**Special topic**

Alexei D. Averin and Irina P. Beletskaya*

# Synthesis of polymacrocyclic compounds *via* Pd-catalyzed amination and evaluation of their derivatives as metal detectors

## Macrocycles and detectors

https://doi.org/10.1515/pac-2018-0714

**Abstract:** A mini-review is dedicated to the application of Pd(0)-catalyzed amination reactions for the synthesis of polymacrocyclic compounds of various architectures. Such molecules comprise diazacrown ether moieties or structural fragments of tri- and tetraazamacrocycles, polyamine or polyoxadiamine chains of different length and aromatic spacers. Polymacrocyclic compounds thus formed possess an increased number of coordination sites and are suitable for testing as potential receptors of metal cations. Some of these macrocyclic compounds were decorated with the exocyclic dansyl fluorophore group or were coupled with porphyrin units to form polymacrocyclic conjugates. Fluorescent spectra of these compounds were studied in the presence of various metal perchlorates and several macrocycles were found to act as chemosensors or molecular probes for such cations like Cu(II), Al(III), Cr(III).

**Keywords:** catalysis; cross-coupling reactions; cryptands; detection; Distinguished Women in Chemistry and Chemical Engineering; fluorescence; macrocycles; palladium; porphyrins.

## Introduction

Oxygen- and nitrogen-containing polymacrocyclic compounds which combine two or more macrocyclic moieties in one molecule have been always of great interest for researchers as they provide an immense scope for constructing versatile receptors of cations, anions and polar organic molecules. A special place in the panel of polymacrocycles is occupied by cryptands which possess two or more macrocyclic units sharing several atoms thus providing a sort of a cage which increases the selectivity and binding constants towards certain coordinated species. About three decades ago the first representatives of all important classes of polymacrocycles were already synthesized and their binding properties began to be explored. To note among them bis(crown) and bis(azacrown) compounds with isolated cavities [1, 2], spiro-conjugated crown ethers [3], bis(crown) ethers with aromatic spacer [4]. Macrobicycles and more complex macrotricycles (which actually are cryptands) can be organized as well without introducing an aromatic spacer [5, 6], they can comprise phenylene [7, 8] or binaphthalene [9] spacers, described are polymacrocycles of complex architecture like azacyclophanes [10] or catenanes [11]. As early as in 1991 many dozens of polymacrocyclic compounds were mentioned in a comprehensive review [12]. Since that time the number of such compounds increased dramatically, new approaches including catalytic methods were applied for their synthesis, and the main contemporary trend is the application of polymacrocycles in chemical sensing. The problems of the cryptands coordination with different metal cations for various purposes have been always of unceasing interest for researchers [13–17], with more demands every year for further research of the cryptands interaction with

***Corresponding author: Irina P. Beletskaya,** Lomonosov Moscow State University, Department of Chemistry, Moscow, Russian Federation, e-mail: beletska@org.chem.msu.ru
**Alexei D. Averin:** Lomonosov Moscow State University, Department of Chemistry, Moscow, Russian Federation

organic compounds [18–22]. Cryptands are widely studied as selective receptors for cations [23–25], anions [26–29] and small organic molecules [30]. Creation of fluorescent chemosensors on the basis of cryptands is an important and prospective trend in the modern techniques of detection [31–33].

The majority of known cryptands have been synthesized *via* convenient synthetic procedure, and until now non-catalytic approaches have been dominant [34, 35]. However, metal-catalyzed synthesis has been applied in some cases to the synthesis of macropolycyclic compounds [36]. We were the first to use Pd-catalyzed amination reactions for the synthesis of nitrogen- and oxygen-containing macrocycles [37, 38]. Among them are macrocycles incorporating phenylene [39], naphthalene [40], anthracene and anthraquinone [41] endocyclic units, as well heterocycles like pyridine [42, 43], 2,2′-bipyridyl [44] and even cholane spacers [45]. We developed the synthesis of macrocyclic colorimetric chemosensors employing 1,8-diaminoanthraquinone and showed their usefulness in the optical detection of Pb(II) cations [46, 47]. A special attention has been paid recently to the synthesis of the macrocycles based on disubstituted quinoline [48] and 1,10-phenanthroline [49] for the synthesis of fluorescent chemosensors for metal cations. The synthesis of the chiral macrocycles with central endocyclic BINAM moiety was important for the creation of enantioselective fluorescent chemosensors for optically active amino alcohols [50, 51]. This mini-review is dedicated to synthesis of polymacrocyclic compounds using Pd(0)-catalyzed amination at the key step and to possibilities of the development of chemosensors for metal cations.

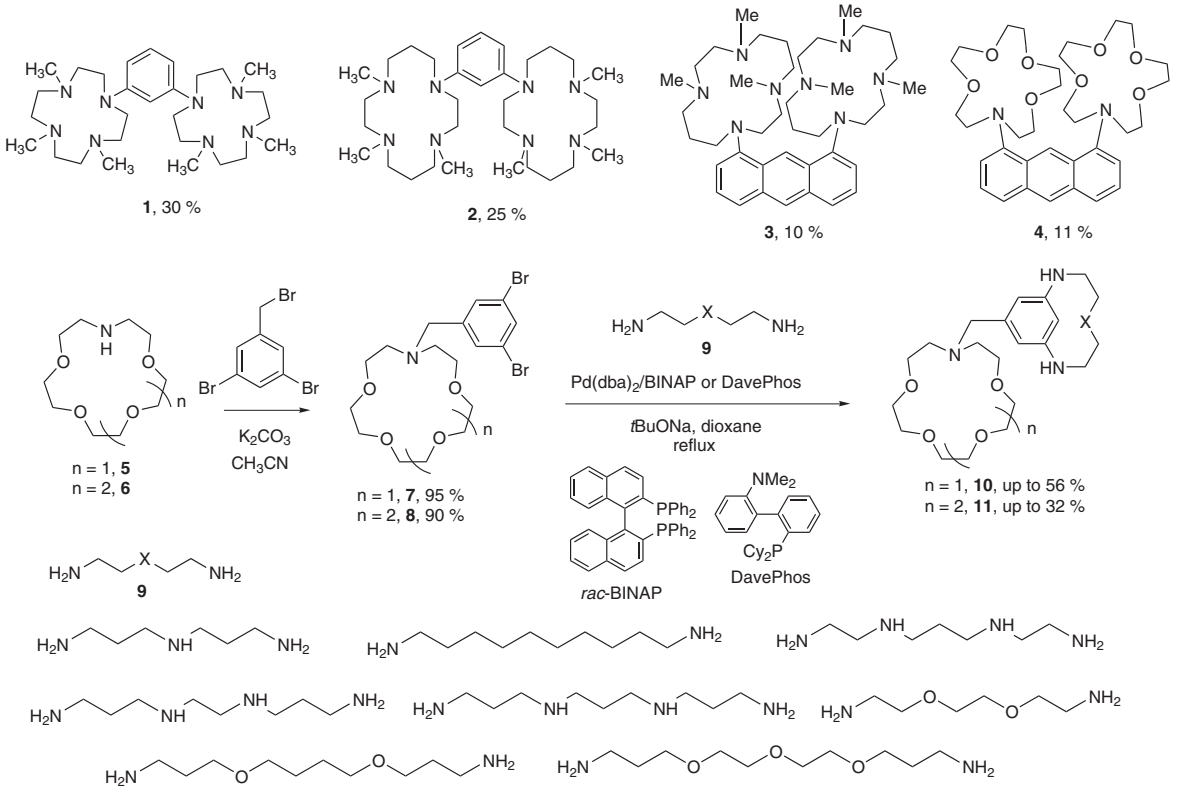
## Bis- and trismacrocyclic compounds

Polymacrocyclic compounds with several isolated macrocyclic rings can be obtained by the reaction of dihaloarenes with polyazamacrocycles catalyzed by Pd(0) complexes. This approach was used by us in a series of works which employed the reactions of 1,3-dibromobenzenes with N,N′,N″-trimethylcyclen and N,N′,N″-trimethylcyclam [52]. The yields of the target bis(cyclen) and bis(cyclam) products **1** and **2** were 30 and 25 %, while analogous reactions of 1,8-dichloroanthracene with N,N′,N″-trimethylcyclam resulted in lower yields of corresponding bismacrocycles **3** and **4** with face-to-face arranged macrorings (Scheme 1) [53, 54]. Another approach to bismacrocycles is based on the catalytic macrocyclization reaction of 3,5-dibromobenzyl-substituted azacrown ethers **7** and **8** with a variety of polyamines and oxadiamines **9** (Scheme 1) [55]. The yields of the corresponding bismacrocycles **10** comprising 1-aza-15-crown ether moiety reached 56 %. BINAP or DavePhos ligands were most commonly employed for the catalytic macrocyclizations with polyamines to obtain the best possible yields. Some of bismacrocycles were tested in coordination with Zn(II) and Cd(II) cations using NMR titration method [56].

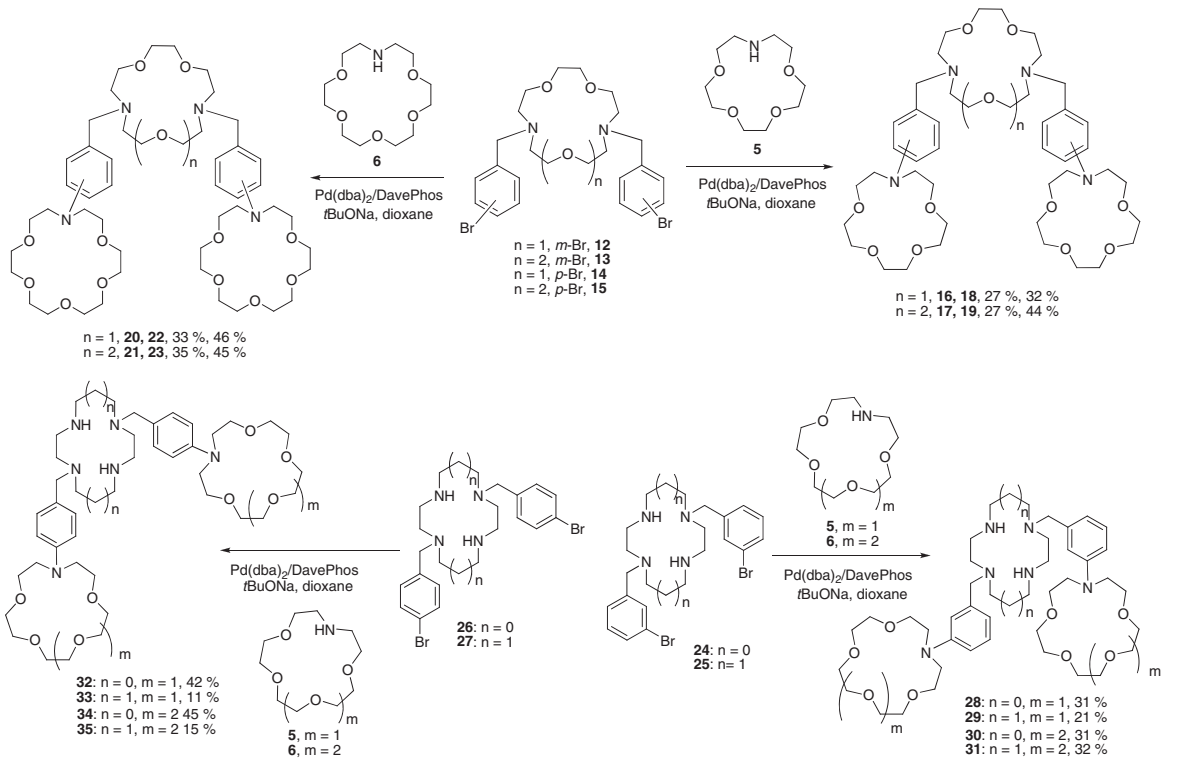
Trismacrocyclic compounds were obtained by reacting N,N′-bis(bromobenzyl) substituted diazacrown ethers **12–15** with two equiv. of azacrown ethers **5** and **6**, in all reactions the catalytic system $Pd(dba)_2$/DavePhos was used (Scheme 2). The yields of the target molecules **16–23** combining one diazacrown and two azacrown ethers were generally better than for bis(tetraazamacrocyclic) derivatives **1–4** and reached 44–46 % [57]. It was equally possible to introduce N,N″-bis(bromobenzyl) compounds **24–27** in the similar reactions [58]. It was found out that in the majority of cases cyclen derivatives were obtained in much better yields (up to 45 %) than corresponding cyclam derivatives (11–32 %).

## Macrobicyclic and macrotricyclic cryptands

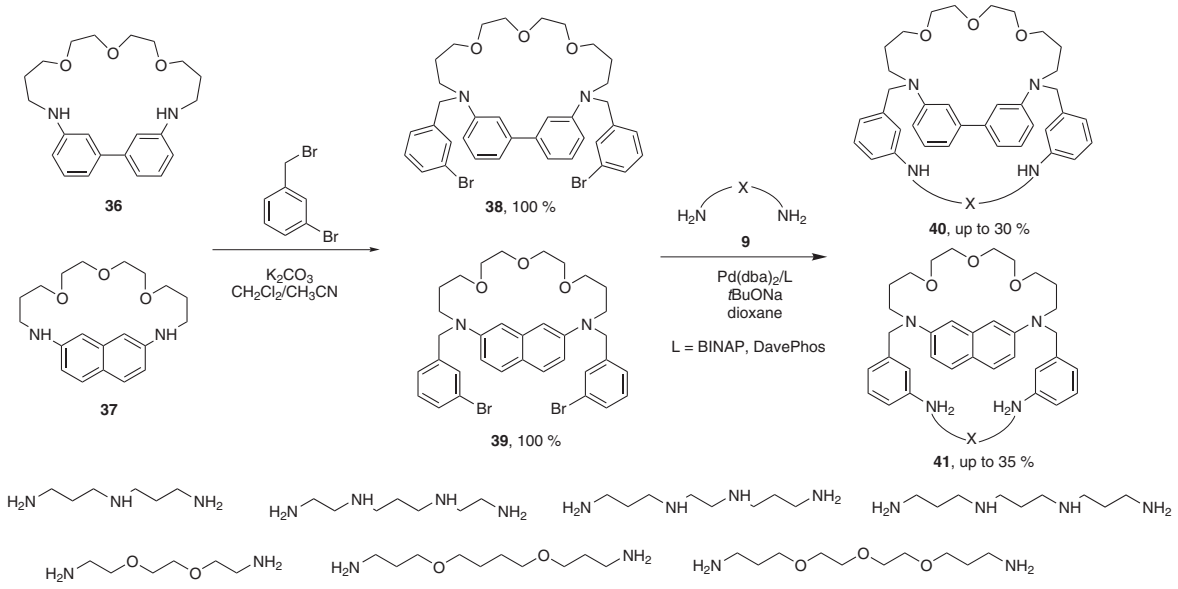
As we gained more experience in the Pd-catalyzed synthesis of various N- and O-containing macrocycles, we decided to use this approach for constructing various cryptands of different architectures. For this purpose macrocycles on the basis of biphenyl and naphthalene **36** and **37** were modified with two 3-bromobenzyl substituents and introduced in the Pd-catalyzed macrocyclization reactions with various polyamines and oxadiamines (Scheme 3). As a result, macrobicycles with the central biphenyl moiety **40** were obtained in




**Scheme 1:** The synthesis of bismacrocyclic compounds with isolated macrocycles.




**Scheme 2:** The synthesis of trismacrocyclic compounds with isolated macrocycles.

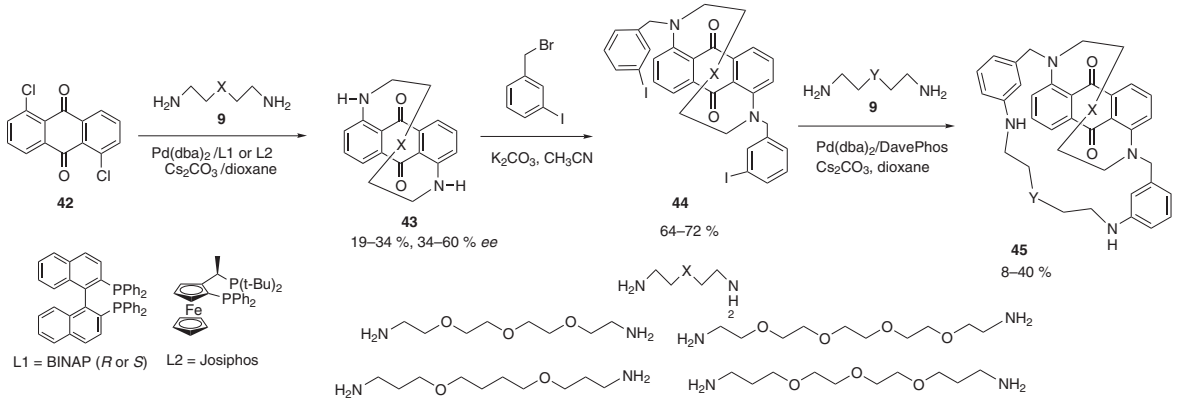



**Scheme 3:** The synthesis of macrobicyclic compounds incorporating disubstituted biphenyl and naphthalene moieties.

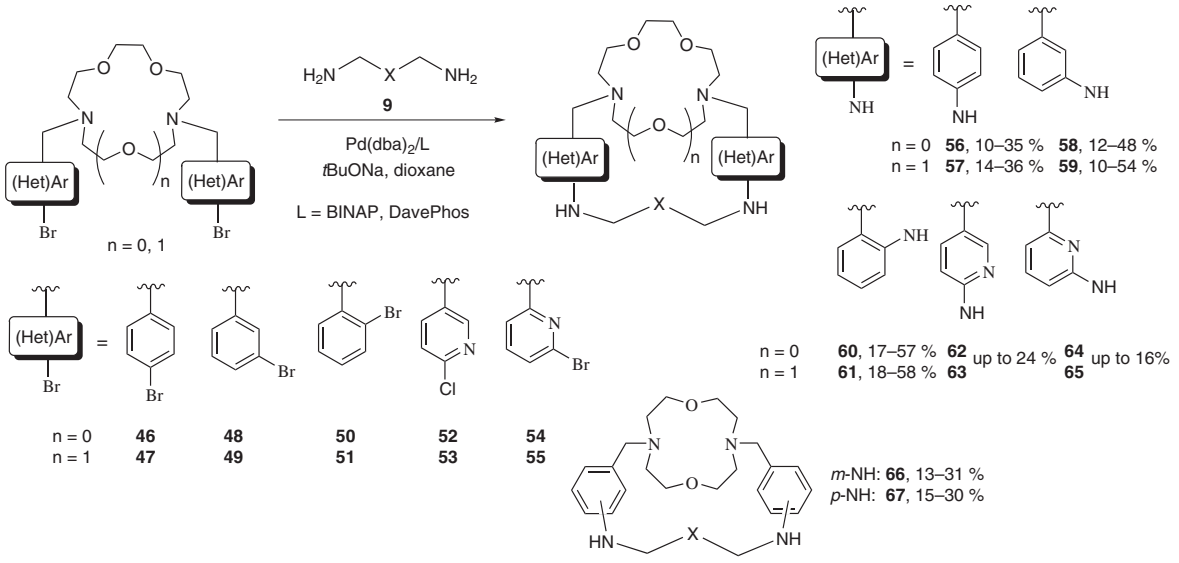
yields up to 30 % [59], while corresponding cryptands with naphthalene moiety **41** were isolated in yields up to 35 % [60]. Needless to say that the result of the macrocyclization processes in all cases strongly depended on the nature of polyamine (chain length, number of nitrogen and oxygen atoms), for this purpose the choice of the correct ligand (BINAP or DavePhos) is indispensable.

Our earlier investigations revealed that the application of chiral phosphine ligands in the catalytic macrocyclization using 1,5-dichloroanthracene led to planar-chiral macrocycles **43** with *ee* up to 60 % [61]. Further on some of these compounds with anthraquinone moieties were modified with 3-iodobenzyl substituents giving compounds **44** which were then introduced in the second macrocyclization reaction (Scheme 4). The yields of parent planar-chiral macrobicycles **45** were critically dependent on the length of the oxadiamine chain and reached 40 % with the longest one [62].

A great variety of cryptands incorporating diazacrown ether moieties was synthesized by Pd-catalyzed macrocyclization reactions using N,N-disubstituted diaza-15-crown and diaza-18-crown ethers bearing bromobenzyl (compounds **46–51**), chloro- and bromopyridinylmethyl (compounds **52–55)** groups (Scheme 5). It was found that BINAP ligand was much more efficient in the reactions employing bromobenzyl derivatives **56–61** while DavePhos was more helpful in the syntheses of pyridinyl-containing cryptands **62–65** [63, 64]. The best yields of the compounds with benzyl spacers were recorded for *ortho*-aminobenzyl derivatives **60**,




**Scheme 4:** The synthesis of macrobicyclic compounds based on 1,5-disubstittued anthraquinone with a planar-chiral fragment.

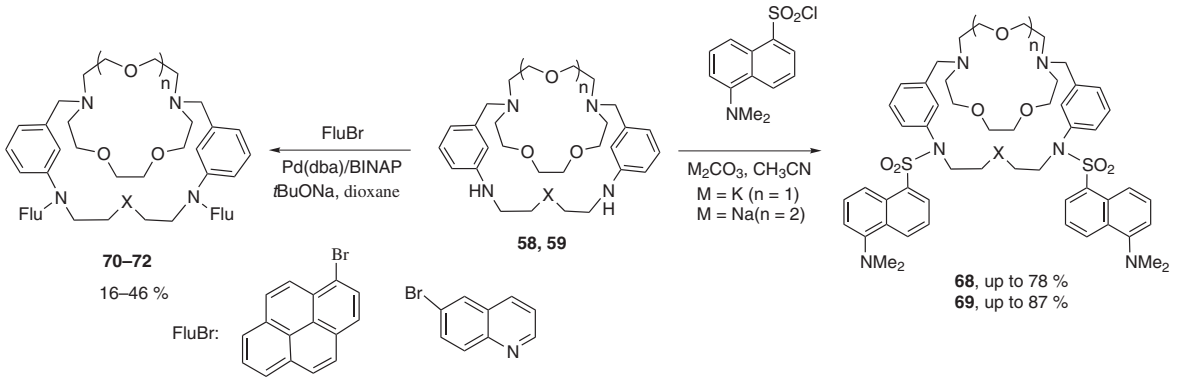



**Scheme 5:** The synthesis of macrobicyclic compounds based on diazacrown ethers.

**61** (up to 58 %) what is the best result among all processes of such type. As for macrobicycles with pyridinyl spacers, their yields were substantially lower, possibly, due to various concurrent catalytic processes with the participation of more active halogen atoms in halopyridine fragments. In accordance with this approach the derivatives with 12-membered diazacrown ether **66** and **67** were prepared as well as similar macrobicycles with diaminoadamantane linkers [65].

The coordination of some of these cryptands with different metal cations was studied using NMR titration. Stoichiometry and binding constants were established for the complexes with Zn(II), Cd(II), Pb(II), Ag(I), Ga(III), In(III), Y(III), and Sr(III) of several cryptands **58–61** while bicycles **66** and **67** were tested in the coordination with Li(I). In order to improve sensing properties of macrobocycles two alternative approaches for introducing fluorophore groups were proposed: the first one is a non-catalytic reaction with the popular dansyl chloride which afforded corresponding didansyl-substituted cryptands **68** and **69** in high yields; the second employed the catalytic arylation with bromosubstituted pyrene and quinoline which gave corresponding derivatives **70–72** (Scheme 6).

Thus modified macrocycles were studied as potential fluorescent chemosensors for metal cations using a panel of perchlorates (Li(I), Na(I), K(I), Mg(II), Ca(II), Ba(II), Al(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), Ag(I), Pb(II)) and nitrates (Ga(III), In(III), Y(III)). The addition of metal salts caused different changes in UV and fluorescence spectra depending on the nature of the central diazacrown moiety and




**Scheme 6:** Modifications of macrobicycles with fluorophore groups.

oxadiamine linker. Fluorescence at 540 nm of dansyl-substituted compounds generally drastically diminished in the presence of Cu(II) and Al(III) perchlorates (Fig. 1) with hypsochromic shift of residual emission maxima (465 nm), while other cations either did not change emission intensity notably, or diminished it partially, or with certain cryptands In(III) (5 equiv.) caused quenching of the initial emission by half and a new emission band with a notable hypsochromic shift (415 nm) emerged. Such behavior of the fluorescent properties of compounds **68**, **69** makes them promising fluorescent molecular probes for Cu(II), Al(III) and, in some cases, for In(III).

A vast series of macrobicyclic compounds was obtained by employing N,N″-*trans*-disubstituted cyclen and cyclam bearing bromobenzyl (compounds **73–77**) and halogenopyridinylmethyl (compounds **87–90**, **93**, **94**) groups (Scheme 7). The yields of the bicyclic benzyl-containing cryptands **78–82** ranged from humble 8 % to quite satisfactory 44 % depending on the nature of polyamines used and the type of the starting tetraazamacrocycle; in the case of cyclen yields were generally notably higher. Interesting macrotricyclic by-products were also obtained and in some cases isolated in individual state [66]. A detailed study was carried out to determine the best route of formation of these macrotricycles and using *in situ* obtained bis(polyamine) derivatives **83** and **84** several cylindrically-shaped cryptands **85** and **86** were synthesized. As in the case with diazacrown derivatives, the cryptands possessing disubstituted pyridine spacers (compounds **91**, **92**, **95**, **96**) were obtained in lower yields [67]. Cyclen-based macrobicycles **99** with naphthalene spacers were synthesized from corresponding bromonaphthalenylmethyl derivatives **98**, they are valuable as potential fluorescent detectors for metal cations [68]. The same approach was applied to the synthesis of unusual cryptands combining cyclen or cyclam central moiety and diaminoadamantane fragments [69].

Some of the cyclen/cyclam-based macrobicycles were studied in the complexation with metal cations using NMR titration technique. 1:1 Stoichiometry was established for all complexes with Zn(II), Cd(II), Pb(II), Ag(I) and Hg(II) and the values of binding constants were shown to be strongly dependent on the nature of the cryptand and metals under investigation.

The development of the approach included the synthesis of macrobicyclic compounds based on tetrasubstituted cyclen and cyclam bearing additional groups at nitrogen atoms. The reactions of dibromotetrabenzyl

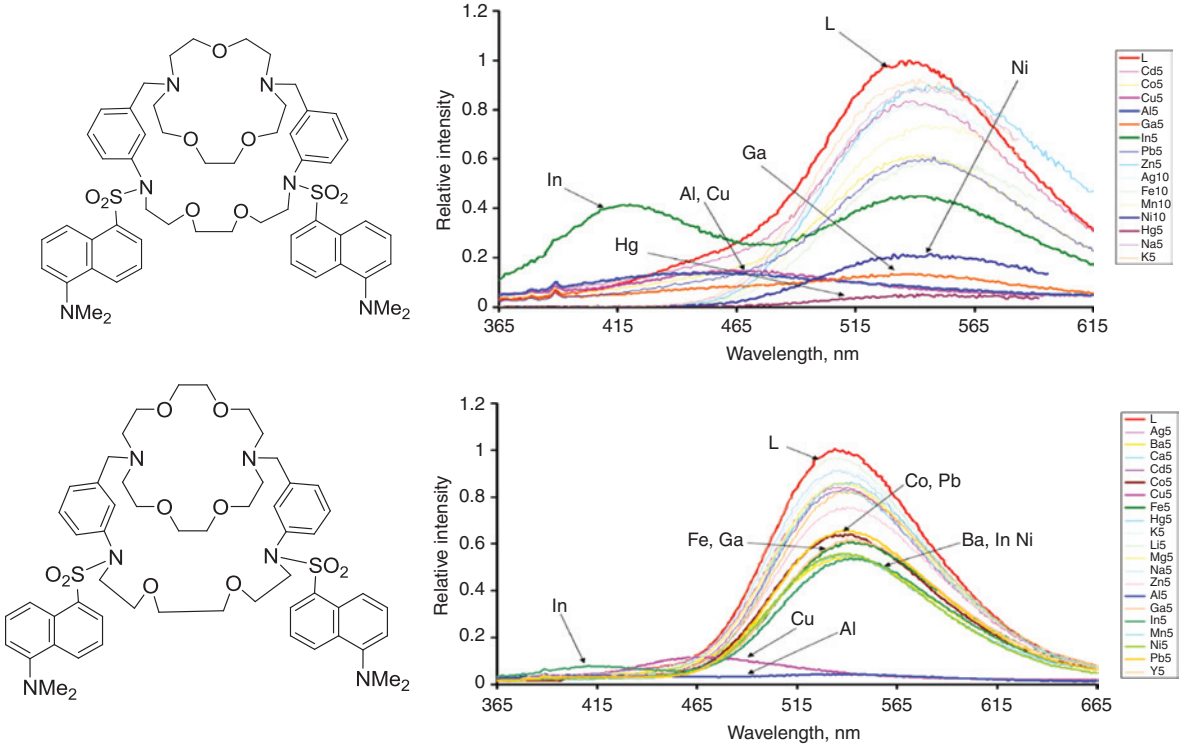
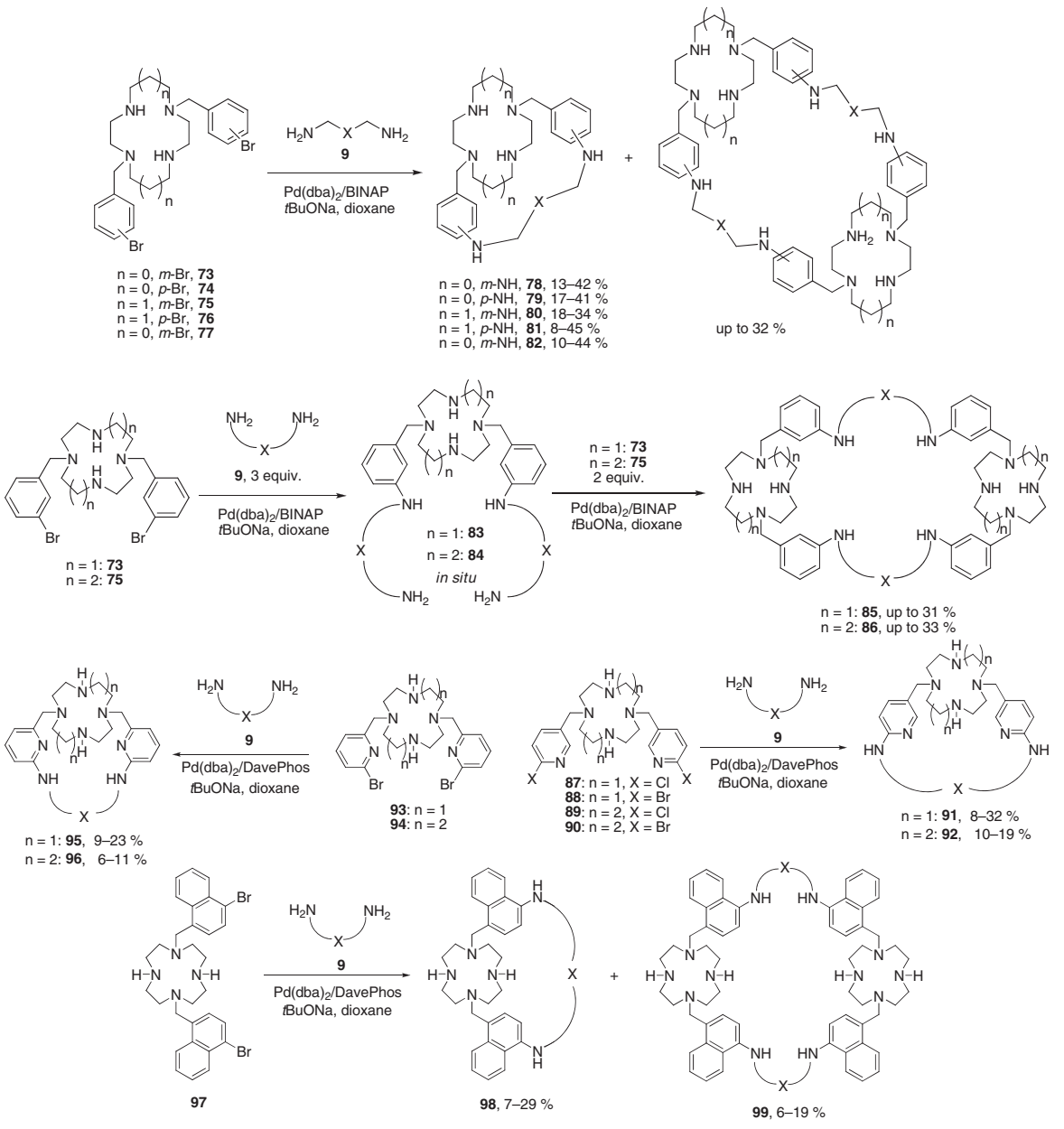
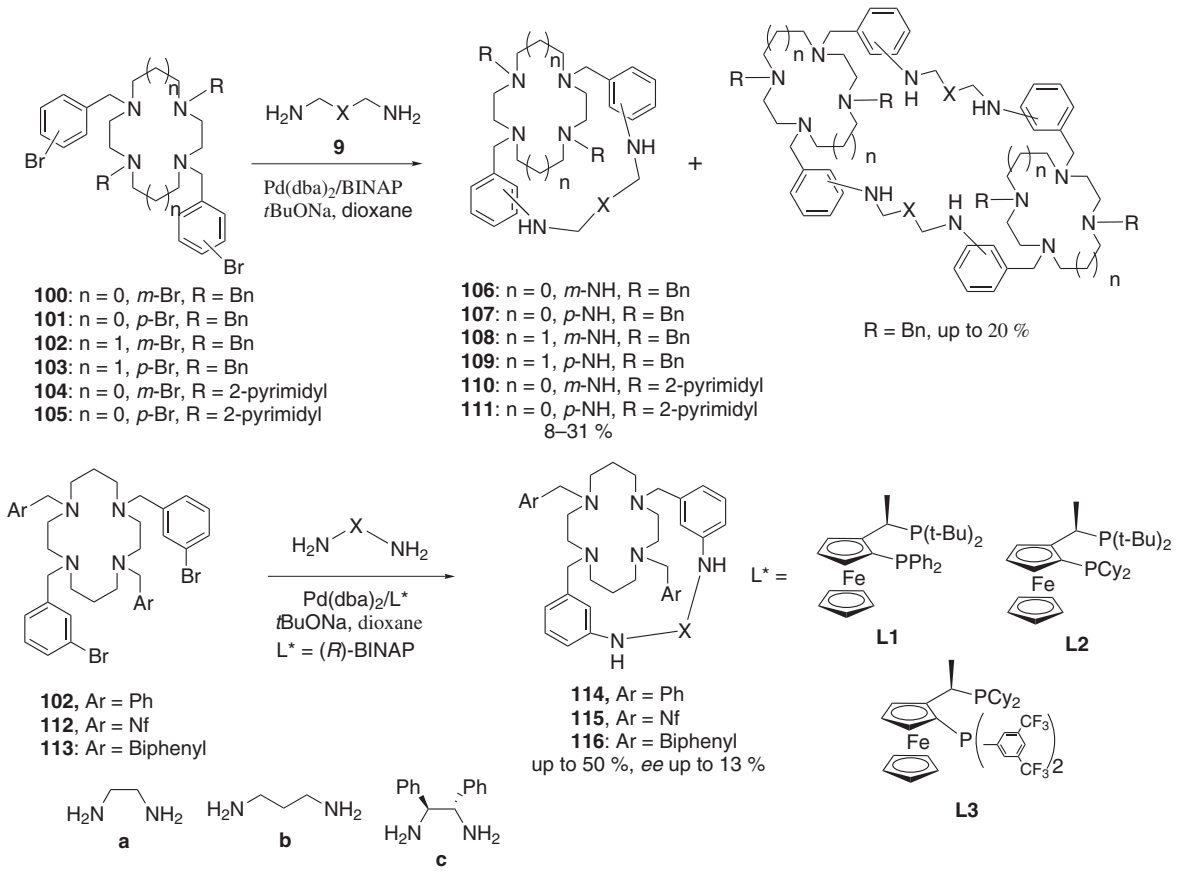



**Fig. 1:** Spectra of fluorescence of selected macrobicycles in the presence of different metals cations (5 equiv.).




**Scheme 7:** The synthesis of macrobicyclic compounds based on disubstituted cyclen and cyclam.

substituted cyclen and cyclam **100–103** with polyamines afforded corresponding macrocycles **106–109** in yields up to 31 %, in many cases macrotricyclic cryptands were obtained in comparable yields (Scheme 8) [70]. The reactions with di(2-pyrimidyl) derivatives of cyclen **104** and **105** gave macrobicycles **110** and **111** also in reasonable yields; these compounds are of interest as they possess additional coordination sites [71]. The combination of appropriate substituents at the nitrogen atoms of cyclam and enough short diamine linkers opens a way to the synthesis of planar-chiral macrobicycles due to restricted rotation of the diamine chain around the tetraazamacrocyclic moiety. Thus, using tetrasubstituted dibromo derivatives of cyclam **102**, **112** and **113** we managed to synthesize a series of such macrobicycles **114–116** with diaminoethane and diaminopropane linkers in quite good yields up to 50 % (Scheme 8). The search for the most efficient chiral phosphine ligand led to a series of Josiphos-type ligands, among which **L1–L3** were demonstrated to be more efficient, however, they provided only very modest enantioinduction [72].

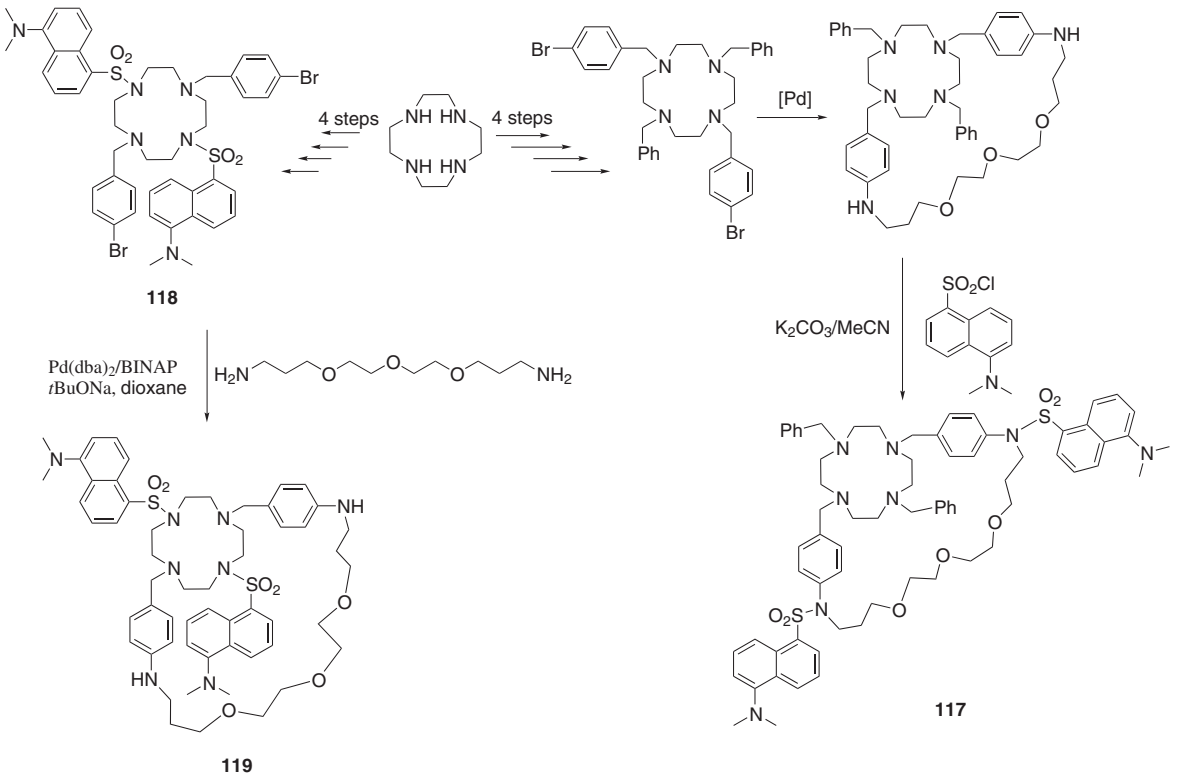



**Scheme 8:** The synthesis of macrobicyclic compounds based on tetrasubstituted cyclen and cyclam.

The elaborated synthesis of macrobicycles comprising tetrasubstituted cyclen moiety allowed the preparation of the macrobicycle **117** with two dansyl fluorophore groups attached to the nitrogen atoms of the trioxadiamine linker. On the other hand, the formation of the didansyl-containing tetrasubstituted cyclen **118** allowed the synthesis of another macrobicycle **119** which bears dansyl groups at the nitrogen atoms of the central cyclen fragment (Scheme 9). The fluorescent titration of compounds **117** and **119** with a variety of metal salts (Fig. 2) showed that compound **119** was more selective towards Cu(II) ions as only this metal quenched emission almost totally while other cations changed it only to some extent. The ligand **117** was less efficient as the addition of Cu(II), Al(III) and Cr(III) ions led only to partial quenching of fluorescence.

Another approach was elaborated for the synthesis of bicyclic ligands based on triazacyclononane (TACN) and triazacyclododecane (TACD) possessing dansyl fluorophore groups. For this purpose one dansyl group was introduced into free triazacycle **120** or **121**, then the compounds **122** and **123** were modified with bromobenzyl substituents to give derivatives **124–126**, the latter compounds were introduced in the Pd-catalyzed macrocyclization reactions with oxadiamines in which DavePhos ligand was found to be advantageous over BINAP (Scheme 10). The resulting bicyclic compounds **127–129** were obtained in rather small yields due to formation of various oligomeric by-products [73].

The sensing properties of the synthesized bicycles were tested using a panel of 20 metal cations and it was revealed that almost all the ligands independent of the oxadiamine linker nature fully quenched their fluorescence in the presence of Cu(II) and Al(III) ions (Fig. 3). However, the selectivity of TACN- and TACD-based bicycles was different as in the latter case other ions (like In, Ga, Hg) also substantially diminished the emission intensity; it means that these cations may mask the action of copper and aluminum ions. On the other hand, the fluorescence of the ligand **129** in the presence of K(I) showed by a notable hypsochromic shift of the emission maximum.




**Scheme 9:** The synthesis of cyclen-based macrobicyclic compounds with dansyl fluorophore groups.

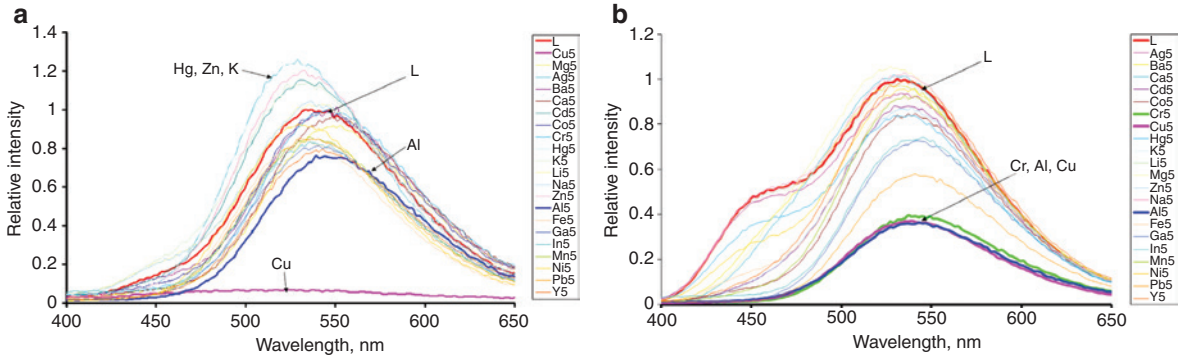
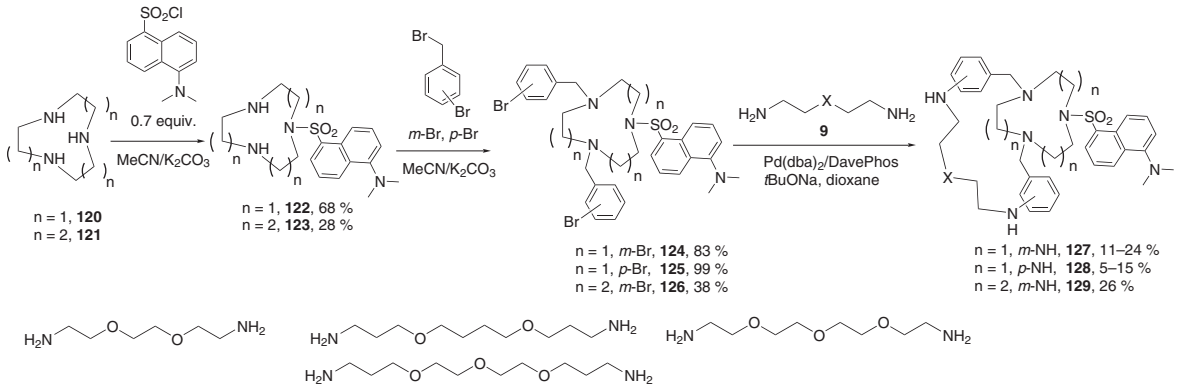



**Fig. 2:** Fluorescence spectra of macrobicycles **119** (a) and **117** (b) in the presence of different metals cations (5 equiv.).

The introduction of another fluorophores (naphthalene, acridine) in the molecule of TACN was achieved *via* the aminal derivative **130** (Scheme 11). The precursor **131** bearing naphthalene moiety and two bromobenzyl substituents was obtained in total 45 % yield via a 4-step procedure while similar acridine-containing derivative **132** was synthesized in 37 % yield after two steps (deprotection step occurred simultaneously together with the alkylation). The macrocyclization with the longest trioxadiamine led to corresponding bicycles **133** and **134** in low yields [74]. It is obvious that the introduction of additional substituents in the parent macrocycles increases the steric hindrances what causes the decrease in the efficiency of the intramolecular cyclization and leads to excessive formation of oligomeric by-products.

The decoration of diazacrown ethers with two 3,5-dibromobenzyl substituents (compounds **135** and **136**) gave a possibility to synthesize trismacrocyclic compounds **137** and **138** (Scheme 12). This double




**Scheme 10:** The synthesis of bicyclic compounds based on triazacyclononanes with dansyl fluorophore groups.

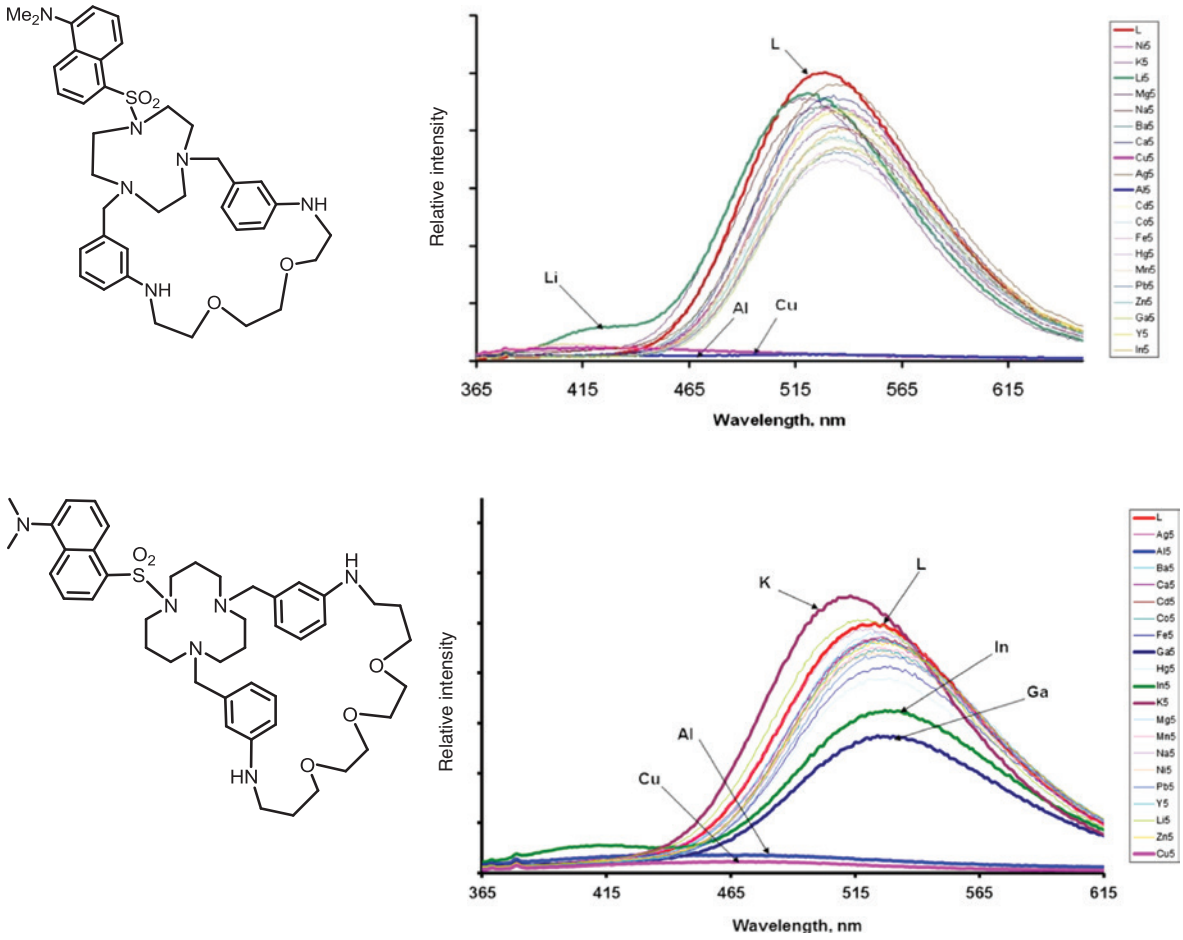
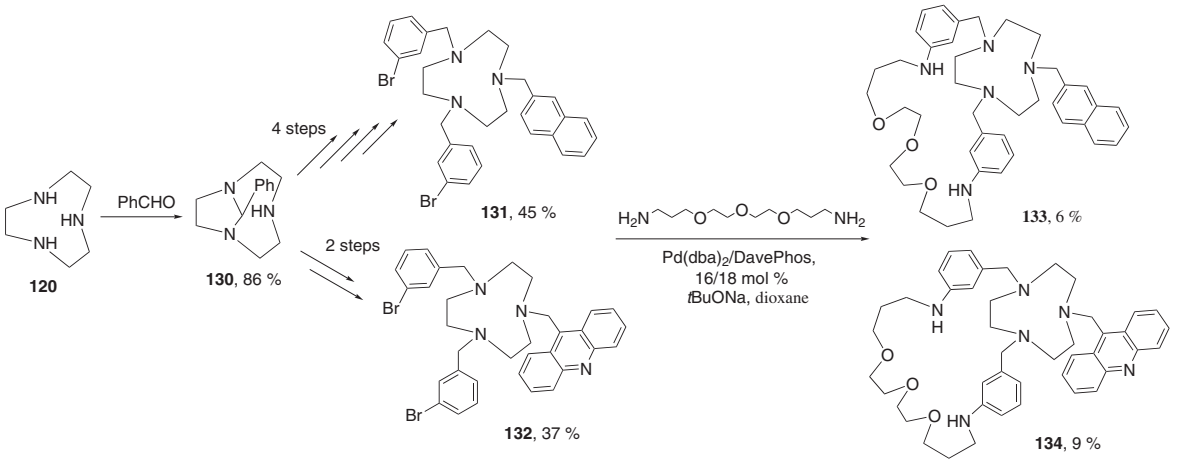
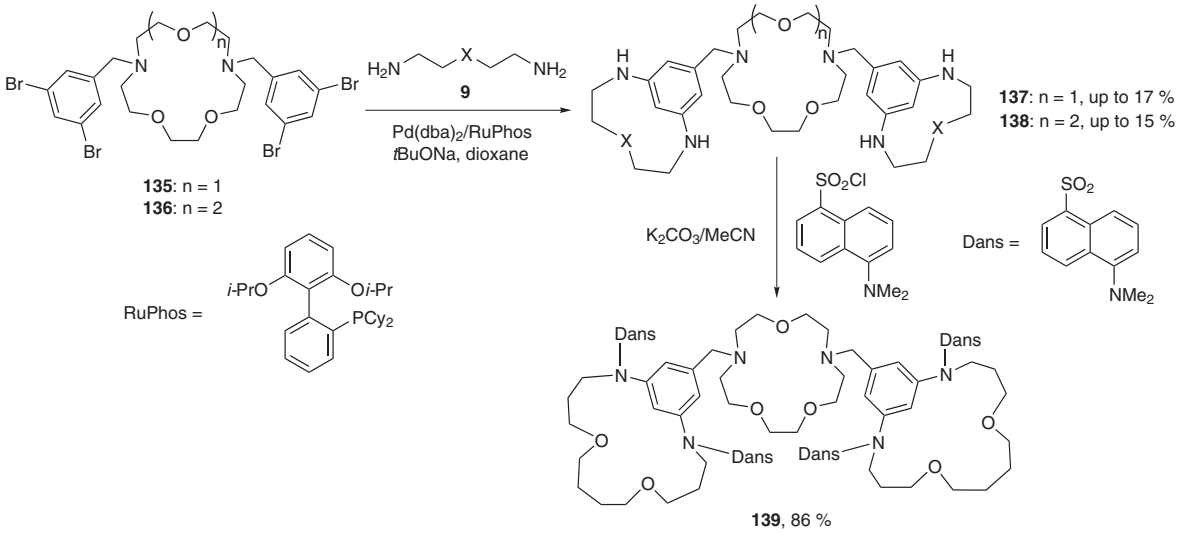



**Fig. 3:** Fluorescence spectra of TACN-based bicycles in the presence of different metals cations (5 equiv.).

macrocyclization process was possible in the presence of RuPhos catalyst. The presence of four reaction centers in the starting compounds made this synthesis a real challenge as only one reaction route out of many possible others was desirable. The modification of one trismacrocycle with four dansyl fluorophore groups afforded compound **139** in high yield, the latter was tested as a fluorescent chemosensor for metal cations [75]. The addition of Cu(II) and Al(III) ions led to full quenching of emission (Fig. 4), however, this ligand was




**Scheme 11:** The synthesis of bicyclic compounds based on TACN with naphthalene and acridine fluorophore groups.




**Scheme 12:** The synthesis of trismacrocyclic derivative of diazacrown ether and its modification with four dansyl fluorophore groups.

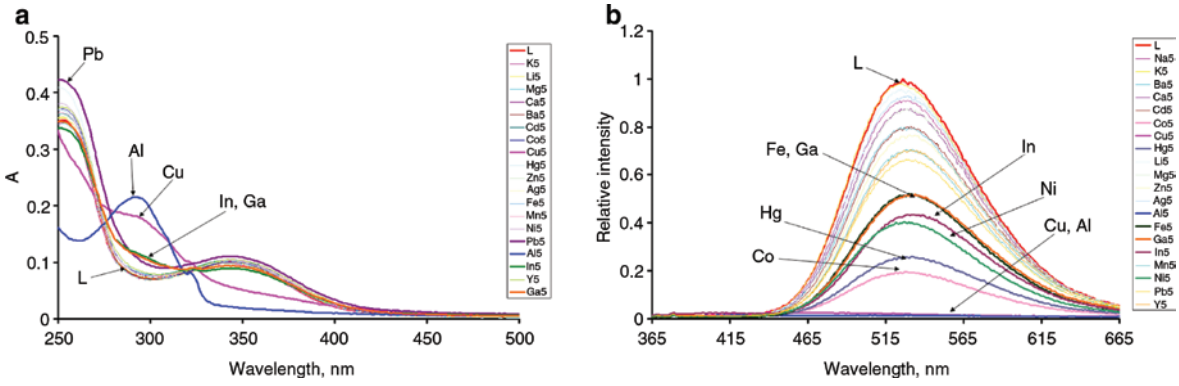
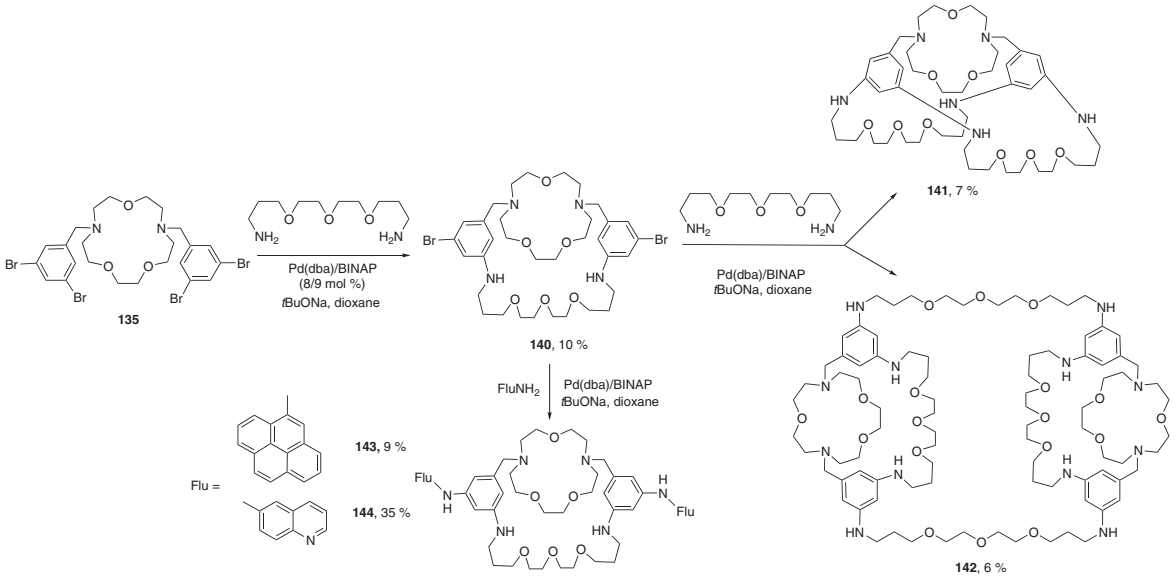
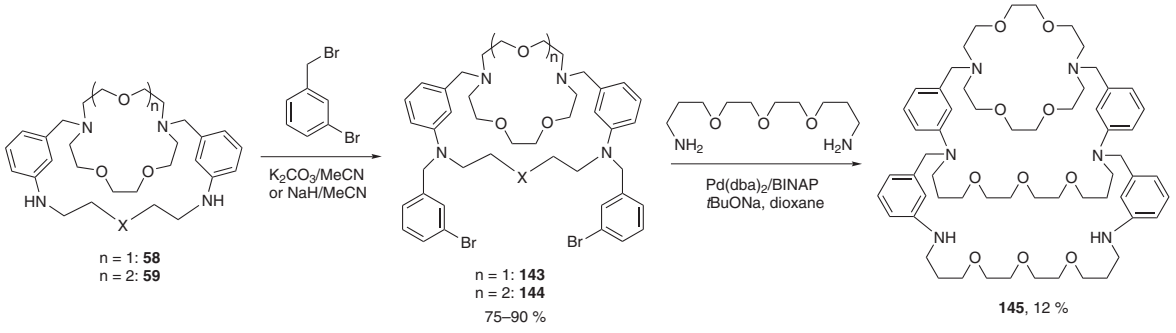



**Fig. 4:** UV (a) and fluorescence (b) spectra of compound **139** in the presence of different metals cations (5 equiv.).




**Scheme 13:** The synthesis of macrotricyclic derivative of diaza-15-crown-5 ether, the catalytic introduction of fluorophore substituents.



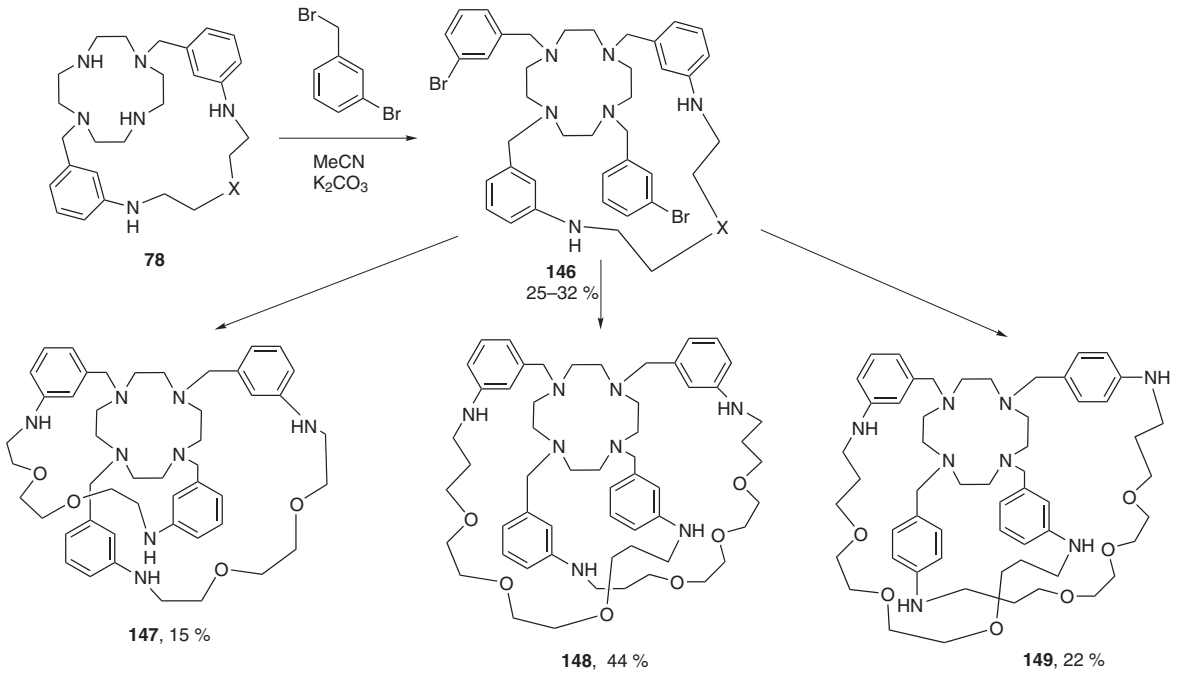

**Scheme 14:** The synthesis of macrotricyclic derivative of diaza-18-crown-6 ether.

less selective compared to macrobicycles described above which contained 1 or 2 dansyl groups: some cations like Fe(III), Ga(III), Ni(II), Co(II), Hg(II) caused notable emission quenching as well. As for UV spectrum of the ligand, only the addition of Cu(II) and Al(III) led to principal spectral changes, thus tricycle **139** can be regarded as a dual-channel molecular probe for these cations.

The possibility of the synthesis of more sophisticated cryptand-type macrotricycle using tetrabromide **135** was demonstrated by the two-step synthesis of compound **141** which employed two Pd-catalyzed macrocyclization reactions (Scheme 13). The intermediate macrobicycle **140** was also used for the modifications with fluorophore groups (pyrene and quinoline) by Pd-catalyzed amination using two resting bromine atoms.

Another approach to macrotricyclic compounds based on diazacrown ether was shown by the two-step modification of the macrobicycles **58**, **59** (Scheme 14). They were provided with two bromobenzyl groups to make corresponding compounds **143** and **144** in high yields, but the macrocyclization reaction was efficient only in one case to give the target cryptand **145** while other intermediates afforded mainly mixtures of oligomers [75].

Three different routes to macrotricyclic compounds containing the central cyclen or cyclam moieties have been proposed. The first one employed accurate modification of macrobicycles with two bromobenzyl substituents by playing with different reactivity of dialkyl and alkylaryl amino groups (Scheme 15). These




**Scheme 15:** The synthesis of spherically-type macrotricyclic derivatives of cyclen.

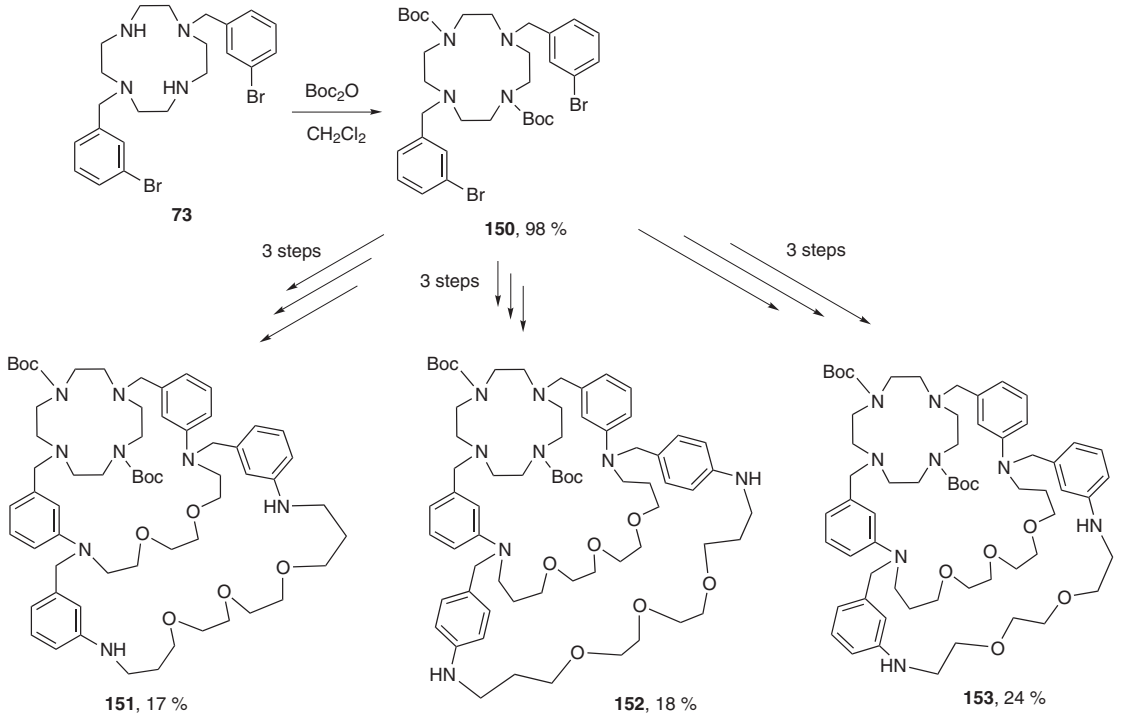
intermediates were introduced in the Pd-catalyzed macrocyclization to give unusual spherically-shaped cryptands **147–149**, surprisingly, the yield in the case of compound **148** attained 44 % [76].

To change the geometry of the macrotricyclic cryptands, two secondary amino groups in N,N′-bis(3-bromobenzyl)cyclen **73** were protected with Boc groups giving derivative **150** which was then transformed *via* three-step sequence of Pd-catalyzed macrocyclization, bromobenzylation and the second Pd-catalyzed macrocyclization to produce macrotricycles **151–153** in reasonable yields (Scheme 16) [76]. Cylindrically-shaped macrotricyclic compounds were successfully obtained by the catalytic amination of N,N′-bis(bromobenzyl) substituted diazacrown ethers **58**, **59** and cyclen or cyclam **73–76** with free diazacrown ethers (Scheme 17). The outcome of these reactions depended strongly on the mutual orientation of bromine and nitrogen reaction centers what is important for such more sterically rigid reactants, and in some cases they yields reached 20–30 % [77].

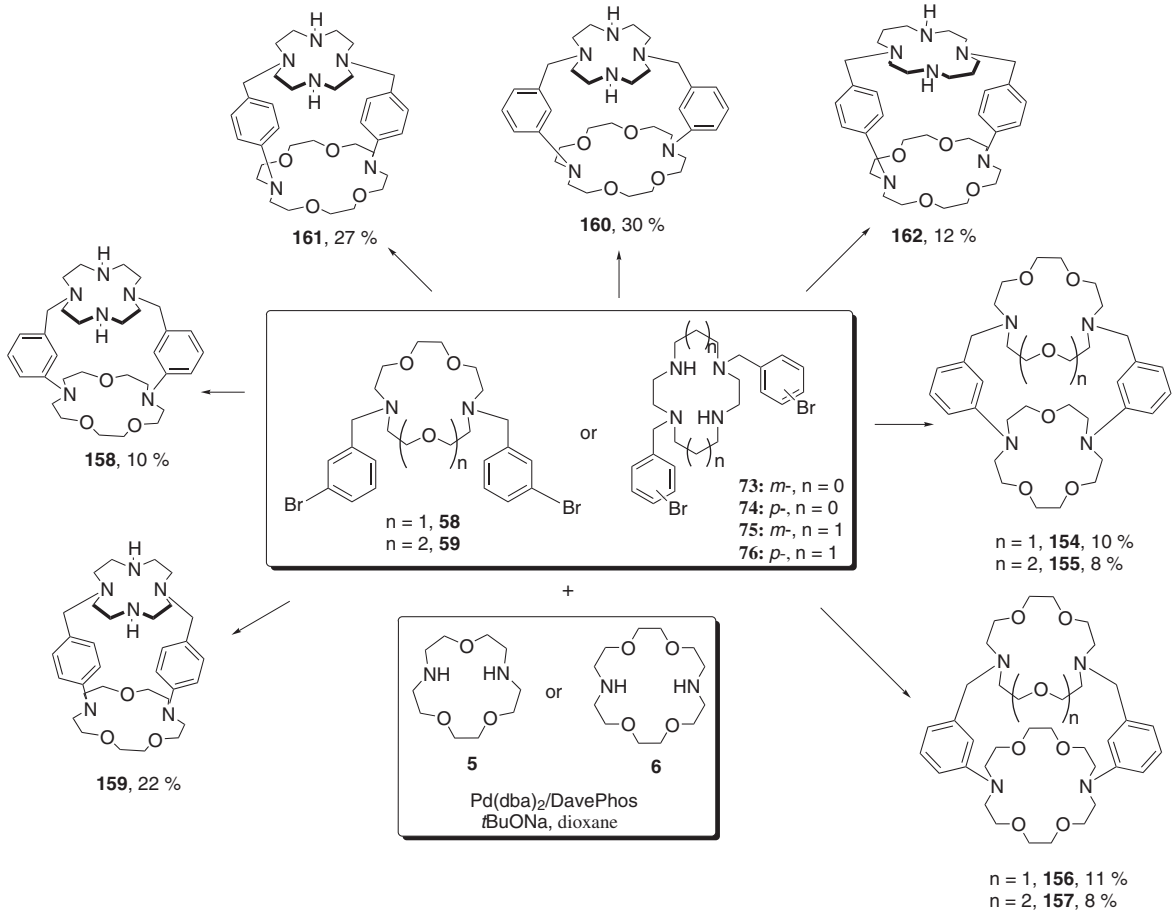
## Polymacrocyclic conjugates with porphyrins

Porphyrins are extremely important and demanded macrocyclic compounds possessing numerous useful and interesting properties among which is their ability to form various metal complexes and unique photophysical characteristics. Taking these facts into consideration, we decided to combine macrocyclic compounds with porphyrins in polymacrocyclic conjugates in view of creating new fluorescent chemosensors for metal cations. Using Pd-catalyzed amination of *meso*-bromophenyl porphyrins **164**, **167** and **168** with diamino derivative of azacrown ethers **163** and **166** we managed to obtain corresponding bis- and trismacrocyclic conjugates **165**, **169** and **170** (Scheme 18) which were tested as potential chemosensors with 17 different metal cations.

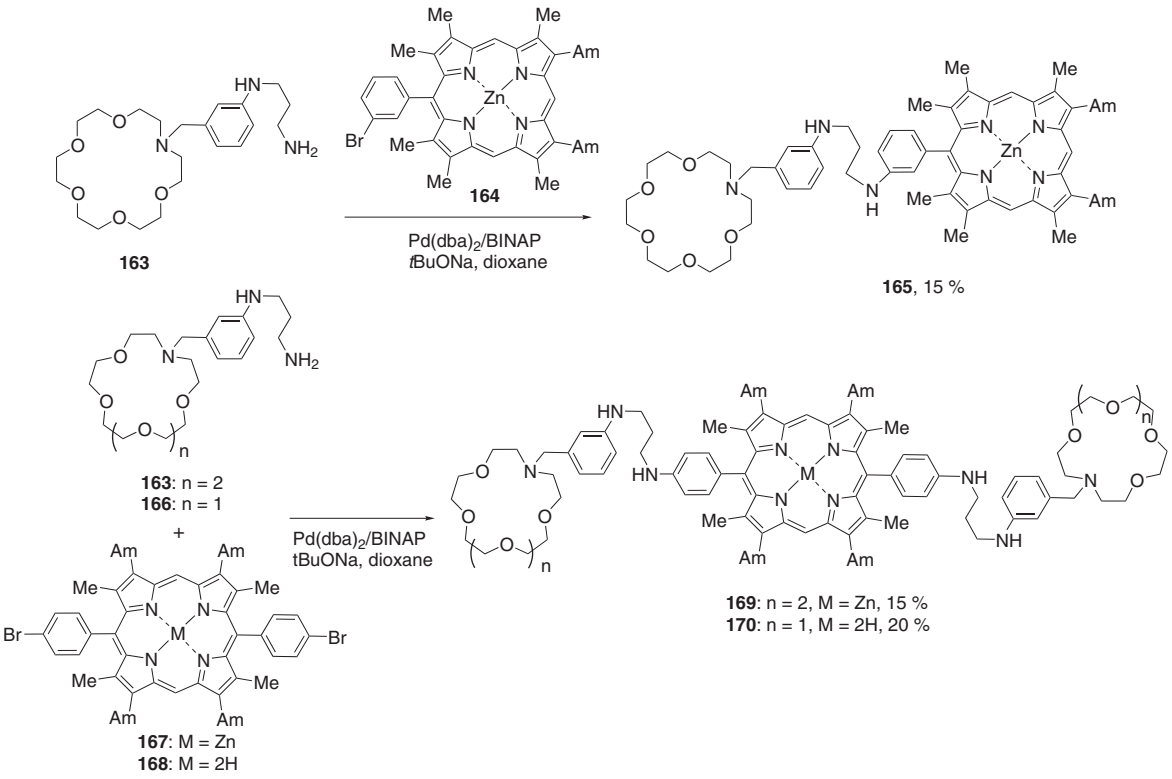
It was established that compounds **165** and **169** could act as selective detectors of Cu(II) ions by full quenching of fluorescence (Fig. 5). Other metals did not intervene in Cu(II) detection. It is worth noting that the conjugate **165** with one azacrown moiety was less sensitive to this metal than the conjugate **169** with two azacrowns attached to 5,15-diphenylporphyrin central unit [78, 79].




**Scheme 16:** The synthesis of Boc-containing macrotricyclic derivatives of cyclen.




**Scheme 17:** The synthesis of cylindrically-shaped macrotricyclic derivatives of diazacrown ethers and tetraazamacrocycles.




**Scheme 18:** The synthesis of bis- and trismacrocyclic conjugates of porphyrins with azacrown ethers.

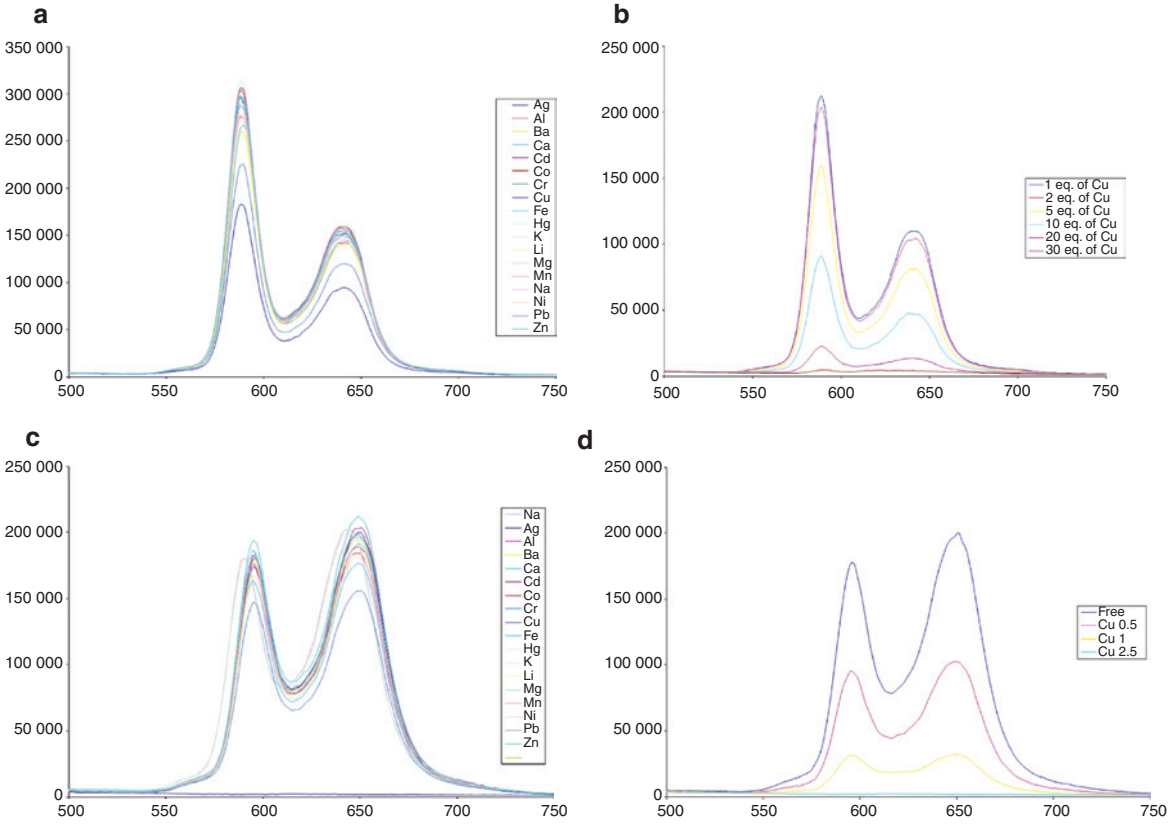
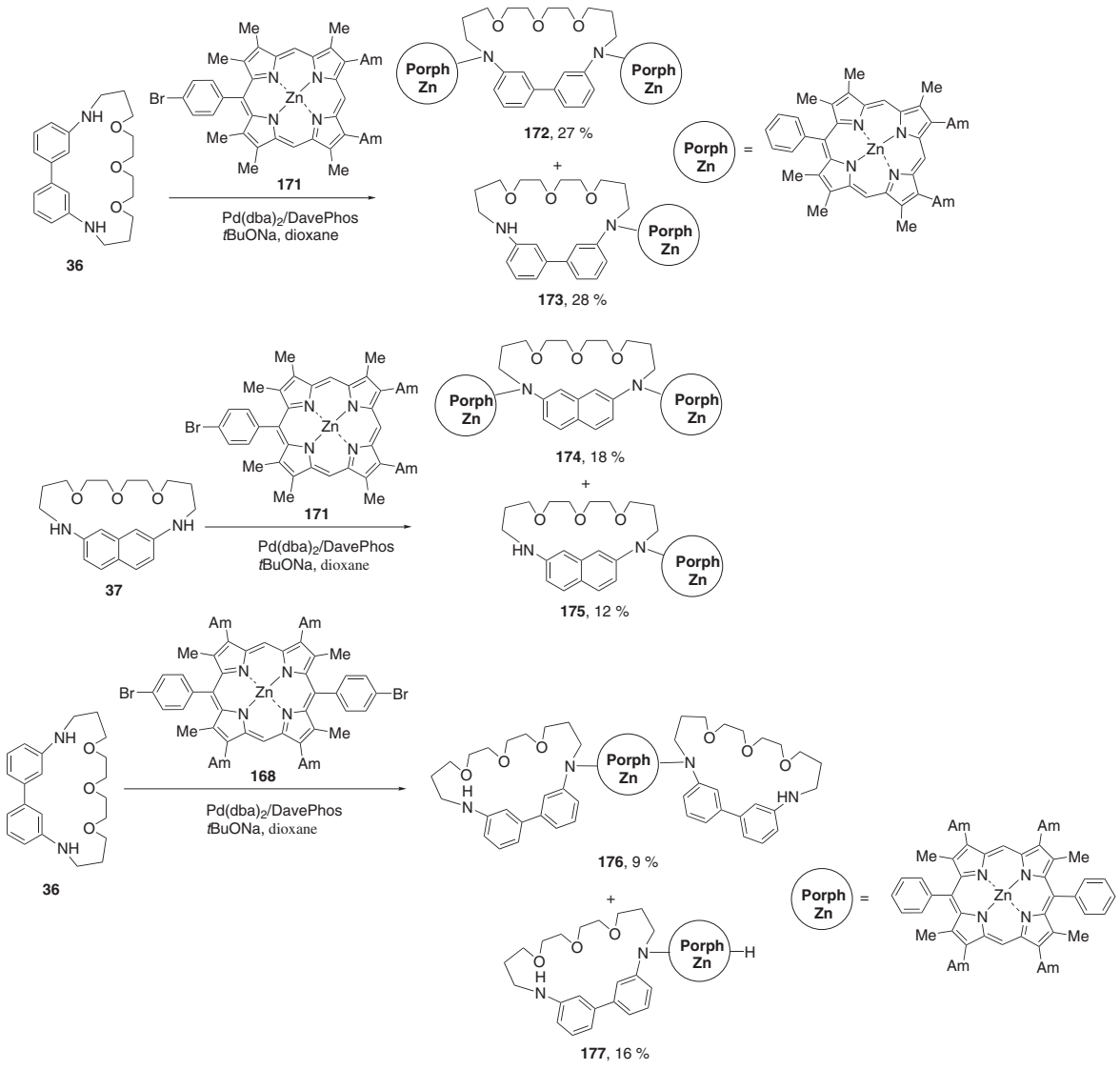



**Fig. 5:** Fluorescence spectra of porphyrin conjugates **165** (a, b) and **169** (c, d) in the presence of 2.5 equiv. metal cations (a, c) and different amounts of Cu(II) perchlorate (b, d).




**Scheme 19:** The synthesis of bis- and trismacrocyclic conjugates of porphyrins with biphenyl- and naphthalene-based diazacrown ethers.

Other porhyrin conjugates were synthesized using previously elaborated trioxadiazacrown ethers on the basis of biphenyl **36** and naphthalene **37**. The arylation of these macrocycles was conducted with Zn(II) mono- and bis(bromophenyl)porphyrinates. As a result, in the reactions with Zn(II) 5-(4-bromophenyl)porphyrinate **171** tris- and bismacrocyclic conjugates **172–175** were obtained: compounds **172** and **174** with two porphyrin units and compounds **173**, **175** with one porphyrin unit (Scheme 19) [80]. The reaction with Zn(II) 5,15-bis(4-bromophenyl)porphyrinate **168** produced trismacrocyclic structure **176** with two trioxadiazamacrocycles and bismacrocycle **177** with one trioxadiazacrown ether unit [81].

The experiments were conducted to find out the most selective chemosensors for metal cations. The emission of trismacrocycle **172** diminished substantially in the presence of Cr(III) cations, while full quenching was observed with Cu(II) and Al(III) (Fig. 6a), bismacrocycle **173** was not so sensitive to the presence of the metal ions and its emission diminished notably with Cu(II) and Pb(II) ions (Fig. 6b). On the other hand, another trismacrocyclic ligand **174** on the basis of the naphthalene-containing trioxadiazacrown ether showed much better selectivity towards Cu(II) cations as only in the presence of this metal its emission quenched totally while other 17 cations altered it insignificantly (Fig. 6c).

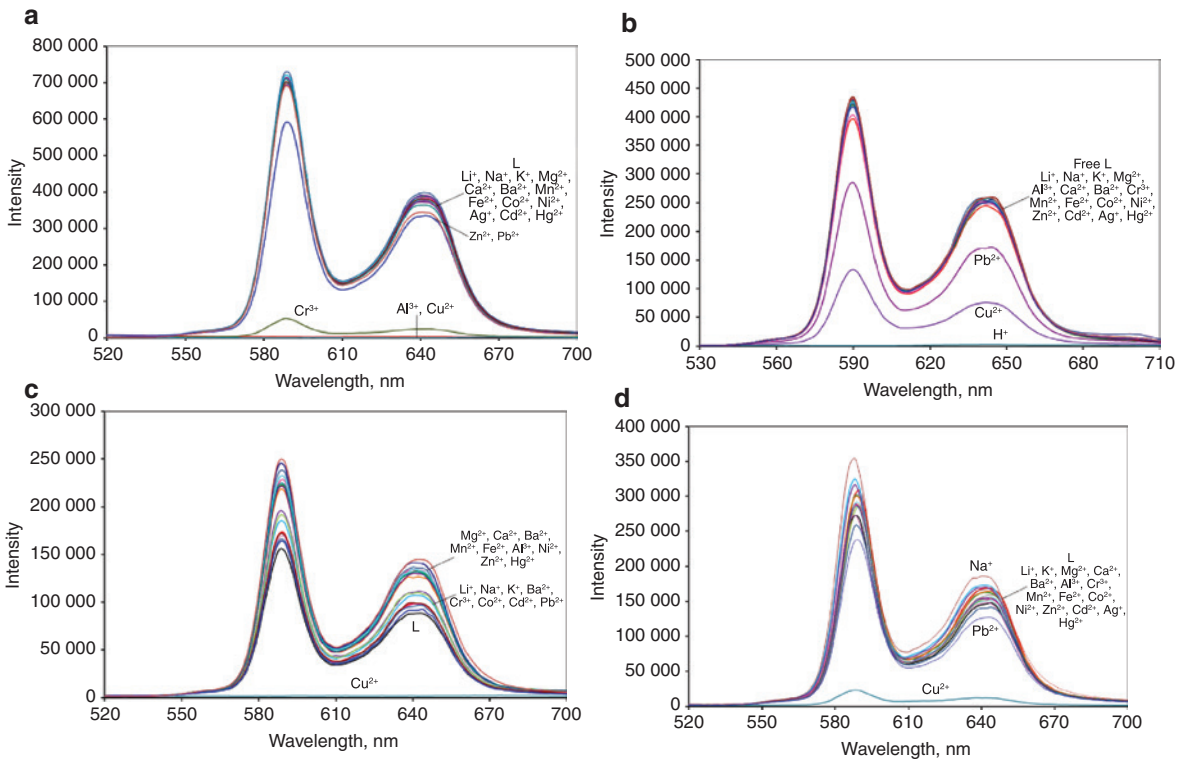
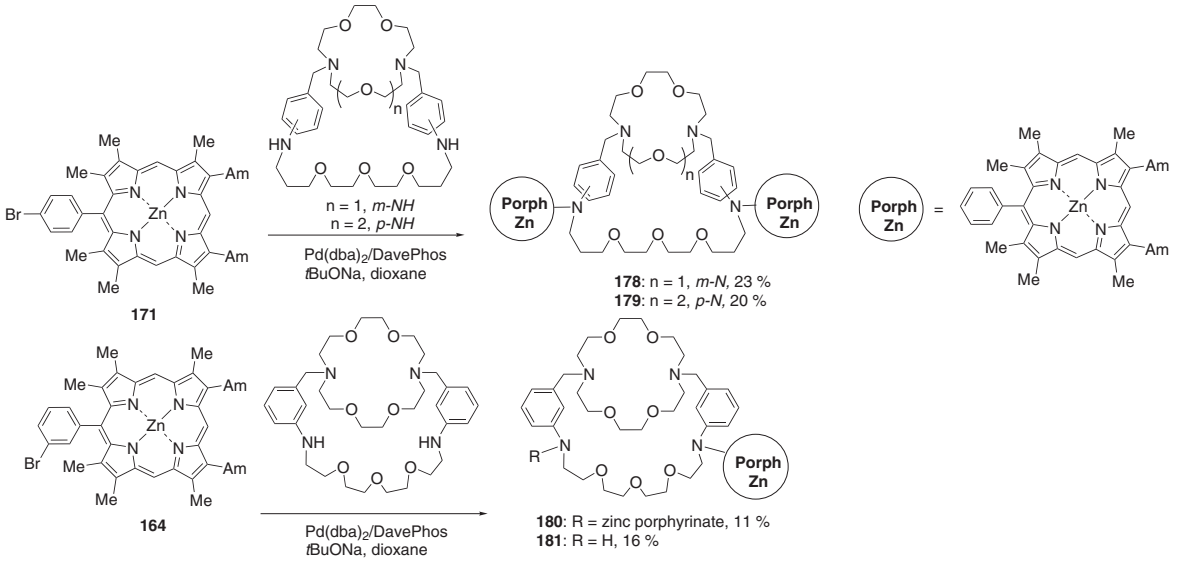



**Fig. 6:** Fluorescence spectra of porphyrin conjugates **172** (a), **173** (b), **174** (c), and **179** (d) in the presence of 5 equiv. metal cations.

More sophisticated polymacrocyclic systems were obtained by the Pd-catalyzed arylation of diazacrown-based macrobicycles with Zn(II) porphyrinates **164** and **171** (Scheme 20) [80, 81]. As in all processes dealing with the arylation of the secondary amino groups in macrocycles with bromophenylporphyrins, the application of $Pd(dba)_2$/DavePhos catalytic system was crucial for successful accomplishment of the process. Compound **179** was shown to be rather selective fluorescent chemosensor for Cu(II) cations as the addition of only this metal led to substantial emission quenching (Fig. 6d).




**Scheme 20:** The synthesis of polymacrocyclic conjugates of porphyrins with diazacrown-based macrobicycles.

## Conclusions

This mini-review demonstrates that on the basis of Pd-catalyzed amination we have successfully developed several approaches to polymacrocyclic compounds with isolated macrocycles and to macropolycyclic cryptands of different architecture. The dependence of the yields of the compounds on the structural types of starting compounds and on the nature of polyamine linkers introduced for the formation of new macrorings was shown. Many compounds thus synthesized were modified with fluorophore groups and tested for the possibility of their application as fluorescent chemosensors of metal cations. The majority of dansyl-containing polymacrocycles proved to be selective towards Cu(II) and Al(III) ions while porphyrin-based conjugates with polyazapolyoxamacrocyclic units can be regarded as prospective fluorescent chemosensors of Cu(II) ions.

**Acknowledgement:** The research was financially supported by the Russian Science Foundation, Funder Id: 10.13039/501100006769 (RSF grant N 14-23-00186P) and partially by the Russian Foundation for Basic Research, Funder Id: 10.13039/501100002261 (RFBR grant N 17-53-16012).

**Article note:** A special collection of invited papers by recipients of the IUPAC Distinguished Women in Chemistry and Chemical Engineering Awards.

## References

[1] E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. Abu El-Fadl, D. N. Reinhoudt. *J. Am. Chem. Soc.* **112**, 6979 (1990).
[2] J. Zavada, J. Koudelka, P. Holy, M. Belohradsky, I. Stibor. *Coll. Czech. Chem. Commun.* **54**, 1043 (1989).
[3] J. Bouquant, A. Delville, J. Grandjean, P. Laszlo. *J. Am. Chem. Soc.* **104**, 686 (1982).
[4] R. C. Helgeson, T. L. Tarnowski, D. J. Cram. *J. Org. Chem.* **44**, 2538 (1979).
[5] S. F. Lincoln, A. Abou-Hamdan. *Inorg. Chem.* **29**, 3584 (1990).
[6] F. H. Kohnke, J. F. Stoddart. *J. Chem. Soc. Chem. Commun.* 314 (1985).
[7] E. Chapoteau, B. P. Czech, A. Kumar, A. Pose. *J. Incl. Phenom.* **6**, 41 (1988).
[8] A. Wallon, J. Peter-Katalinic, U. Werner, W. M. Muller, F. Vogtle. *Chem. Ber.* **123**, 375 (1990).
[9] J. M. Lehn, J. Simon, A. Moradpour. *Helv. Chim. Acta.* **61**, 2407 (1978).
[10] Y. Murakami, J. Kikuchi, T. Ohno, T. Hirayama. *Chem. Lett.* **18**, 881 (1989).
[11] A.-M. Albrecht-Gary, C. O. Dietrich-Buchecker, Z. Saad, J.-P. Sauvage, J. Weiss. *J. Chem. Soc. Chem. Commun.* 1325 (1986).
[12] R. M. Izatt, K. Pawlak, J. S. Bradshaw, R. L. Bruening. *Chem. Rev.* **91**, 1721 (1991).
[13] J. L. Bourque, P. D. Boyle, K. M. Baines. *Chem. Eur. J.* **21**, 9790 (2015).
[14] J. Pitarch-Jarque, R. Belda, F. Lloret, J. Ferrando-Soria, P. Navarro, A. Lopera, E. García-España. *Dalton Trans.* **44**, 3378 (2015).
[15] K. V. Tan, P. A. Pellegrini, B. W. Skelton, C. F. Hogan, I. Greguric, P. J. Barnard. *Inorg. Chem.* **53**, 468 (2014).
[16] D. Over, X. Zeng, C. Bornholdt, J. Marrot, O. Reinaud. *Inorg. Chem.* **52**, 14089 (2013).
[17] G. X. Jin, M. D. Bailey, M. J. Allen. *Inorg. Chem.* **55**, 9085 (2016).
[18] R. F. Zhang, W. J. Hu, Y. A. Liu, X. L. Zhao, J. S. Li, B. Jiang, K. Wen. *J. Org. Chem.* **81**, 5649 (2016).
[19] J. F. Xu, Y. Z. Chen, L. Z. Wu, C. H. Tung, Q. Z. Yang. *Org. Lett.* **16**, 684 (2014).
[20] Y. Habata, M. Ikeda, A. K. Sah, K. Noto, S. Kuwahara. *Inorg. Chem.* **52**, 11697 (2013).
[21] G. Y. Xie, L. Jiang, T. B. Lu. *Dalton Trans.* **42**, 14092 (2013).
[22] X. Ji, M. Zhang, X. Yan, J. Li, F. Huang. *Chem. Commun.* **49**, 1178 (2013).
[23] A. Lélias-Vanderperre, J. C. Chambron, E. Espinosa, P. Terrier, E. Leize-Wagner. *Org. Lett.* **9**, 2961 (2007).
[24] Y. Nakahara, T. Kida, Y. Nakatsuji, M. Akashi. *Org. Biomol. Chem.* **3**, 1787 (2005).
[25] A. Brown, T. Bunchuay, C. Crane, N. White, A. Thompson, P. D. Beer. *Chem. Eur. J.* **24**, 1 (2018).
[26] S. Chakraborty, S. Saha, L. M. P. Lima, U. Warzok, S. Sarkar, B. Akhuli, M. Nandi, S. Bej, N. N. Adarsh, C. A. Schalley, R. Delgado, P. Ghosh. *J. Org. Chem.* **82**, 10007 (2017).
[27] S. Porwanski, F. Moretti, F. Dumarcay-Charbonnier, A. Marsura. *Ann. Pharm. Fr.* **74**, 198 (2016).
[28] J. Pitarch-Jarque, R. Belda, L. García-España, J. M. Llinares, F. Pan, K. Rissanen, P. Navarro, E. García-España. *Dalton Trans.* **44**, 7761 (2015).
[29] P. Mateus, R. Delgado, V. André, M. Teresa Duarte. *Org. Biomol. Chem.* **13**, 834 (2015).
[30] E. Brunetti, A. Inthasot, F. Keymeulen, O. Reinaud, I. Jabin, K. Bartik. *Org. Biomol. Chem.* **13**, 2931 (2015).
[31] J. Li, D. Yim, W. D. Jang, J. Yoon. *Chem. Soc. Rev.* **46**, 2437 (2017).
[32] M. Denis, J. Pancholi, K. Jobe, M. Watkinson, S. M. Goldup. *Angew. Chem. Int. Ed.* **57**, 5310 (2018).
[33] M. Cheng, J. Zhang, X. Ren, S. Guo, T. Xiao, X. Y. Hu, J. Jiang, L. Wang. *Chem. Commun.* **53**, 11838 (2017).

[34] N. Kon, H. Takemura, K. Otsuka, K. Tanoue, S. Nakashima, M. Yasutake, K. Tani, J. Kimoto, T. Shinmyozu, T. Inazu. *J. Org. Chem.* **65**, 3708 (2000).
[35] T. L. Price Jr., H. R. Wessels, C. Slebodnick, H. W. Gibson. *J. Org. Chem.* **82**, 8117 (2017).
[36] H. Struthers, T. L. Mindt, R. Schibli. *Dalton Trans.* **39**, 675 (2010).
[37] I. P. Beletskaya, A. D. Averin, A. G. Bessmertnykh, F. Denat, R. Guilard. *Russ. J. Org. Chem.* **46**, 947 (2010).
[38] A. D. Averin, S. M. Kobelev, M. V. Anokhin, A. G. Bessmertnykh Lemeune, R. Guilard, I. P. Beletskaya. in *Targets in Heterocyclic Systems: Chemistry and Properties*, Vol. 15. O. A. Attanasi, D. Spinelli (Eds.), pp. 193–225 (2011).
[39] A. D. Averin, A. V. Shukhaev, S. L. Golub, A. K. Buryak, I. P. Beletskaya. *Synthesis* 2995 (2007).
[40] A. D. Averin, A. N. Uglov, I. P. Beletskaya. *Chem. Lett.* **37**, 1074 (2008).
[41] I. P. Beletskaya, A. D. Averin, A. G. Bessmertnykh, R. Guilard. *Tetrahedron Lett.* **42**, 4983 (2001).
[42] I. P. Beletskaya, A. D. Averin, N. A. Pleshkova, A. A. Borisenko, M. V. Serebryakova, F. Denat, R. Guilard. *Synlett* 87 (2005).
[43] I. P. Beletskaya, A. D. Averin, O. A. Ulanovskaya, I. A. Fedotenko, A. A. Borisenko, M. V. Serebryakova, F. Denat, R. Guilard. *Chem. Lett.* **34**, 1100 (2005).
[44] A. D. Averin, A. N. Uglov, A. K. Buryak, A. G. Bessmertnykh, R. Guilard, I. P. Beletskaya. *Heterocycles* **80**, 957 (2010).
[45] A. D. Averin, E. R. Ranyuk, N. V. Lukashev, S. L. Golub, A. K. Buryak, I. P. Beletskaya. *Tetrahedron Lett.* **49**, 1188 (2008).
[46] E. Ranyuk, C. Morkos-Douaihy, A. Bessmertnykh, F. Denat, A. Averin, I. Beletskaya, R. Guilard. *Org. Lett.* **11**, 987 (2009).
[47] E. Ranyuk, A. Uglov, M. Meyer, A. Bessmertnykh Lemeune, F. Denat, A. Averin, I. Beletskaya, R. Guilard. *Dalton Trans.* **40**, 10491 (2011).
[48] A. S. Abel, A. D. Averin I. P. Beletskaya. *New J. Chem.* **40**, 5818 (2016).
[49] A. S. Abel, A. Yu. Mitrofanov, Y. Rousselin, F. Denat, A. Bessmertnykh-Lemeune, A. D. Averin, I. P. Beletskaya. *ChemPlusChem.* **81**, 35 (2016).
[50] O. K. Grigorova, A. D. Averin, O. A. Maloshitskaya, I. P. Beletskaya. *Macroheterocycles* **9**, 425 (2016).
[51] O. K. Grigorova, A. D. Averin, O. A. Maloshitskaya, I. P. Beletskaya. *Macroheterocycles* **10**, 446 (2017).
[52] A. D. Averin, A. V. Shukhaev, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Macroheterocycles* **2**, 281 (2009).
[53] I. P. Beletskaya, A. D. Averin, A. G. Bessmertnykh, F. Denat, R. Guilard. *Tetrahedron Lett.* **43**, 1193 (2002).
[54] I. P. Beletskaya, A. G. Bessmertnykh, A. D. Averin, F. Denat, R. Guilard. *Eur. J. Org. Chem.* 281 (2005).
[55] M. V. Anokhin, A. D. Averin, A. K. Buryak, I. P. Beletskaya. *Mendeleev Commun.* **21**, 132 (2011).
[56] M. V. Anokhin, A. D. Averin, A. K. Buryak, I. P. Beletskaya. *Russ. Chem. Bull.* **60**, 992 (2011).
[57] A. A. Yakushev, M. V. Anokhin, A. D. Averin, O. A. Maloshitskaya, I. P. Beletskaya. *Russ. Chem. Bull.* **61**, 1474 (2012).
[58] S. M. Kobelev, A. D. Averin, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Macroheterocycles* **7**, 28 (2014).
[59] A. D. Averin, A. N. Uglov, G. A. Zubrienko, E. A. Tarasenko, A. K. Buryak, I. P. Beletskaya. *Curr. Org. Synth.* **14**, 918 (2017).
[60] A. N. Uglov, G. A. Zubrienko, A. S. Abel, A. D. Averin, O. A. Maloshitskaya, A. Bessmertnykh-Lemeune, F. Denat, I. P. Beletskaya. *Heterocycles* **88**, 1213 (2014).
[61] E. R. Ranyuk, A. D. Averin, I. P. Beletskaya. *Adv. Synth. Catal.* **352**, 2299 (2010).
[62] O. K. Grigorova, A. D. Averin, O. A. Maloshitskaya, V. B. Rybakov, I. P. Beletskaya. *Macroheterocycles* **9**, 418 (2016).
[63] A. A. Yakushev, N. M. Chernichenko, M. V. Anokhin, A. D. Averin, A. K. Buryak, F. Denat, I. P. Beletskaya. *Molecules* **19**, 940 (2014).
[64] N. M. Chernichenko, A. D. Averin, A. K. Buryak, I. P. Beletskaya. *Russ. Chem. Bull.* **63**, 2056 (2014).
[65] A. A. Yakushev, M. V. Anokhin, A. D. Averin, O. A. Maloshitskaya, E. N. Savelyev, G. M. Butov, B. S. Orlinson, I. A. Novakov, I. P. Beletskaya. *Macroheterocycles* **6**, 40 (2013).
[66] A. D. Averin, A. V. Shukhaev, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Tetrahedron Lett.* **49**, 3950 (2008).
[67] A. D. Averin, K. S. Tyutenov, A. V. Shukhaev, S. M. Kobelev, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Heterocycles* **86**, 1341 (2012).
[68] A. D. Averin, A. V. Shukhaev, A. I. Vovk, V. P. Kukhar, F. Denat, R. Guilard, I. P. Beletskaya. *Macroheterocycles* **7**, 174 (2014).
[69] S. M. Kobelev, A. D. Averin, A. K. Buryak, E. N. Savelyev, B. S. Orlinson, G. M. Butov, I. A. Novakov, F. Denat, R. Guilard, I. P. Beletskaya. *ARKIVOC* **vii**, 196 (2012).
[70] S. M. Kobelev, A. D. Averin, A. K. Buryak, A. I. Vovk, V. P. Kukhar, F. Denat, R. Guilard, I. P. Beletskaya. *Heterocycles* **90**, 989 (2015).
[71] S. M. Kobelev, A. D. Averin, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Heterocycles* **82**, 1447 (2011).
[72] S. M. Kobelev, A. D. Averin, O. A. Maloshitskaya, F. Denat, R. Guilard, I. P. Beletskaya. *Macroheterocycles* **5**, 389 (2012).
[73] N. M. Chernichenko, V. N. Shevchuk, A. D. Averin, O. A. Maloshitskaya, I. P. Beletskaya. *Synlett* **28**, 2800 (2017).
[74] A. D. Averin, N. M. Chernichenko, V. N. Shevchuk, O. A. Maloshitskaya, F. Denat, I. P. Beletskaya. *Macroheterocycles* **11**, 141 (2018).
[75] N. M. Chernichenko, A. D. Averin, I. P. Beletskaya. *Lett. Org. Chem.* **15**, 425 (2018).
[76] S. M. Kobelev, A. D. Averin, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Tetrahedron Lett.* **53**, 210 (2012).
[77] S. M. Kobelev, A. D. Averin, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya. *Macroheterocycles* **7**, 28 (2014).
[78] A. A. Yakushev, A. D. Averin, O. A. Maloshitskaya, S. A. Syrbu, O. I. Koifman, I. P. Beletskaya. *Macroheterocycles* **9**, 65 (2016).
[79] A. A. Yakushev, A. D. Averin, O. A. Maloshitskaya, S. A. Syrbu, O. I. Koifman, I. P. Beletskaya. *Mendeleev Commun.* **26**, 199 (2016).
[80] A. A. Yakushev, A. D. Averin, O. A. Maloshitskaya, O. I. Koifman, S. A. Syrbu, I. P. Beletskaya. *Macroheterocycles* **11**, 135 (2018).
[81] A. D. Averin, A. A. Yakushev, O. A. Maloshitskaya, O. I. Koifman, S. A. Syrbu, I. P. Beletskaya. *Russ. Chem. Bull.* **66**, 1456 (2017).