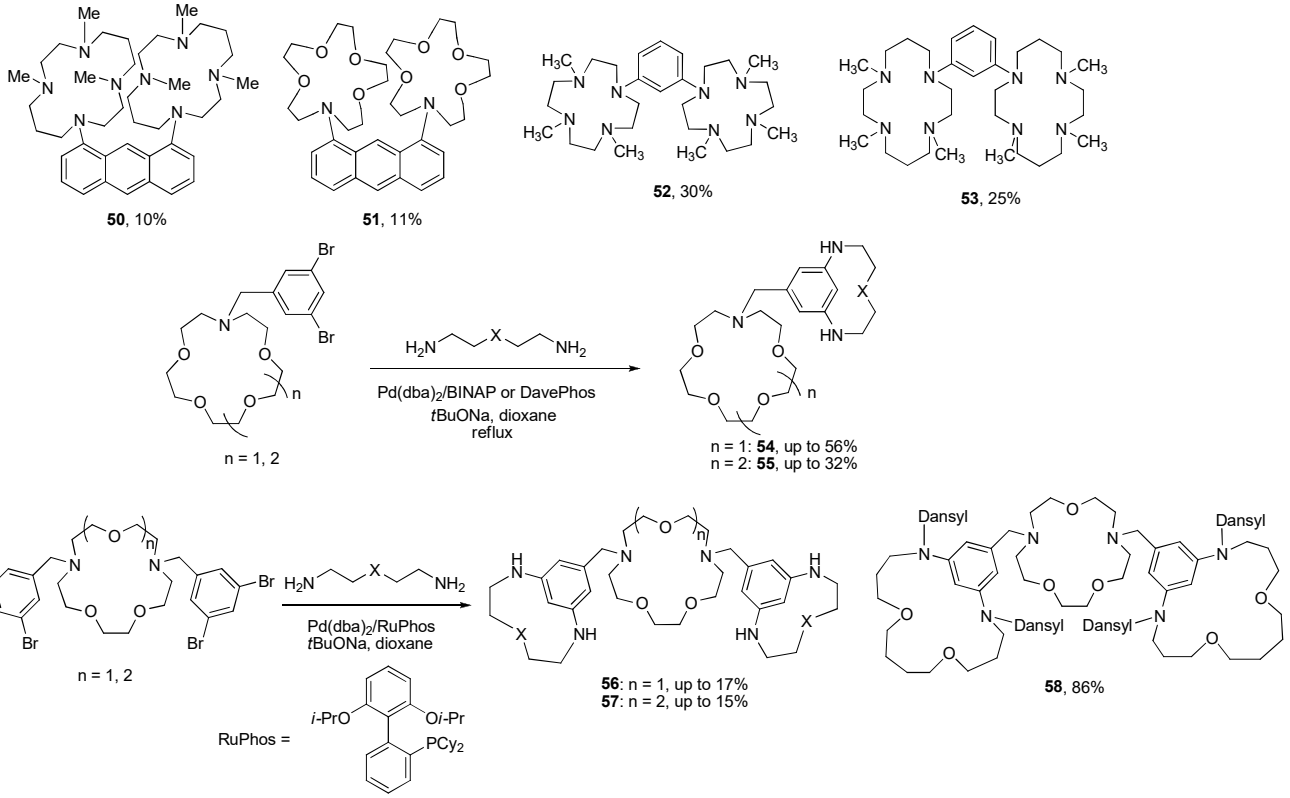


Figure 2. Derivatives of (*S*)-BINAM-containing macrocycles with additional exocyclic chiral groups.



Scheme 8. Examples of various types of bis- and trismacrocyclic compounds obtained via Pd(0)-catalyzed amination reactions.

4. Polymacrocycles

First polymacrocyclic compounds **52** and **53** with isolated macrocycles were obtained using the diamination of 1,8-dichloroanthracene in view of synthesizing molecules with face-to-face oriented *N*- and *O*-containing macrocycles.[12,46] The synthesis of these compounds demanded meticulous adjustment of the catalytic system and though target molecules were at last at hand, their yields were tiny (10-11%) (Scheme 8) and the majority of 1,8-dichloroanthracene was transformed into monoamination products with either residual chlorine atom or without it due to the side catalytic reduction. Moreover, it was possible to introduce only monoazacrown ethers and *N,N',N''*-trimethylcyclam in this reaction because parent free cyclen and cyclam led to almost full reduction of C-Cl bonds. It was due to great difficulties of the catalytic arylation of the secondary aliphatic amino groups in these substrates.

A special study was then undertaken to elucidate the problems and to find out the best catalytic system using the reactions of the simplest 1,3-dibromobenzene. Product of

diamination **50** and **51** with trimethylcyclen and trimethylcyclam, respectively, were isolated in yields up to 30 and 25%.[47] Using $Pd(dba)_2$/DavePhos catalytic system and certain dibromobenzene to amine ratio helped to partially solve the problem.

Another approach to bismacrocyclic compounds is the modification of the azacrown ethers with 3,5-dibromobenzyl group followed by the catalytic macrocyclization with various oxadiamines and polyamines (Scheme 8). It allowed the synthesis of compounds **54** and **55** varying by the size of the cavity and the number of the N and O atoms of the second macrocycles.[48,49] In some cases the yields of the products were even higher than those of monomacrocycles obtained from a parent 1,3-dibromobenzene (see Scheme 1).

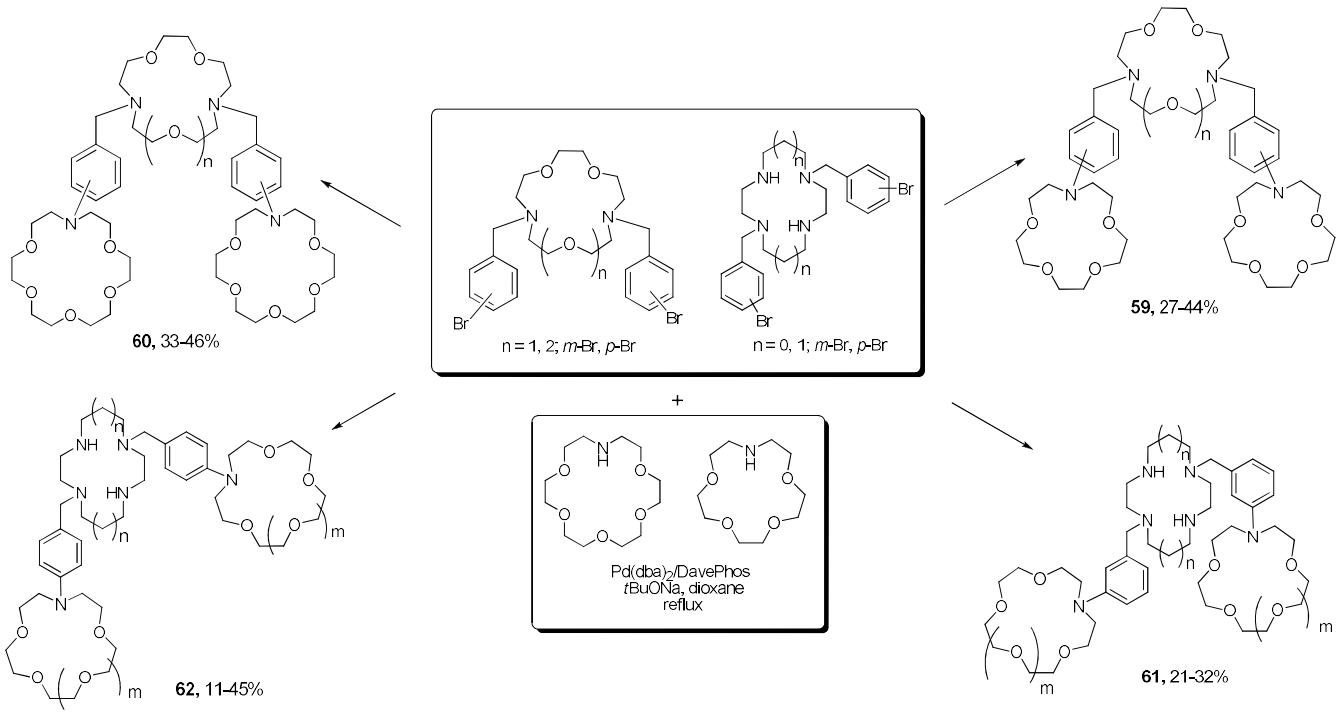
The application of the same methodology for the construction of trismacrocyclic compounds using *N,N'*-di(3,5-dibromobenzyl) derivatives of diazacrown ethers was more complicated. It was necessary to adjust the catalytic system which would allow the macrocyclization preferably involving two bromine atoms at the same arene moiety. RuPhos ligand (2,6-diisopropoxy-2'-dicyclohexylphosphinobiphenyl) was found to be the best choice and it allowed the formation of the desired trismacrocycles **56** and **57**, though in low yields (Scheme 8).[50] One of these trismacrocycles was decorated with four dansyl groups giving compound **58** which was studied for metal cations detection.

Another approach to trismacrocycles includes the modification of diazacrown ethers and tetraazamacrocycles with two bromobenzyl substituents which are able for further Pd(0)-catalyzed amination with free azacrown ethers (Scheme 9).[51,52] In all cases DavePhos should be used as a ligand, and the yields of the trismacrocycles **59-62** were found to be seriously dependent on the structure of the starting compounds: the nature of the first macrocycle, the position of the bromine atom. The main side reaction was the catalytic reduction of C-Br bond leading to monoamination products.

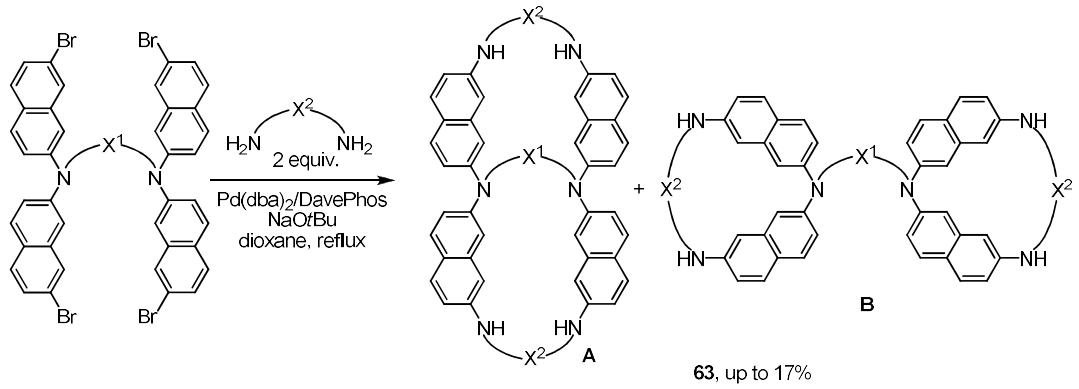
A good deal of research was dedicated to the synthesis of other types of bis-, tris- and polymacrocycles with porphyrin moieties.[53-63] All these sophisticated molecules were obtained using Pd(0)-catalyzed amination reactions. Among them are porphyrin dyads and triads which possess interesting optical properties and coordination behaviour. A series of works was aimed at the conjugation of porphyrins with macrocycles, cryptands and diaminocalix[4]arenes.[64-67] All these compounds have been recently reviewed by us[68] and will not be described here.

5. Macropolycycles (cryptands)

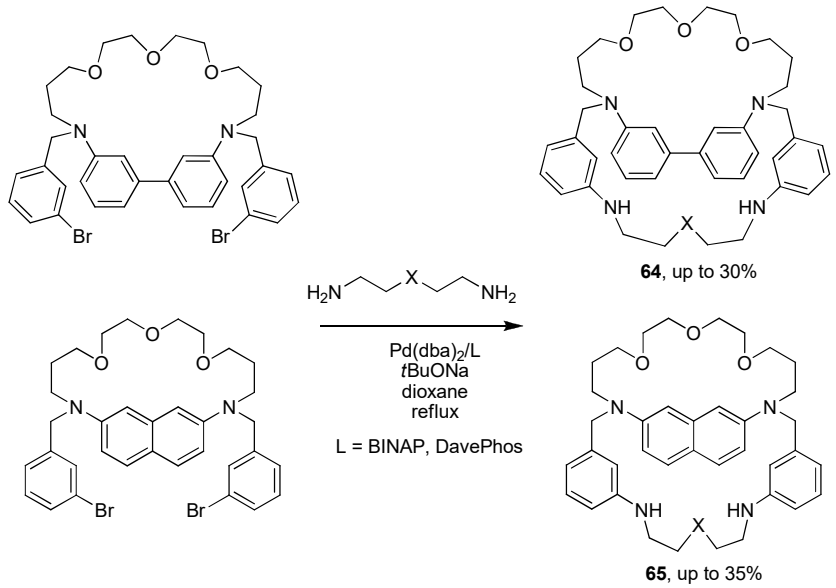
Various routes to macropolycycles (cryptands) were elaborated, each employing palladium-catalyzed amination at the macrocyclization step. On the basis of preliminary investigations which employed *N,N*-di(bromoaryl) derivatives of monoamines in the macrocyclizations reactions,[69] it was shown that a principal possibility to obtain macrobicyclic compounds **63A** from *N,N,N'N'*-tetrakis(7-bromonaphthalen-2-yl) derivatives of diamines and oxadiamines exists, though simultaneously isomeric bismacrocycles **63B** were formed. Their separation was found to be impossible by means of common chromatography, moreover, the overall outcome in the reactions was too low (Scheme 10).[70] Enough simple macrobicycles **64** and **65** were obtained from the biphenyl- and naphthalene-based macrocycles by modifying them with two 3-bromobenzyl substituents followed by the macrocyclization step (Scheme 11), and this approach was much more attractive providing yields of the corresponding cryptands up to 30-35%.[71,72]



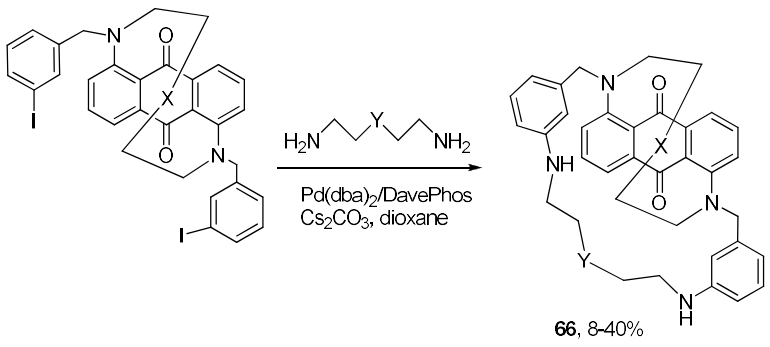
Scheme 9. Synthesis of trismacrocyclic compounds by Pd(0)-catalyzed amination reactions.



Scheme 10. Synthesis of the isomeric bismacrocyclic derivatives comprising 2,7-diaminonaphthalene moieties.



Scheme 11. Synthesis of the cryptands comprising 3,3'-diaminobiphenyl and 2,7-diaminonapthalene moieties.



Scheme 12. Synthesis of the cryptands with planar-chiral structural fragments.

It was possible to introduce planar-chiral macrocycles on the basis of 1,5-diaminoanthraquinone in the second macrocyclization reaction. For this purpose the starting macrocycles were modified with two 3-iodobenzyl substituents and subjected to Pd(0)-catalyzed macrocylization reaction in the presence of $Pd(dba)_2$/DavePhos catalytic system using Cs_2CO_3 as a base (Scheme 12).[42] The yields of unusual cryptands **66** possessing a planar chiral moiety proved to be dramatically dependent on the nature of two oxadiamine chains (initial and completed).

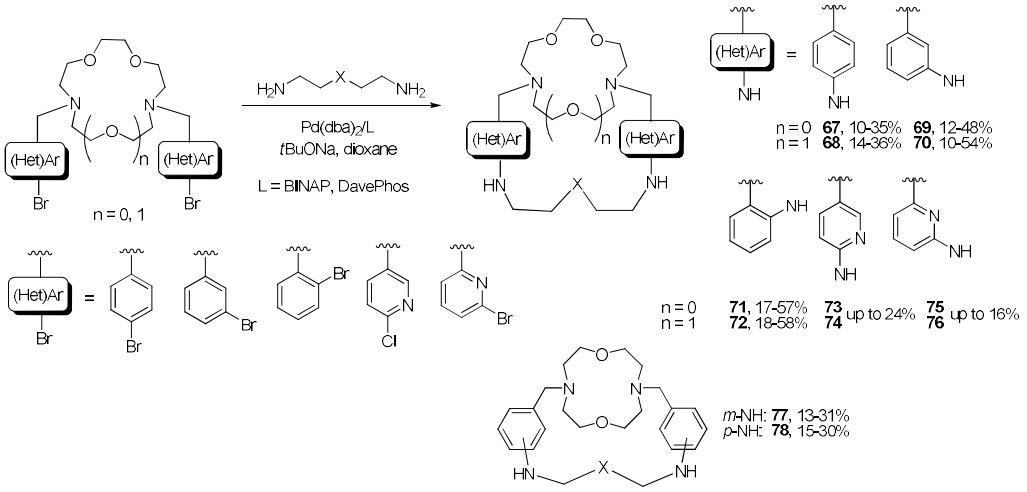
A wide series of macrobicyclic cryptands – derivatives of diazacrown ethers was synthesized using a general

method including the modification of starting *N,O*-macrocycles with halogeno(hetero)aryl substituents (Scheme 13).[66,73,74] Various derivatives of diazacrown ethers were obtained for this purpose which contain *para*-, *meta*- and *ortho*-bromobenzyl groups, chloro- and bromopyridinylmethyl groups. The Pd(0)-catalyzed macrocyclization reactions with polyamines were enough successful, however, the yields of the desired cryptands were different depending on the nature of starting compounds. Cryptands **67-72** with benzyl spacers were obtained in notably higher yields (up to 58%) than those with pyridine-containing spacers **73-76**. In some cases interesting macrotricyclic dimers were isolated. To note, cryptands **77**, **78** with a smaller central diaza-12-crown-4 moiety were synthesized according to this general approach.

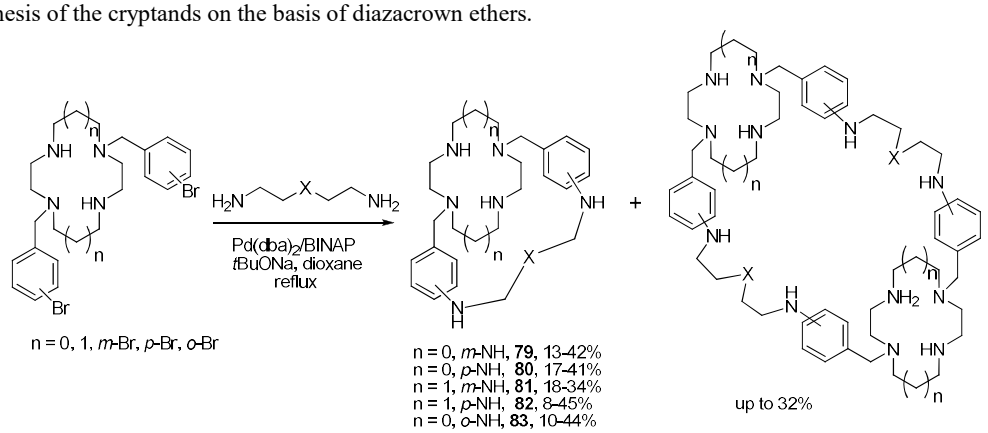
The same method was applied to the synthesis of the cryptands based on cyclen and cyclam (Scheme 14).[75,76] The yields of the macrobicycles **79-83** in the best cases surpassed 40% and second products in the macrocyclization reactions, *i.e.* macrotricycles were isolated in several cases. As in the case with diazacrown ethers, the cryptands **84-87** possessing pyridine spacers were also synthesized but generally in lower yields (Scheme 15).[77] It was shown possible to introduce naphthalene as a spacer which afforded macrobicycles **88**.[78] These compounds possess more interesting fluorescent properties.

After encouraging results with the macrocyclization reactions of disubstituted tetraazamacrocycles, the extension of the method to tetrasubstituted cyclen and cyclam was an obvious step. Corresponding compounds bearing four benzyl substituents with two bromine atoms at different positions were reacted with a variety of oxadiamines and polyamines to produce macrobicycles **89-92** (Scheme 16).[79] Better yields (up to 31%) were obtained, as usually, with the derivatives of cyclen. In many cases corresponding macrotricyclic cyclodimers were isolated as well, though their yields were lower (up to 20%). Tetraazamacrocycles were also modified with 2-pyrimidyl substituents to increase the number of nitrogen atoms and, consequently, the amount of possible coordination sites. These di(bromobenzyl)-di(pyrimid-2-yl) derivatives of cyclen and cyclam were introduced in the Pd(0)-catalyzed macrocyclization reactions to afford corresponding cryptands **93** and **94** in yields up to 31% (Scheme 16).[80] It is to be noted that in general macrocyclization reactions with tetrasubstituted cyclen and cyclam gave somewhat lower yields than corresponding disubstituted tatraazamacrocycles, obviously due to steric hindrances.

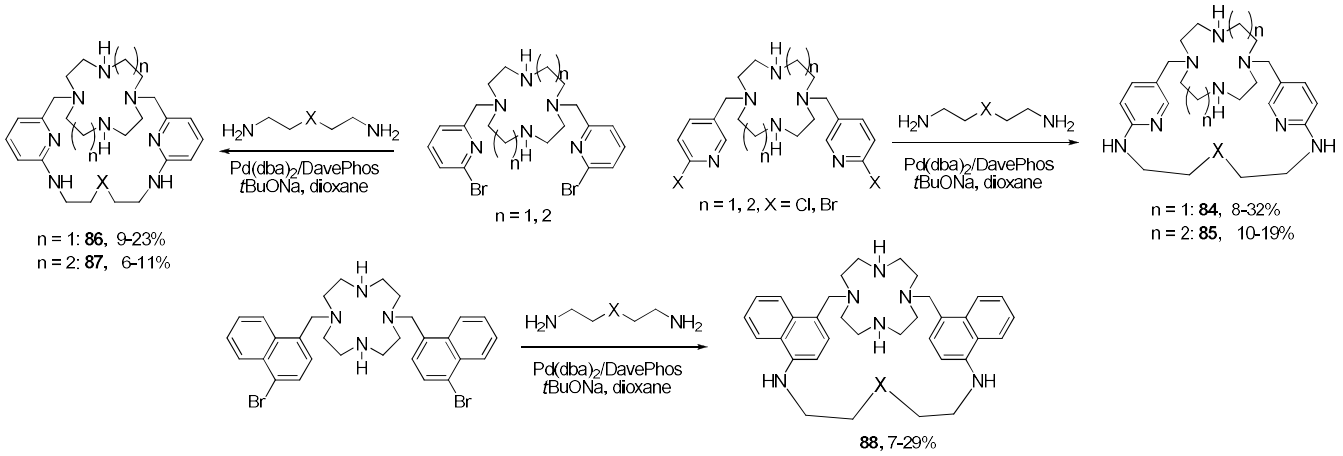
Several tetrasubstituted cyclams bearing additional benzyl, 2-naphthyl and 4-biphenyl substituents were tried for the synthesis of planar chiral macrobicycles. For this purpose diamines with short chains were used which would not allow to rotate around the central plane of the cyclam macrocycle (Scheme 16).[81] Various chiral phosphine ligands of the JosiPhos family were tested, three of them proved to be efficient to produce good chemical yields of the macrobicycles **95-97** (up to 50%), though enantiomeric excess was low and did not surpass 13%.



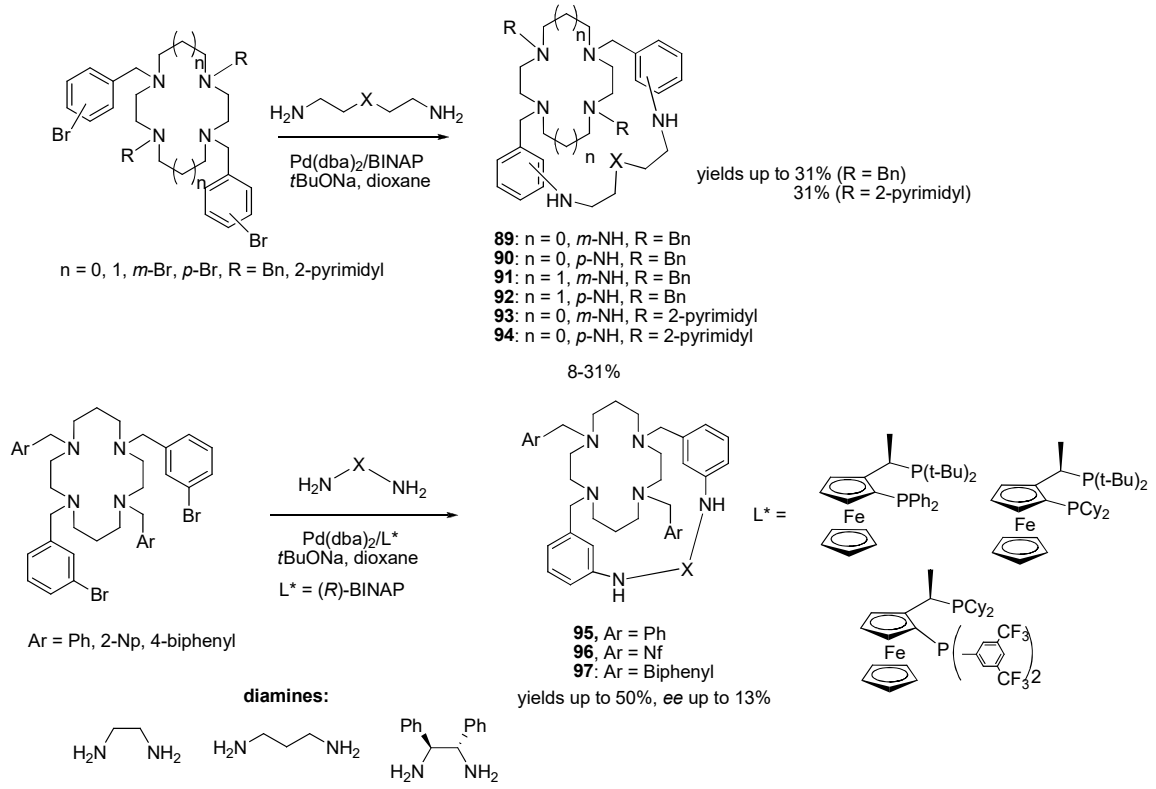
Scheme 13. Synthesis of the cryptands on the basis of diazacrown ethers.



Scheme 14. Synthesis of the cryptands on the basis of disubstituted tetraazamacrocycles.



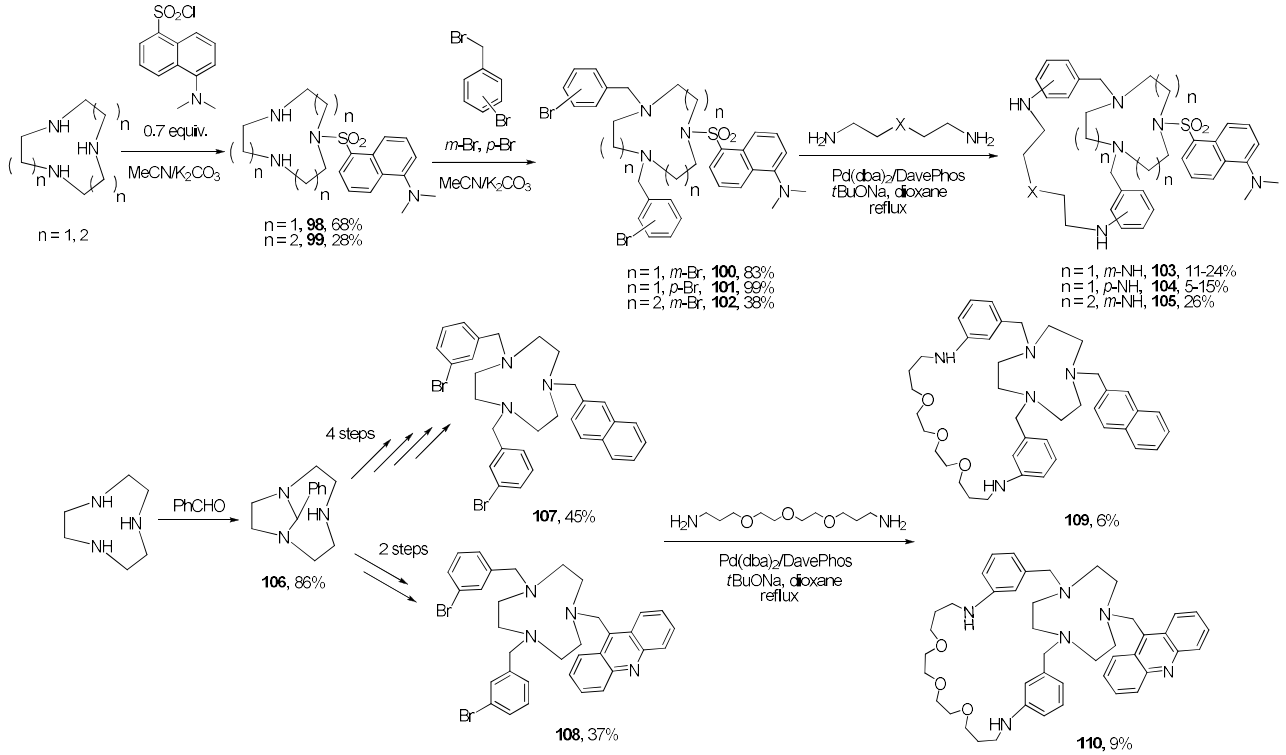
Scheme 15. Synthesis of the cryptands on the basis of disubstituted tetraazamacrocycles.



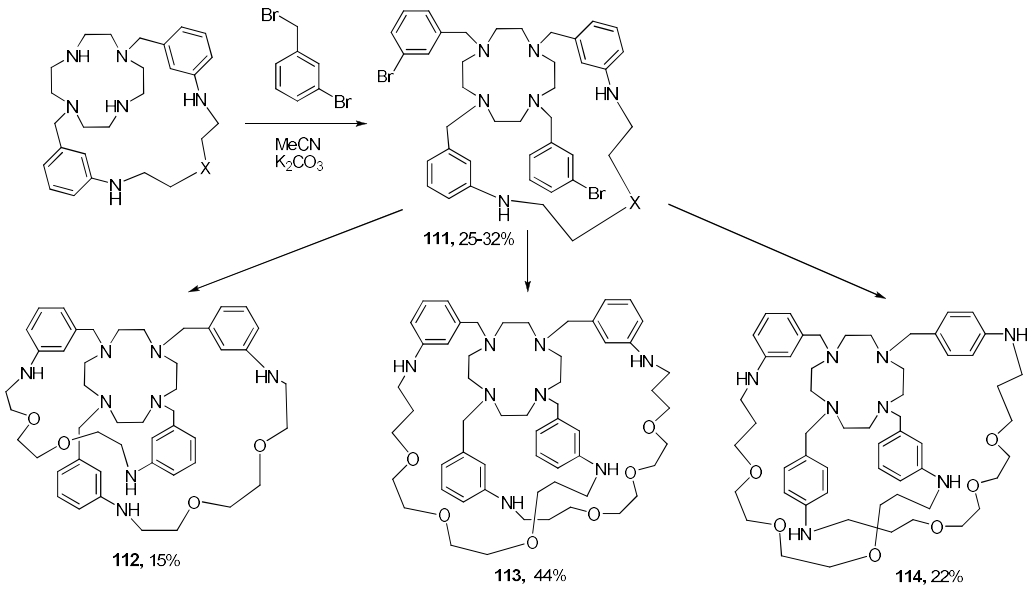
Scheme 16. Synthesis of the cryptands on the basis of tetrasubstituted tetraazamacrocycles.

Another series of cryptands decorated with the dansyl fluorophore groups (dansyl = 5-dimethylaminonaphthalene-1-sulphonyl) were synthesized on the basis of 1,4,7-triazacyclononane (TACN) and 1,5,9-triazacyclododecane (TACD) (Scheme 17). Starting free triazacycles were provided with one dansyl moiety, then compounds **98** and **99** were modified with two bromobenzyl groups, and resulting compounds **100-102** were introduced in the Pd(0)-catalyzed macrocyclization with various oxadiamines. DavePhos ligand was crucial for this process to proceed, but the yields of desired cryptands **103-105** were not high and reached only 26% in the best case.[82] It was also interesting to try the possibility to obtain similar cryptands with methylnaphth-2-yl and acridin-9-yl substituents which, as dansyl in the previous series of compounds, also serve as fluorophore substituents. The essential difference of this approach from the described above is the use of the protected TACN **106**; macrocyclization steps were difficult to carry out, and the yields of the target cryptands **109** and **110** were low.[83]

More sophisticated spherically-shaped macrotrycyclic cryptands were synthesized on the basis of cyclen (Scheme 18). Initial macrobicycles (synthesized according to Scheme 14) were modified with 3-bromobenzyl substituents and then the second macrocyclization step was carried out. Compounds **112-114** were isolated in rather good yields up to 44%), however, the outcome of the reactions was strongly dependent on the nature of both reagents.[84]



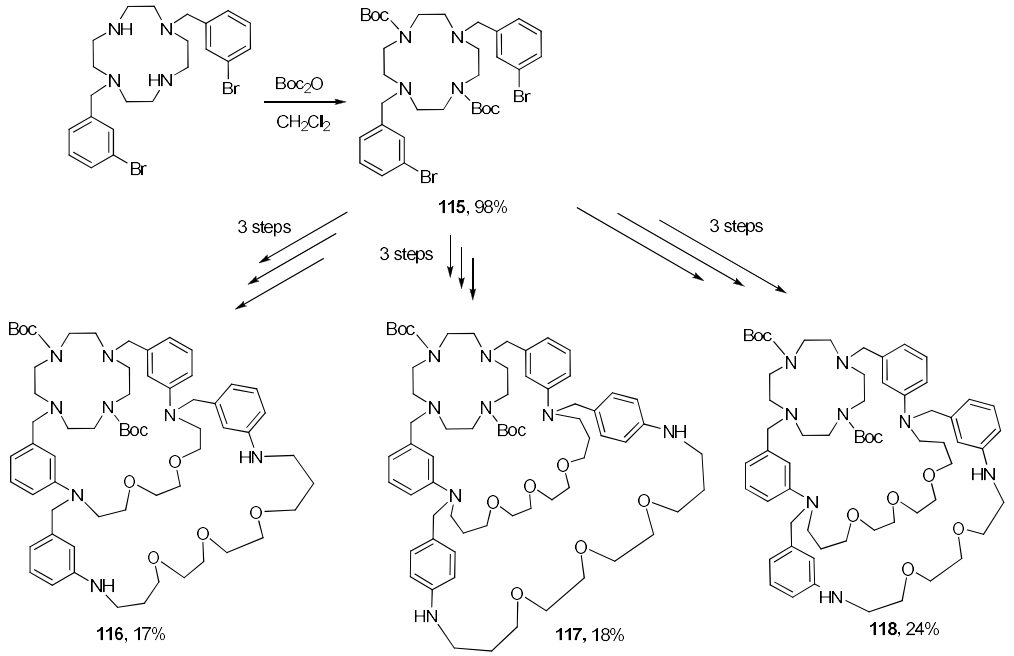
Scheme 17. Synthesis of the cryptands comprising 1,4,9-triazacyclononane and 1,5,9-triazacyclododecane.



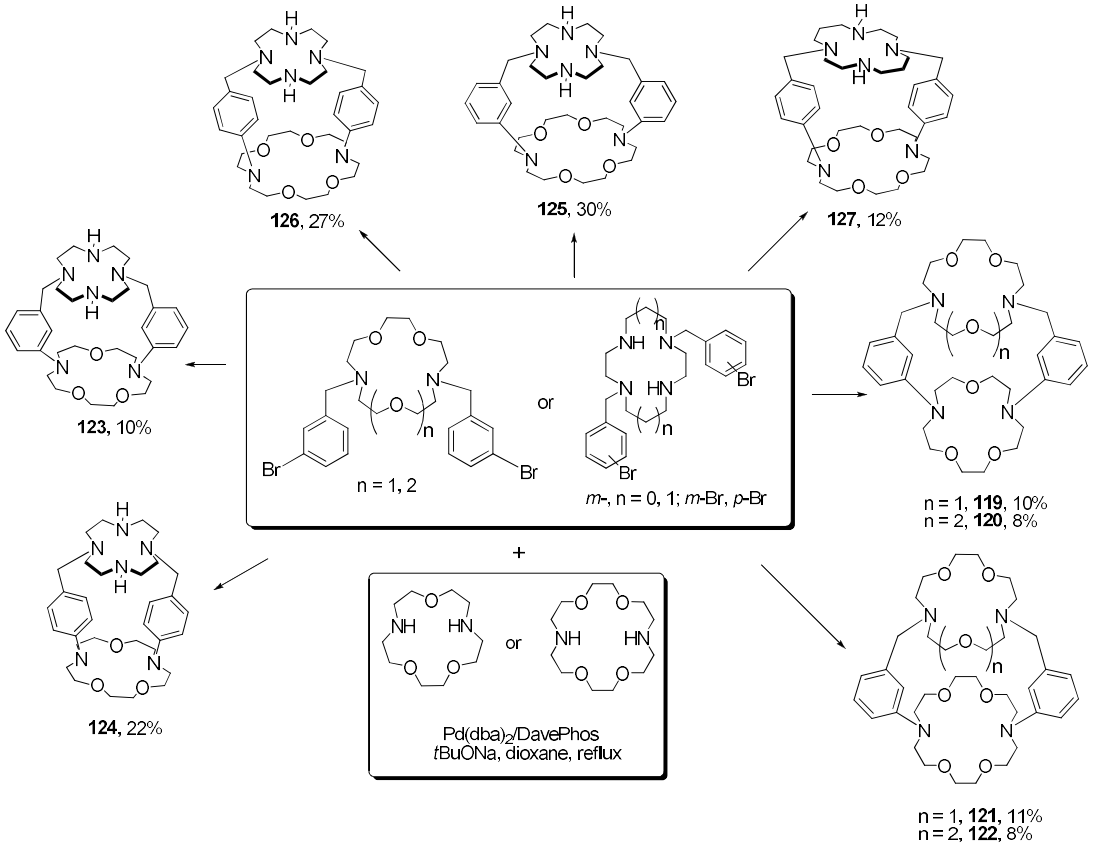
Scheme 18. Synthesis of the macrotricyclic cryptands– derivatives of cyclen.

An alternative route to macrotricycles is the use of N,N'-diBoc-protected di(3-bromobenzyl) cyclen **115** (Scheme 19). This compound was first introduced in the macrocyclization reactions with oxadiamines to produce corresponding macrobicycles, then they were again modified with two 3-bromobenzyl substituents, and the second macrocyclization was carried out. Thus macrotricyclic cryptands **116-118** were obtained.[84] It is important that the approaches to macrotricycles depicted on Scheme 18 and 19 are possible only with oxadiamines because they include the introduction of bromobenzyl substituents at the intermediate steps and this excludes the application of polyamines containing secondary amino groups.

Cylindrically-shaped macrotricyclic cryptands were obtained according to a one-step procedure starting from di(bromobenzyl)substituted diazacrown ethers and tetraazamacrocycles (Scheme 20). The reactions with free diazacrown ethers were catalysed with $Pd(dba)_2$/DavePhos system, the yields of the products with cyclen **123-126** were the best among others; the reactions of diazacrown derivatives with diazacrown ethers were enough reluctant.[85]

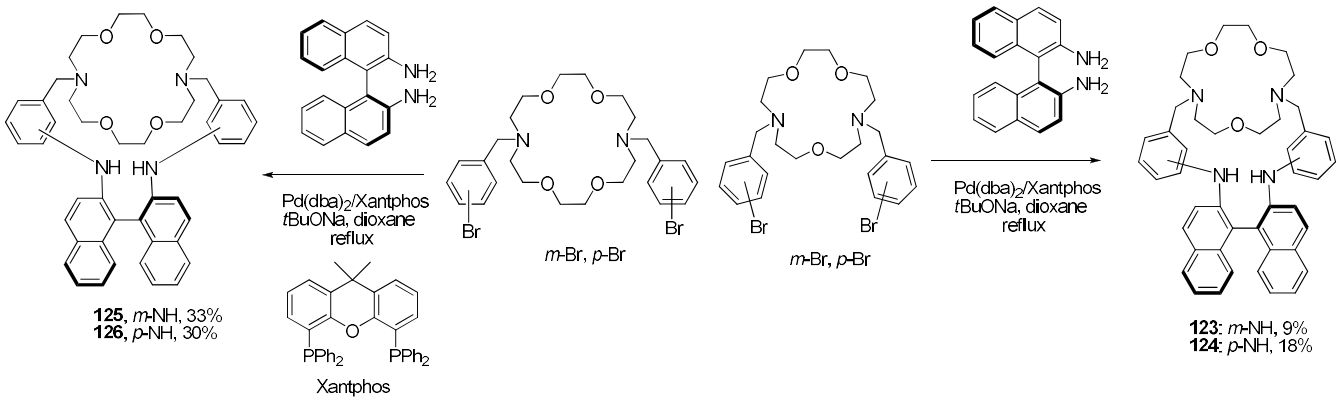


Scheme 19. Synthesis of the macrotricyclic cryptands – derivatives of diBoccyclen.

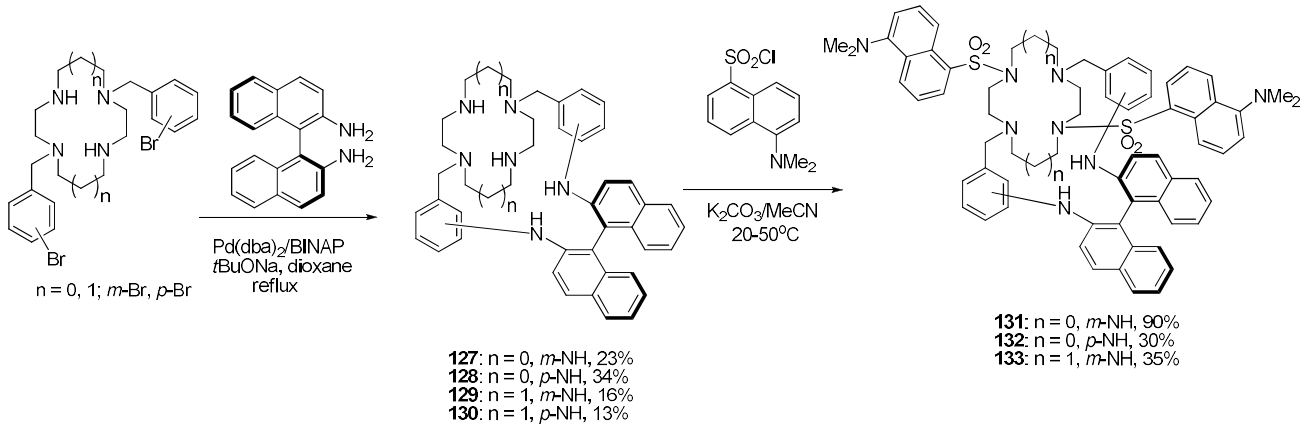


Scheme 20. Synthesis of cylindrically-shaped macrotricyclic derivatives of diazacrown ethers and tetraazamacrocycles.

Chiral cryptands possessing (*S*)-BINAM moieties **123-126** were obtained by the reactions of di(bromobenzyl) derivatives of diazacrown ethers with free (*S*)-BINAM in the presence of $Pd(dba)_2$/Xantphos (Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene) (Scheme 21).[86] Better yields were observed for the derivatives of a larger diaza-18-crown-6, probably due to better reciprocal positions of the damino groups in free BINAM and two bromine atoms in the diazacrown derivative.



Scheme 21. Synthesis of the cryptands incorporating BINAM and diazacrown moieties.



Scheme 22. Synthesis of the cryptands on the basis of BINAM and cyclen or cyclam.

Analogous reaction was carried out for the bromobenzyl derivatives of cyclen and cyclam (Scheme 22), again better yields of the chiral cryptands were obtained in the case of cyclen-based compounds **127** and **128**.[87] It was possible to introduce two dansyl fluorophores in the cryptands; it is notable that in one case the reaction proceeded smoothly and provided compound **131** in almost quantitative yield, in two other cases (derivatives **132** and **133**) it was more difficult, possibly to more steric hindrances at the cyclic secondary amino groups.

Conclusions

To conclude, the elaborated general approach to macrocyclic and polymacrocyclic compounds utilizing Pd(0)-catalyzed amination reactions proved to be very convenient and allowed the synthesis of hundreds of new compounds. They vary in their architecture, composition, possess various valuable aromatic and heteroaromatic endocyclic moieties. Many of them have already proved to be interesting hosts for metal cations, those containing fluorophore groups may serve as fluorescent chemosensors and molecular probes. Also the syntheses of various chiral macrocyclic compounds including chiral cryptands were elaborated, they are being studied now as enantioselective detectors of organic molecules. Many regularities of the catalytic macrocyclization reactions were revealed, scope and limitations for various reagents were disclosed. The possibilities of further modifications of the macrocyclic compounds were studied and the data obtained are used now for the synthesis of new molecules.

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References

1. Ruiz-Castillo P., Buchwald S.L. *Chem. Rev*. **2016**, *116*, 12564–12649.
2. Heravi M.M., Kheilkordi Z., Zadsirjan V., Heydari M., Malmir M. *J. Organomet. Chem.* **2018**, *861*, 17–104.
3. Dorel R., Grugel C.P., Haydl A.M. *Angew. Chem. Int. Ed*. **2019**, *58*, 17118–17129.
4. Guram A.S., Rennels R.A., Buchwald S.L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.
5. Louie J., Hartwig J.F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
6. Yang B., Buchwald S.L. *J. Organomet. Chem*. **1999**, *576*, 125–146.

7. Hartwig J.F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067.
8. Davydov D.V., Beletskaya I.P. *Russ. Chem. Bull.* **1995**, *44*, 1141–1141.
9. Guilard R., Bessmertnykh A.G., Beletskaya I.P. *Tetrahedron Lett*. **1997**, *38*, 2287–2290.
10. Beletskaya I.P., Bessmertnykh A.G., Guilard R. *Synlett* **1999**, *1999*, 1459–1461.
11. Wolfe J.P., Tomori H., Sadighi J.P., Yin J., Buchwald S.L. *J. Org. Chem*. **2000**, *65*, 1158–1174.
12. Beletskaya I.P., Bessmertnykh A.G., Averin A.D., Denat F., Guilard R. *Eur. J. Org. Chem*. **2005**, *2005*, 261–280.
13. Averin A.D., Shukhaev A.V., Buryak A.K., Beletskaya I.P. *Russ. J. Org. Chem.* **2009**, *45*, 1353–1364.
14. Beletskaya I.P., Averin A.D., Borisenko A.A., Denat F., Guilard R. *Tetrahedron Lett.* **2003**, *44*, 1433–1435.
15. Averin A.D., Shukhaev A.V., Golub S.L., Buryak A.K., Beletskaya I.P. *Synthesis* **2007**, *2007*, 2995–3012.
16. Averin A.D., Uglov A.N., Buryak A.K., Beletskaya I.P. *Mendeleev Commun.* **2010**, *20*, 1–3.
17. Averin A.D., Uglov A.N., Buryak A.K., Beletskaya I.P. *Macroheterocycles* **2009**, *2*, 275–280.
18. Averin A.D., Uglov A.N., Beletskaya I.P. *Chem. Lett.* **2008**, *37*, 1074–1075.
19. Beletskaya I.P., Averin A.D., Bessmertnykh A.G., Guilard R. *Tetrahedron Lett.* **2001**, *42*, 4983–4986.
20. Beletskaya I.P., Averin A.D., Bessmertnykh A.G., Guilard R. *Tetrahedron Lett.* **2001**, *42*, 4987–4989.
21. Beletskaya I.P., Bessmertnykh A.G., Averin A.D., Denat F., Guilard R. *Eur. J. Org. Chem.*, **2005**, *2005*, 281–305.
22. Averin A.D., Ranyuk E.R., Buryak A.K., Savelyev E.N., Orlinson B.S., Novakov I.A., Beletskaya I.P. *Mendeleev Commun.* **2009**, *19*, 136–138.
23. Ranyuk E.R., Averin A.D., Buryak A.K., Savel'ev E.N., Orlinson B.S., Novakov I.A., Beletskaya I.P. *Russ. J. Org. Chem.* **2009**, *45*, 1555–1566.
24. Uglov A.N., Averin A.D., Buryak A.K., Beletskaya I.P. *ARKIVOC* **2011**, *viii*, 99–122.
25. Uglov A.N., Averin A.D., Buryak A.K., Bessmertnykh Lemeune A., Guilard R., Beletskaya I.P. *Macroheterocycles* **2013**, *6*, 33–39.
26. Averin A.D., Ranyuk E.P., Buryak A.K., Beletskaya I.P. *J. Org. Chem.* **2008**, *44*, 1671–1685.
27. Averin A.D., Ranyuk E.R., Buryak A.K., Beletskaya I.P. *Chem. Lett.* **2008**, *37*, 161–161.
28. Beletskaya I.P., Averin A.D., Pleshkova N.A., Borisenko A.A., Serebryakova M.V., Denat F., Guilard R. *Synlett* **2005,** *2005*, 87–90.
29. Averin A.D., Ulanovskaya O.A., Pleshkova N.A., Borisenko A.A., Beletskaya I.P. *Collect. Czech. Chem. Commun.* **2007**, *72*, 785–819.
30. Averin A.D., Ulanovskaya O.A., Borisenko A.A., Serebryakova M.V., Beletskaya I.P. *Tetrahedron Lett.* **2006**, *47*, 2691–2694.
31. Beletskaya I.P., Averin A.D., Ulanovskaya O.A., Fedotenko I.A., Borisenko A.A., Serebryakova M.V., Denat F., Guilard R. *Chem. Lett.* **2005**, *34*, 1100–1101.
32. Averin A.D., Ulanovskaya O.A., Fedotenko I.A., Borisenko A.A., Serebryakova M.V., Beletskaya I.P. *Helv. Chim. Acta* **2005**, *88*, 1983–2002.
33. Averin A.D., Uglov A.N., Buryak A.K., Bessmertnykh A.G., Guilard R., Beletskaya I.P. *Heterocycles* **2010**, *80*, 957–975.
34. Abel A.S., Averin A.D., Beletskaya I.P. *New J. Chem.* **2016**, *40*, 5818–5828.
35. Abel A.S., Mitrofanov A.Yu., Rousselin Y., Denat F., Bessmertnykh-Lemeune A., Averin A.D., Beletskaya I.P. *ChemPlusChem* **2016**, *81*, 35–39.
36. Kurashov I.A., Kharlamova A.D., Abel A.S., Averin A.D., Beletskaya I.P. *Molecules* **2023**, *28*, 512.
37. Averin A.D., Ranyuk E.R., Lukashev N.V., Beletskaya I.P. *Chemistry Eur. J.* **2005**, *11*, 1730–1739.
38. Valkonen A., Sievänen E., Ikonen S., Lukashev N.V., Donez P.A., Averin A.D., Lahtinen M., Kolehmainen E. *J. Mol. Struct.* **2007**, *846*, 65–73.
39. Averin A.D., Ranyuk E.R., Lukashev N.V., Golub S.L., Buryak A.K., Beletskaya I.P. *Tetrahedron Lett.* **2008**, *49*, 1188–1191.
40. Averin A.D., Uglov A.N., Ranyuk E.R., Lukashev N.V., Beletskaya I.P. *J. Org. Chem.* **2009**, *45*, 273–284.
41. Ranyuk E.R., Averin A.D., Beletskaya I.P. *Adv. Synth. Catal.* **2010**, *352*, 2299–2305.
42. Grigorova O.K., Averin A.D., Maloshitskaya O.A., Rybakov V.B., Beletskaya I.P. *Macroheterocycles* **2016**, *9*, 418–424.
43. Grigorova O.K., Averin A.D., Maloshitskaya O.A., Beletskaya I.P. *Macroheterocycles* **2016**, *9*, 425–432.
44. Grigorova O.K., Averin A.D., Maloshitskaya O.A., Beletskaya I.P. *Macroheterocycles* **2017**, *10*, 446–453.
45. Averin A.D., Grigorova O.K., Malysheva A.S., Shaferov A.V., Beletskaya I.P. *Pure Appl. Chem*. **2020**, *92*, 1367–1386.
46. Beletskaya I.P. Averin A.D., Bessmertnykh A.G., Denat F., Guilard R. *Tetrahedron Lett.* **2002**, *43*, 1193–1196.
47. Averin A.D., Shukhaev A.V., Buryak A.K., Denat F., Guilard R. Beletskaya I.P. *Macroheterocycles* **2009**, *2*, 281–285
48. Anokhin M.V., Averin A.D., Buryak A.K., Beletskaya I.P. *Mendeleev Commun.* **2011**, *21*, 132–133.
49. Anokhin M.V., Averin A.D., Buryak A.K., Beletskaya I.P. *Russ. Chem. Bull.* **2011**, *60*, 992–1003.
50. Chernichenko N.M., Averin A.D., Beletskaya I.P. *Lett. Org. Chem.* **2018**, *15*, 425–430.
51. Yakushev A.A., Anokhin M.V., Averin A.D., Maloshitskaya O.A., Beletskaya I.P. *Russ. Chem. Bull.* **2012**, *61*, 1474–1482.
52. Kobelev S.M., Averin A.D., Buryak A.K., Denat F., Guilard R., Beletskaya I.P. *Macroheterocycles* **2014**, *7*, 28–33.
53. Artamkina G.A., Sazonov P.K., Shtern M.M., Grishina G.V., Veselov I.S., Semeikin A.S., Syrbu S.A., Koifman O.I., Beletskaya I.P. *Synlett* **2008**, 45–48.
54. Artamkina G.A., Sazonov P.K., Shtern M.M., Grishina G.V., Veselov I.S., Semeikin A.S., Syrbu S.A., Koifman O.I., Beletskaya I.P. *Russ. J. Org. Chem.* **2008**, *44*, 421–431.
55. Mikhalitsyna E.A., Tyurin V.S., Beletskaya I.P. *J. Porphyrins Phthalocyanines* **2015**, *19*, 874–886.
56. Tyurin V.S., Mikhalitsyna E.A., Semeikin A.S., Beletskaya I.P. *Macroheterocycles* **2015**, *8*, 358–364.
57. Polevaya Y.P., Tyurin V.S., Beletskaya I.P. *J. Porphyrins Phthalocyanines* **2014**, *18*, 20–34.
58. Yaschuk Y.P., Tyurin V.S., Beletskaya I.P. *Macroheterocycles* **2012**, *5*, 302–307.
59. Mikhalitsyna E.A., Tyurin V.S., Khrustalev V.N., Lonin I.S., Beletskaya I.P. *Dalton Trans.* **2014**, *43*, 3563–3575.
60. Mikhalitsyna E.A., Tyurin V.S., Zamilatskov I.A., Khrustalev V.N., Beletskaya I.P. *Dalton Trans.* **2012**, *41*, 7624–7637.
61. Ranyuk E.R., Filatov M.A., Averin A.D., Cheprakov A.V., Beletskaya I.P. *Synthesis* **2012**, *44*, 393–398.
62. Yakushev A.A., Averin A.D., Maloshitskaya O.A., Syrbu S.A., Koifman O.I., Beletskaya I.P. *Macroheterocycles* **2016**, *9*, 65–72.
63. Yakushev A.A., Averin A.D., Maloshitskaya O.A., Syrbu S.A., Koifman O.I., Beletskaya I.P. *Mendeleev Commun.* **2016**, *26*, 199–201.
64. Averin A.D., Yakushev A.A., Maloshitskaya O.A., Syrbu S.A., Koifman O.I., Beletskaya I.P. *Russ. Chem. Bull*. **2017**. *66*, 1456–1466.
65. Yakushev A.A., Averin A.D., Maloshitskaya O.A., Koifman O.I., Syrbu S.A., Beletskaya I.P. *Macroheterocycles* **2018**, *11*, 135–140.
66. Yakushev A.A., Chernichenko N.M., Anokhin M.V., Averin A.D., Buryak A.K., Denat F., Beletskaya I.P. *Molecules* **2014**, *19*, 940–965.

67. Yakushev A.A., Averin A.D., Sakovich M.V., Vatsouro I.M., Kovalev V.V., Syrbu S.A., Koifman O.I., Beletskaya I.P. *J. Porphyrins Phthalocyanines* **2019**, *23*, 1551–1562.
68. Koifman O.I., Ageeva T.A., Beletskaya I.P., Averin A.D., Yakushev A.A., Tomilova L.G., Dubinina T.V., Tsivadze A.Yu., Gorbunova Yu.G., Martynov A.G., Konarev D.V., Khasanov S.S., Lyubovskaya R.N., Lomova T.N., Korolev V.V., Zenkevich E.I., Blaudeck T., Ch. von Borczyskowski, Zahn D.R.T., Mironov A.F., Bragina N.A., Ezhov A.V., Zhdanova K.A., Stuzhin P.A., Pakhomov G.L., Rusakova N.V., Semenishyn N.N., Smola S.S., Parfenyuk V.I., Vashurin A.S., Makarov S.V., Dereven'kov I.A., Mamardashvili N.Zh., Kurtikyan T.S., Martirosyan G.G., Burmistrov V.A., Aleksandriiskii V.V., Novikov I.V., Pritmov D.A., Grin M.A., Suvorov N.V., Tsigankov A.A., Fedorov A.Yu., Kuzmina N.S., Nyuchev A.V., Otvagin V.F., Kustov A.V., Belykh D.V., Berezin D.B., Solovieva A.B., Timashev P.S., Milaeva E.R., Gracheva Yu.A., Dodokhova M.A., Safronenko A.V., Shpakovsky D.B., Syrbu S.A., Gubarev Yu.A., Kiselev A.N., Koifman M.O., Lebedeva N.Sh., Yurina E.S. *Macroheterocycles* **2020**, *13*, 311–467.
69. Abel A.S., Averin A.D., Buryak A.K., Orlinson B.S., Beletskaya I.P. *Russ. Chem. Bull.* **2014**, *63*, 102–108.
70. Averin A.D., Uglov A.N., Zubrienko G.A., Abel A.S., Buryak A.K., Beletskaya I.P. *Russ. Chem. Bull.* **2021**, *70*, 2164–2179.
71. Averin A.D., Uglov A.N., Zubrienko G.A., Tarasenko E.A., Buryak A.K., Beletskaya I.P. *Curr. Org. Synth.* **2017**, *14*, 918–926.
72. Uglov A.N., Zubrienko G.A., Abel A.S., Averin A.D., Maloshitskaya O.A., Bessmertnykh-Lemeune A., Denat F., Beletskaya I.P. *Heterocycles* **2014**, *88*, 1213–1231.
73. Yakushev A.A., Anokhin M.V., Averin A.D., Maloshitskaya O.A., Savelyev E.N., Butov G.M., Orlinson B.S., Novakov I.A., Beletskaya I.P. *Macroheterocycles* **2013**, *6*, 40–46.
74. Chernichenko N.M., Averin A.D., Buryak A.K., Beletskaya I.P. *Russ. Chem. Bull.* **2014**, *63*, 2056–2063.
75. Averin A.D., Shukhaev A.V., Buryak A.K., Denat F., Guilard R., Beletskaya I.P. *Tetrahedron Lett.* **2008**, *49*, 3950–3954.
76. Kobelev S.M., Averin A.D., Buryak A.K., Savelyev E.N., Orlinson B.S., Butov G.M., Novakov I.A., Denat F., Guilard R., Beletskaya I.P. *ARKIVOC* **2012**, *vii*, 196–209.
77. Averin A.D., Tyutenov K.S., Shukhaev A.V., Kobelev S.M., Buryak A.K., Denat F., Guilard R., Beletskaya I.P. *Heterocycles* **2012**, *86*, 1341–1366.
78. Averin A.D., Shukhaev A.V., Vovk A.I., Kukhar V.P., Denat F., Guilard R., Beletskaya I.P. *Macroheterocycles* **2014**, *7*, 174–180.
79. Kobelev S.M., Averin A.D., Buryak A.K., Vovk A.I., Kukhar V.P., Denat F., Guilard R., Beletskaya I.P. *Heterocycles* **2015**, *90*, 989–1017.
80. Kobelev S.M., Averin A.D., Buryak A.K., Denat F., Guilard R., Beletskaya I.P. *Heterocycles* **2011**, *82*, 1447–1476.
81. Kobelev S.M., Averin A.D., Maloshitskaya O.A., Denat F., Guilard R., Beletskaya I.P. *Macroheterocycles* **2012**, *5*, 389–395.
82. Chernichenko N.M., Shevchuk V.N., Averin A.D., Maloshitskaya O.A., Beletskaya I.P. *Synlett* **2017**, *28*, 2800–2806.
83. Averin A.D., Chernichenko N.M., Shevchuk V.N., Maloshitskaya O.A., Denat F., Beletskaya I.P. *Macroheterocycles* **2018**, *11*, 141–149.
84. Kobelev S.M., Averin A.D., Buryak A.K., Denat F., Guilard R., Beletskaya I.P. *Tetrahedron Lett.* **2012**, *53*, 210–213.
85. Kobelev S.M., Averin A.D., Buryak A.K., Denat F., Guilard R., Beletskaya I.P. *Macroheterocycles* **2014**, *7*, 28–33.
86. Grigorova O.K., Gusev D.I., Averin A.D., Maloshitskaya O.A., Beletskaya I.P. *Russ. Chem. Bull.* **2019**, *68*, 848–854.
87. Grigorova O.K., Averin A.D., Maloshitskaya O.A., Denat F., Beletskaya I.P. *Macroheterocycles* **2019**, *12*, 312–318.

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