Conference paper

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Pd(0)-catalyzed amination in the synthesis of chiral derivatives of BINAM and their evaluation as fluorescent enantioselective detectors

https://doi.org/10.1515/pac-2020-0205

Abstract: A mini-review covers recent successes in the synthesis of (*S*)-1,1′-binaphthyl-2,2′-diamine (BINAM) using Pd(0)-catalyzed amination reactions. As a result, versatile compounds with *C*2-chiral backbone were synthesized, among them are derivatives bearing additional chiral amino and fluorophore groups like dansyl amide, 7-methoxycoumarin, 6-aminoquinoline, different macrocyclic compounds with oxadiamine and polyamine linkers were obtained as well. BINAM derivatives of various structures were evaluated as fluorescent enantioselective detectors for a series of model amino alcohols. Many of them were shown to be efficient in sensing certain enantiomers of the amino alcohols by selective changes in the emission in the presence of these analytes. Small changes in the structure of the BINAM derivatives lead to serious difference in the recognition ability of the compounds under investigation.

Keywords: Amination; amines; 1,1′-binaphthyl-2,2′-diamine; chirality; detection; fluorescence; macrocycles; Mendeleev-21; Pd catalysis.

Introduction

The necessity for the development of reliable and express methods for the analysis of optical isomers of the organic compounds stems from the boosting synthesis of medicaments and agrochemicals in enantiomerically pure form, performing enantioselective catalytic reactions which increasingly demand various chiral catalysts, wide-scale monitoring of environment in which biologically relevant, i.e., optically pure compounds play a crucial role. Diverse analytical tools involving spectra of fluorescence are advantageous in sensitivity, selectivity and, in line with the miniaturization of spectrofluorometers, such analyses become more and more handy.

Article note: A collection of invited papers based on presentations at the 21st Mendeleev Congress on General and Applied Chemistry (Mendeleev-21), held in Saint Petersburg, Russian Federation, 9–13 September 2019.

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The investigation of the spectra of fluorescence of optically active compounds and their dependence on the presence of individual enantiomers of analytes aimed at the construction of fluorescent enantioselective detectors begins from late 1970s. In 1978 the fluorescence quenching of 1,1′-binaphthalene in the presence of *N*,*N*-dimethyl-α-phenylethylamine was reported [1], later the fluorescence of a more complex compound, immobilized BINOLphosphoric acid monoamide (BINOL = 1,1′-bi-2,2′-naphthol), was studied using the same amine [2]. Beginning from 1992 systematic investigations of the influence of chiral amines on the optically pure BINOL [3] laid the basis for the application of this most demanded molecule in the enantiomers recognition using fluorescence spectroscopy. Up to present several reviews dealing with this problem were published [4–7], they encompass various types of fluorescent detectors, in some works the emphasis is made on the application of macrocyclic compounds [8, 9], other describe the role of synthetic and supramolecular oligomers, polymers, nanoparticles and organometallic compounds in fluorescent sensing of various chiral objects [9, 10]. It should be noted that natural amino acids, their *N*- and *O*-derivatives are the preferred analytes almost in all publications.

The detection of individual enantiomers of optically active compounds using fluorescence spectroscopy is based on the systematic changes in the emission spectra (quenching or enhancement) of a chiral detector upon the formation of a molecular complex with a particular enantiomer of the analyte. Two opposite enantiomers form two diastereomers with the detector which is also taken as an individual optical isomer, and as physical properties of two diastereomers differ to much or less extent, the same is true for their spectra of fluorescence. In this case, another enantiomer either does not cause considerable changes in the fluorescence of the detector due to a significantly lower stability constant of the molecular complex, or the complexation is accompanied by a change in the fluorescence with a sign opposite to that caused by another enantiomer. On the other hand, while the alteration of the emission by opposite enantiomers differing in the intensity but with the same sign is not suitable for qualitative observations, it can be employed for quantification, i.d. for the control of optical purity of the analyte, provided the changes are substantial and well distinguishable.

The fact that the majority of studies are dedicated to the use of BINOL derivatives is due to the inherent chirality and fluorescent properties of this unique molecule. As a result of the presence of two close hydroxyl groups in its structure it easily forms molecular complexes with various polar organic compounds. To enhance the selectivity, various modifications of BINOL were elaborated. The introduction of the substituents at positions 3 and 3′ resulted in the creation of chemosensors for *N*-Boc-alanine and *N*-Boc-phenylalanine exploiting emission quenching in the presence of one enantiomer [11, 12]. The combination of two BINOL fragments with an amine linker via their oxygen atoms allowed the formation of efficient sensors for mandelic acid, in this case the enhancement of the fluorescence was used for detection [13, 14]. The same analyte can be analyzed by the compound obtained by the introduction of two BINOL groups and two chiral moieties of 1,2-diaminocyclohexane in a macrocycle [15, 16]. Various substituents were tested in 3 and 3′-positions of BINOL, like amines [17, 18], diamines [19], and amino alcohols [20, 21], the resulting compounds were used as chemosensors for *N*-Boc derivatives of amino acids and α-oxycarboxylic acids. BINOLs modified with chiral ureas and thioureas at the oxygen atoms were employed for the recognition of enantiomers of phenylglycine, tryptophan, mandelic and malic acids [22–24]. Heterocycles like imidazoline were used in the synthesis of linear [25] and macrocyclic [26] BINOL derivatives, a complex macrocycle with BINOL, two triazine and two chiral amino acid linkers was useful to increase stereodiscrimination in the formation of complexes with various enantiomers [26].

In some cases the inherent fluorescence of BINOL is thought to be insufficient, thus additional fluorophores are introduced in the molecules to take advantage of the fluorescence at longer wavelengths, e.g., the derivative with two BODIPY groups at 3 and 3′ positions of BINOL was described [27]. To analyze chiral amines and amino alcohols, dimeric, oligomeric, or dendrimeric BINOL derivatives are employed which contain substituents at positions 3,3′ or 6,6′ [28–32]. An unusual oligoBINOL macrocycle was obtained by self-assembling in which the moieties are linked through rhenium complexes [33]. Different ways exist to couple BINOL with various macrocycles. Thus, to detect anions of the tartaric acid, bis(triazacyclononanyl) derivative of BINOL was tested [34], the side arm of the calix[4]crown ether was modified with BINOL [35]. The enantiomeric recognition of optically active amines and amino acids was carried out using a crown ether derivative

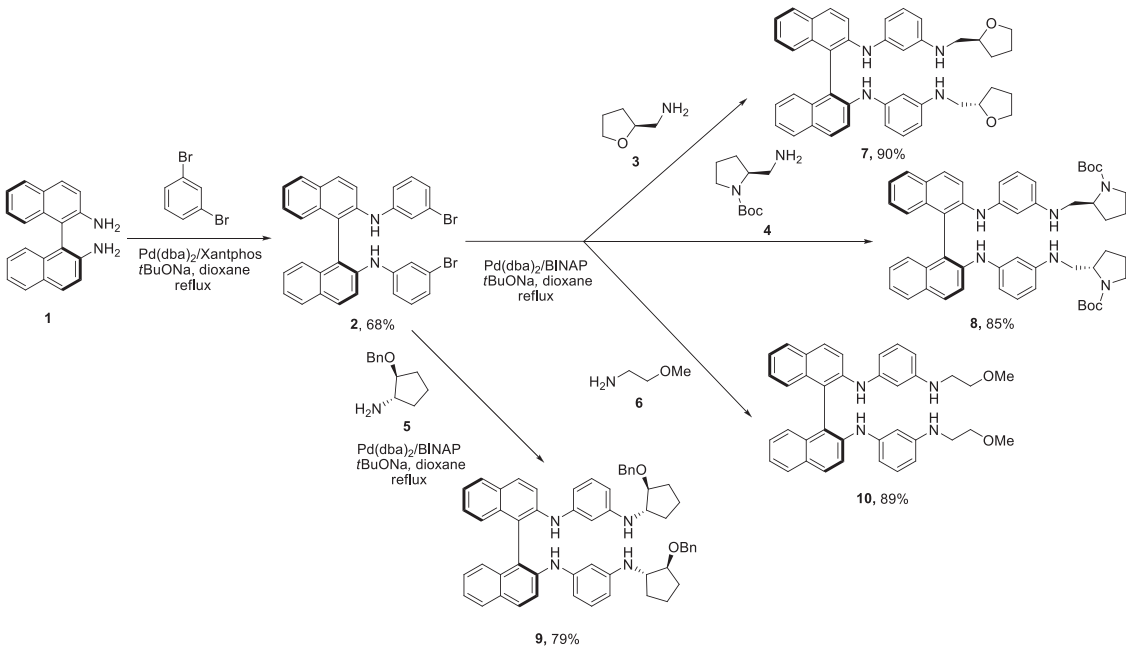
of BINOL containing two additional chiral endocyclic carbon centers [36]. The BINOL-containing derivative of the crown ether with an additional dinitrophenyl chromophore group [37], azacrown ether bearing endocyclic BINOL fragment and exocyclic anthracene fluorophore [38] are examples of the peculiar combinations of various receptor and sensing units. The latter can be used not only for the recognition of chiral alkylammonium salts but also for detecting Hg(II), Cu(II) and Zn(II) cations. It was possible even to combine two BINOL and two coplanar porphyrin macrocycles in one polymacrocyclic compound [39, 40]. Recently described BINOL-containing macrocycle can be used for amino acids detection [41], another macrocycle with the same chiral moiety is able to assess enantiomeric excess of chiral carboxylates [42]. An interesting macrocyclic chemosensor combining BINOL and deoxycholic acid units gives a selective response in the presence of Hg(II), while the complex formed allows the recognition of amino acids enantiomers [43].

It is worth noting that though the nitrogen-containing analogue of BINOL, i.e., 2,2′-diamino-1,1′-binaphthalene (BINAM) was studied as a potential fluorescent detector quite a long ago and showed its efficiency in the recognition of α-phenylethylamine enantiomers [44], it was not yet developed further. Only scarce information about the application of this compound and its derivatives can be found in literature. Thus, the attempts to recognize tryptophan enantiomers using free BINAM were undertaken [45], BINAM was combined with two residues of chiral thiourea to detect mandelic acid [46]. Chiral polymers were synthesized on the basis of BINOL and BINAM for the detection of phenylalanine by the enhancement of emission intensity [47]. However, further systematic investigations were not carried out in this direction. Taking these facts into consideration we decided to develop the synthesis of BINAM-containing detectors using a powerful synthetic tool, i.e., palladium-catalyzed amination reactions [48, 49]. We acquired good experience in the synthesis of macrocyclic compounds with the help of this catalytic reaction [50, 51], among molecules synthesized by us are those containing endocyclic fluorophore moieties like diaminonaphthalene [52], 2,2′-bipyridine [53], anthracene [54], anthraquinone [55], quinoline [56], 1,10-phenanthroline [57]. Also we managed to obtain planar-chiral macrocycles comprising 1,5-diaminoanthraquinone moiety which possesses fluorescent properties [58, 59]. In this paper our progress in the synthesis of BINAM-based compounds of various architecture is described.

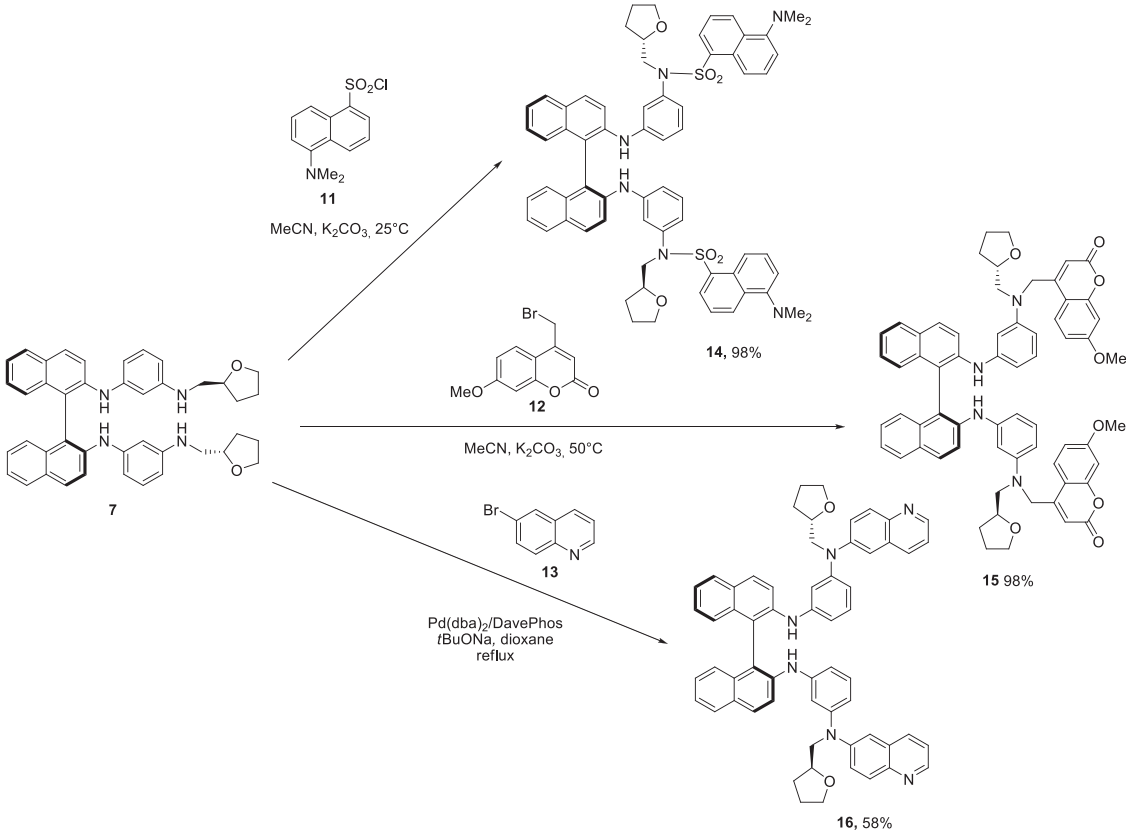
(*S*)-BINAM substituted with chiral and fluorophore groups

First (*S*)-BINAM (**1**) was modified with two 3-bromophenyl substituents using Pd(0)-catalyzed amination reaction and the resulting compound **2** was further used in various transformations (Scheme 1) [60]. Also, under the conditions of the palladium catalysis, by the action of optically pure amines **3–5** it was transformed into derivatives **7–9** each possessing two chiral substituents. This was performed to enhance possible stereodiscrimination of the resulting products due to the presence of additional chiral groups able of forming complexes with polar molecules. The reaction of **2** with 2-methoxyethylamine (**6**) afforded compound **10** which possesses two short non-chiral *N*,*O*-podands. All reactions gave high yields of the corresponding products of diamination **7–10** (79–90%).

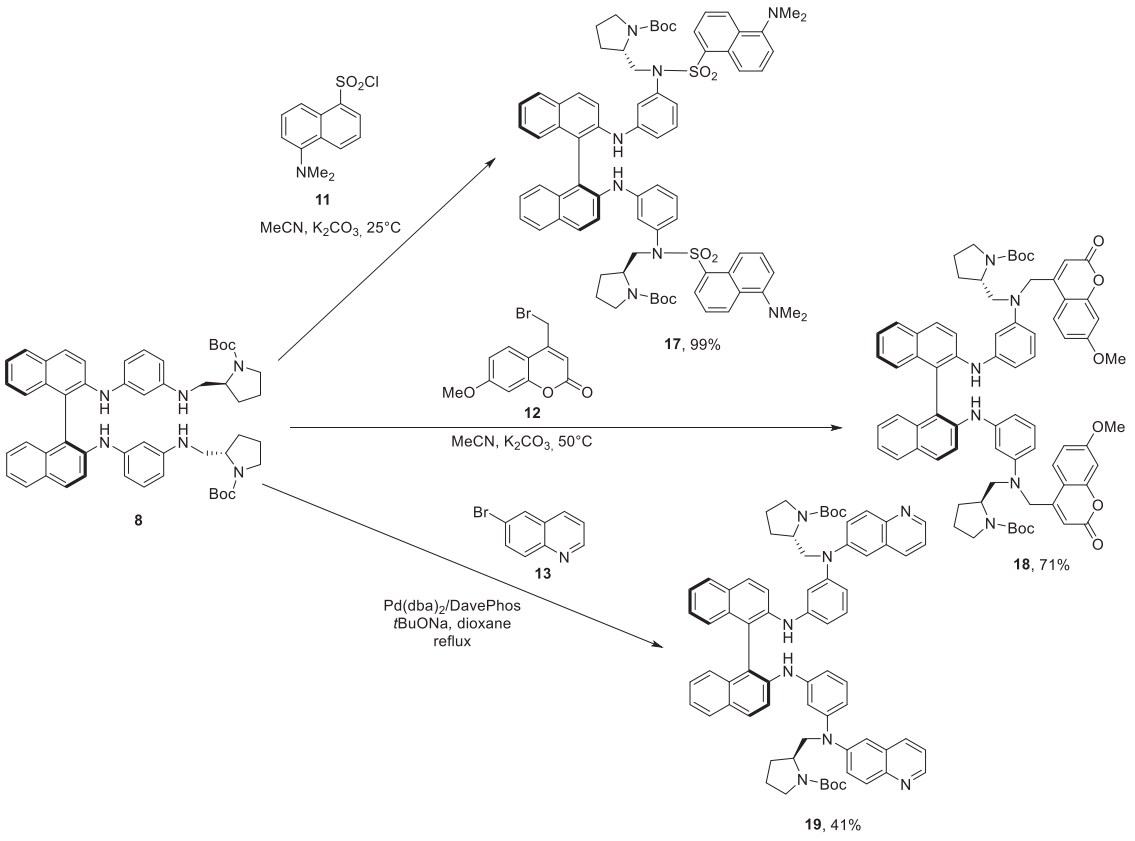
The BINAM derivatives **7**, **8**, **10** were further transformed into more complex compounds by introducing additional fluorophore groups. It was done in view of the improvement of the fluorescent properties of the detectors by red-shifting the emission maxima, also this could change the coordination properties of these compounds as all tested fluorophore groups (dansylamide, 7-methoxycoumarin and quinoline) possess additional donor sites able to participate in the molecular complex formation. As for the bis(tetrahydrofurfurylamino) substituted compound **7**, it was modified with two dansylamide and 7-methoxycoumarin groups according to simple nucleophilic substitution reactions affording corresponding derivatives **14** and **15** in almost quantitative yields (Scheme 2), while to obtain diquinolinyl derivative **16**, 4 equivalents of 6-bromoquinoline were needed alongside with high catalyst loadings as the arylation of the secondary amino group as usually is not a simple task [61].



Scheme 1: Pd(0)-catalyzed modification of BINAM with *N*- and *O*-containing groups including chiral ones.



Scheme 2: Modification of the compound **7** with fluorophore groups.



Scheme 3: Modification of the compound **8** with fluorophore groups.

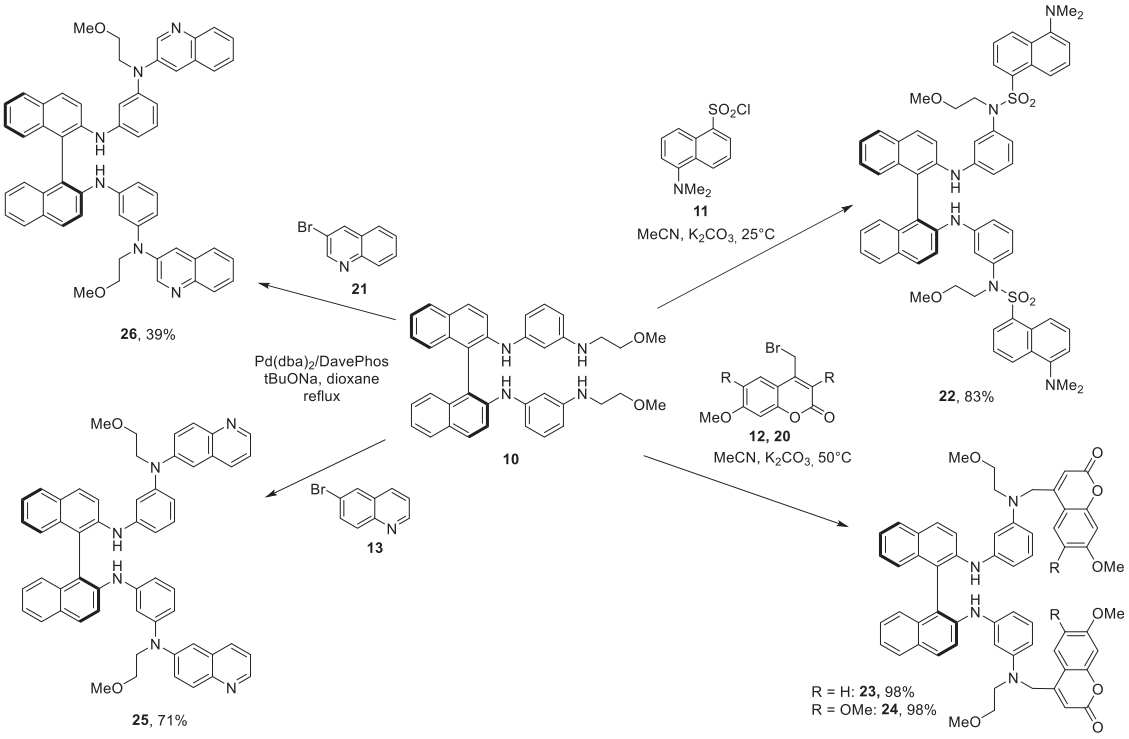
The same reactions with di(*N*-Boc-pyrrolidinyl) compound **8** produced didansylated derivative **17** in almost quantitative yield, its decoration with two 7-methoxycoumarin groups was also efficient, however, catalytic transformation to introduce quinoline fluorophore carried out with 6-bromoquinoline was somewhat less efficient (Scheme 3) [60]. Probably, this was due to difficulties in the separation of the target product **19** from resting bromoquinolines taken in 2-fold excess.

The attempts to fulfill the same reactions in the case of the bis(benzyloxycyclopentylamino) derivative **9** were totally unsuccessful due to the steric hindrances at the secondary amino groups. Even simple nucleophilic substitution with the most active dansyl chloride **11** did not proceed at all. Thus this compound should be used as a possible detector as it is, using the inherent fluorescence of the BINAM unit.

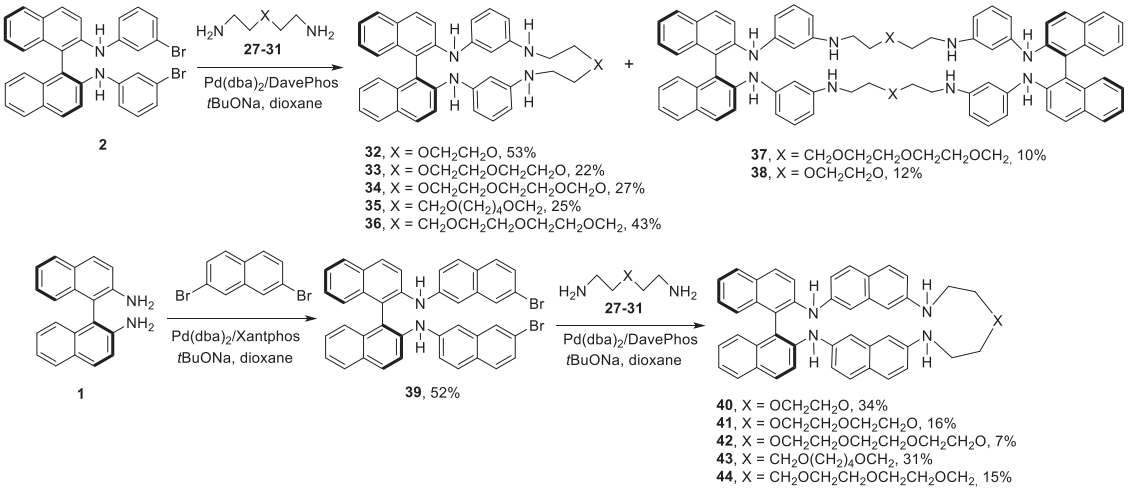
The modifications of the bis(2-methoxyethylamino) BINAM derivative **10** were carried out using dansyl chloride **11**, 7-methoxy- and 6,7-dimethoxy-4-bromomethylcoumarins **12** and **20**, 6-bromo- and 3-bromoquinolines **13** and **21** (Scheme 4). Except for the last reaction, in all other syntheses the yields of the target products **22–25** were high (71–98%). Thus, a substantial variety of BINAM derivatives bearing different additional chiral and fluorophore groups was synthesized by the combination of the catalytic and non-catalytic approaches.

Macrocyclic derivatives of (*S*)-BINAM

The next approach to BINAM modification is the introduction of this fluorescent chiral unit into macrocyclic structures. For this purpose we carried out a series of Pd(0)-catalyzed macrocyclization reactions of *N*,*N*′-di(3-bromophenyl) substituted BINAM **2** with various oxadiamines **27–31** which gave corresponding



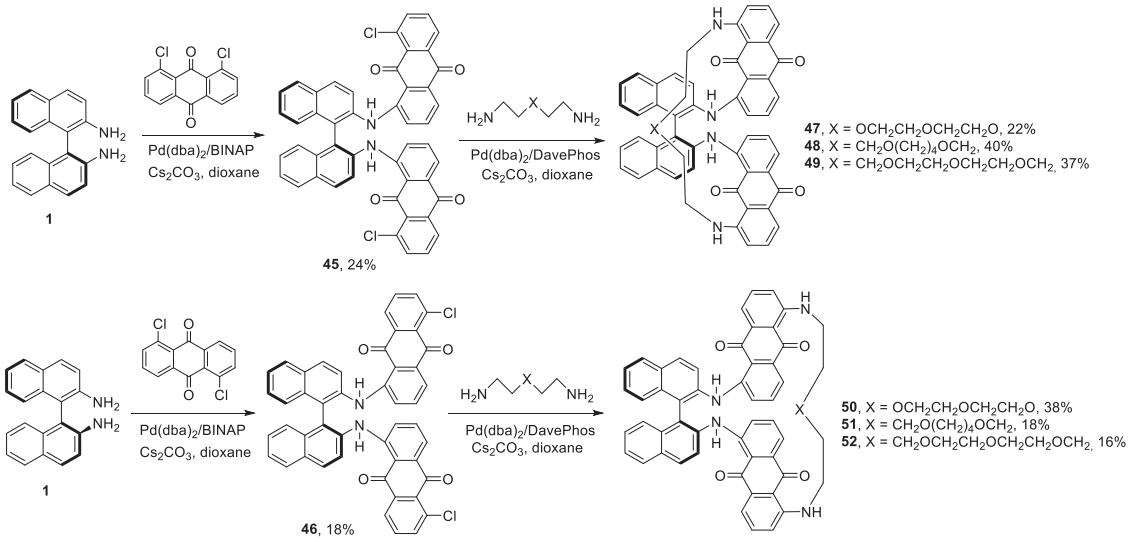
Scheme 4: Modification of the compound **10** with fluorophore groups.



Scheme 5: Synthesis of BINAM-containing macrocycles with phenylene and napththalene spacers.

chiral macrocyclic compounds **32–36** (Scheme 5) [62]. Their yields were dependent on the nature of the starting oxadiamines (chain length, number of oxygen atoms and methylene groups between N and O atoms), and in the best case (compound **32**) exceeded 50%. Also cyclic dimers **37** and **38** were isolated in individual state as second products. The formation of the macrocycles with naphthalene spacers **40–44** was also successful, though the yields were lower and did not surpass 34%.

Interesting macrocycles were obtained in the reactions of isomeric 1,8- and 1,5-dichloroanthraquinones with (*S*)-BINAM followed by the catalytic macrocyclization processes (Scheme 6) [63]. The resulting molecules **47–52** possess diaminoanthraquinone moieties which exhibit more intensive fluorescence in comparison with



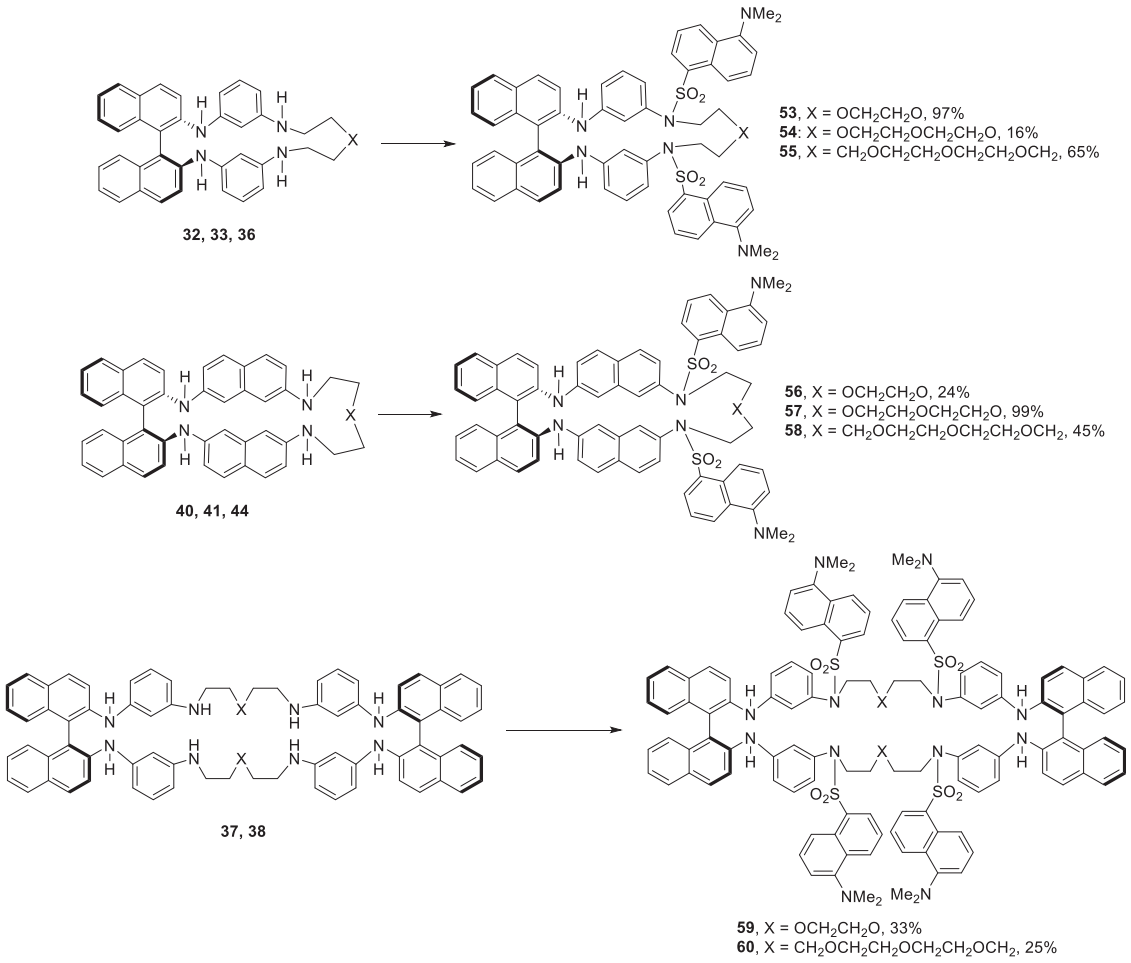
Scheme 6: Synthesis of BINAM-containing macrocycles with anthraquinone spacers.

that of BINAM, but with the emission maximum blue-shifted. Compounds **47–49** and **50–52** differ by the reciprocal positions of aromatic and aliphatic parts of these sophisticated macrocycles, their yields proved to be seriously dependent on the nature of starting compound and ranged from 16 to 40%.

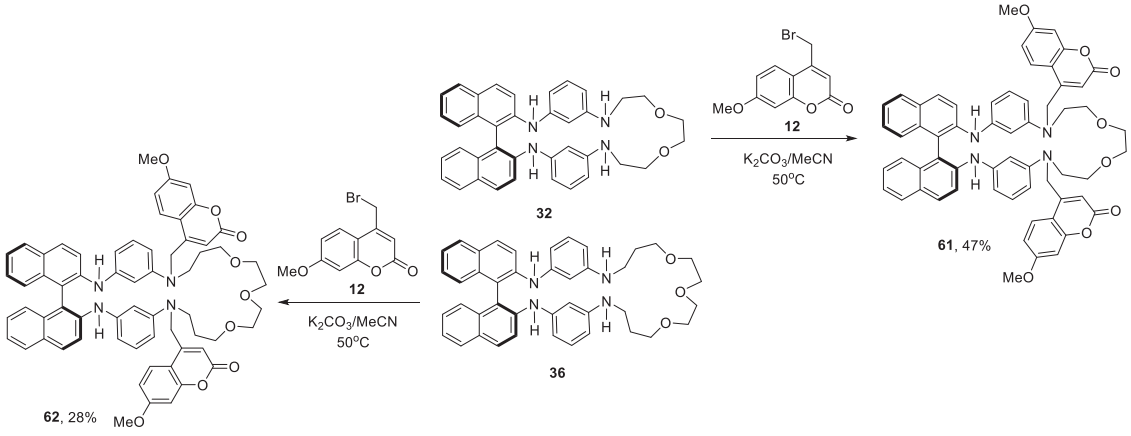
Macrocycles with phenylene and naphthalene spacers were modified with dansyl amide exocyclic fluorophore groups (Scheme 7). The reactions with dansyl chloride (**11**) were found to be crucially dependent on the structure of starting compounds. Unexpectedly the yields of the products **53–58** varied from very low 16% (product **54**) up to 97-99% (compounds **53**, **57**). Probably, the reason is the difference in the nucleophilicity of the nitrogen atoms caused by the conformational features arising from the different structures of oxadiamine linkers in these molecules. The application of excess dansyl chloride or running the reactions at elevated temperature did not improve the results.

The modifications of the macrocycles with another fluorophore group, i.e., 7-methoxycoumarin, was not a simple task, it demanded carrying out the process at 50 °C to ensure better consumption of the starting bromide **12**, however, the isolation of the target products **61** and **62** in pure state was quite tedious and modest yields 47 and 28% well correspond to this fact (Scheme 8). In contrast, the catalytic heteroarylation reactions of the selected macrocycles **32**, **36**, **40**, **44** with 6-bromoquinoline or 3-bromoquinoline turned to be generally more efficient, providing 36–73% yields of the corresponding diquinolinyl derivatives **63–68** (Scheme 9). As in the case with simpler BINAM derivatives described above, application of 4 equivalents of bromoquinolines was inevitable to ensure better conversion of the macrocycles into desirable derivatives.

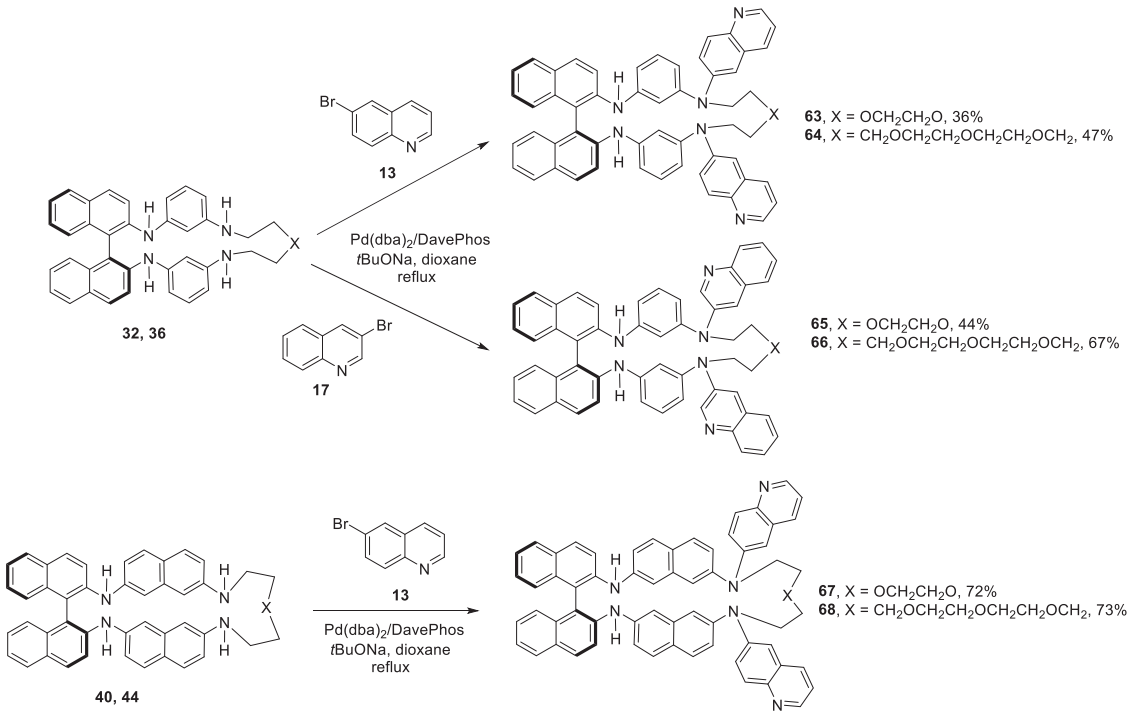
We also attempted the synthesis of BINAM-containing macrocycles with tri- and tetraamino linkers in order to diversify the nature of the coordination sites of the detectors (Scheme 10). It was crucial to proceed the reactions using 1.5 excess of corresponding polyamines **69–72** as was found to be helpful in our previous works on the 1,4,7-triazacyclononane-based cryptands synthesis [64–66]. The yields of the desirable products **73–76** were dramatically dependent on the polyamine structure, and in the case of the most capricious tris(3--aminopropyl)amine **72**, the right choice of the ligand (Josiphos) was important to ensure a better yield of **76**. Compounds **74** and **76** were modified with the dansyl amide fluorophore groups, in both cases the application of small excess of dansyl chloride was important to ensure full substitution at all nitrogen atoms. Thus, tetra- and tridansylated compounds **77** and **78**, respectively, were obtained. As a result, a series of various macrocycles with the central chiral BINAM moiety was elaborated and many of them were further equipped with additional exocyclic fluorophore groups.



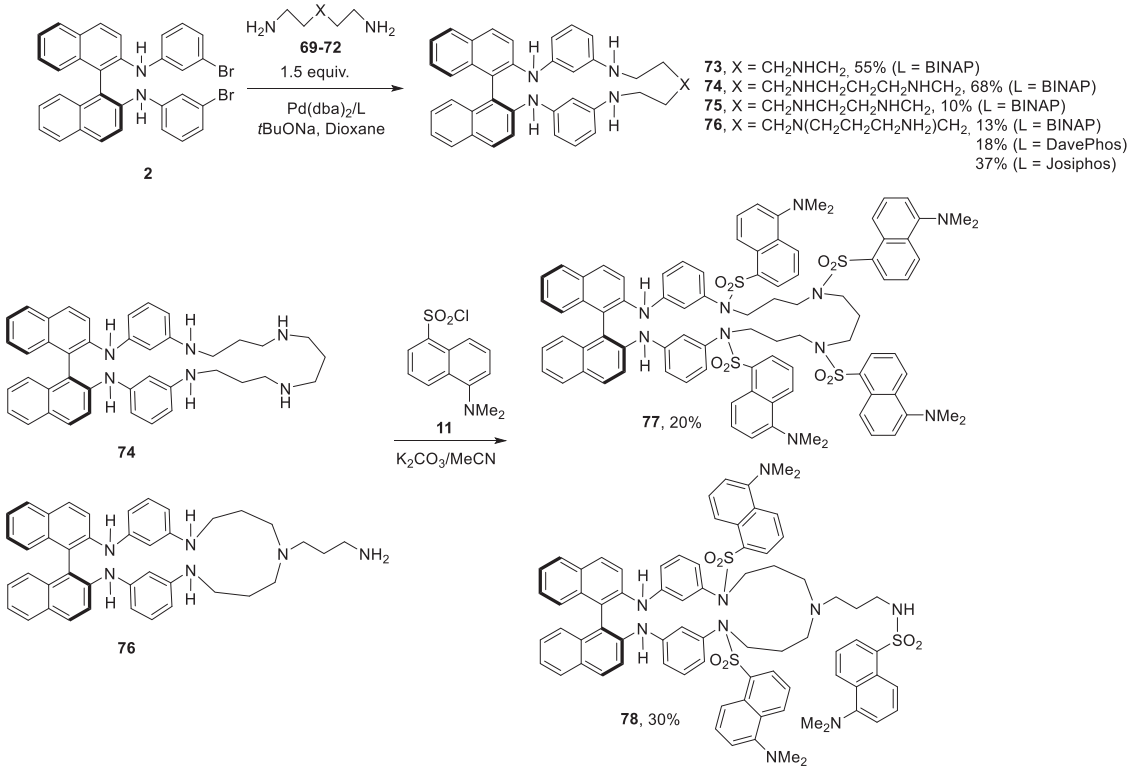
Scheme 7: Introduction of exocyclic dansylamide fluorophores into BINAM-containing macrocycles.



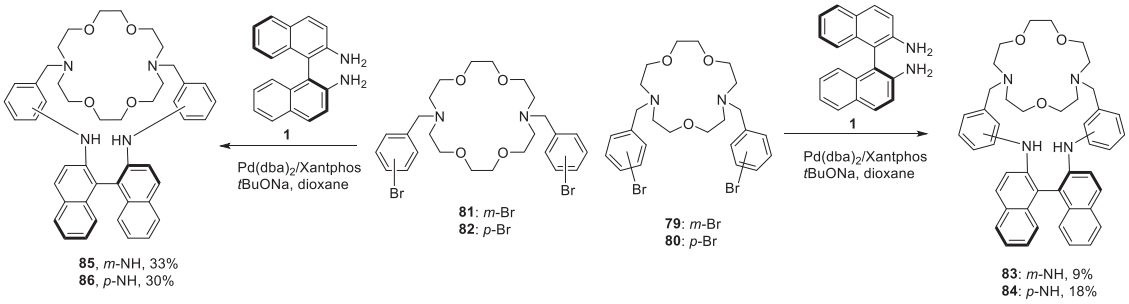
Scheme 8: Introduction of exocyclic 7-methoxycoumarin fluorophores into BINAM-containing macrocycles.



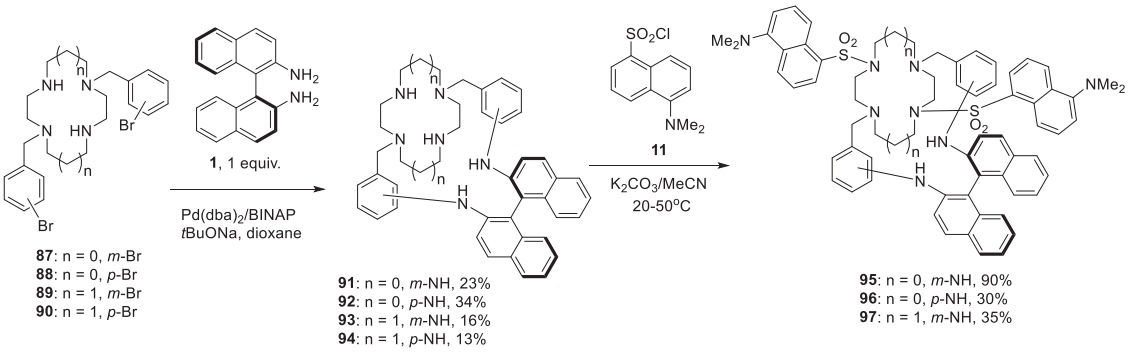
Scheme 9: Introduction of exocyclic quinoline fluorophores into BINAM-containing macrocycles.



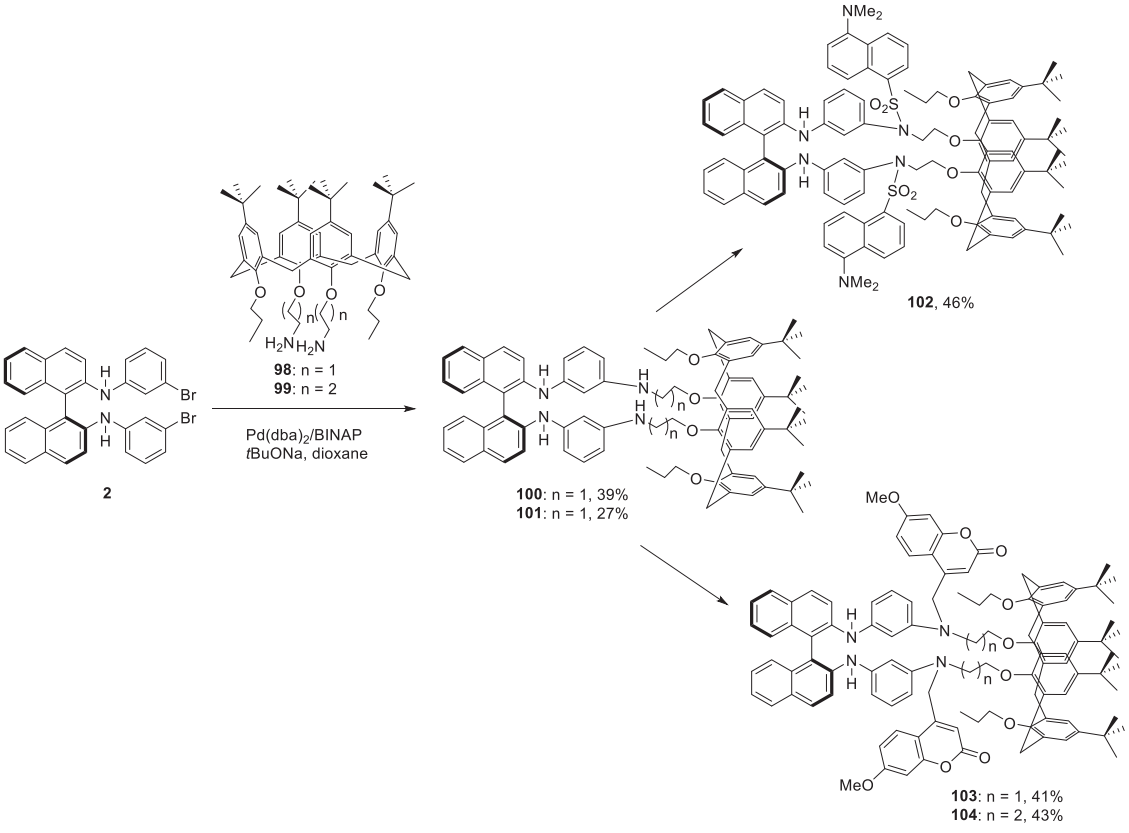
Scheme 10: Synthesis of the BINAM-containing macrocyclic with polyamine linkers.



Scheme 11: Formation of the cryptands incorporating BINAM and diazacrown moieties.



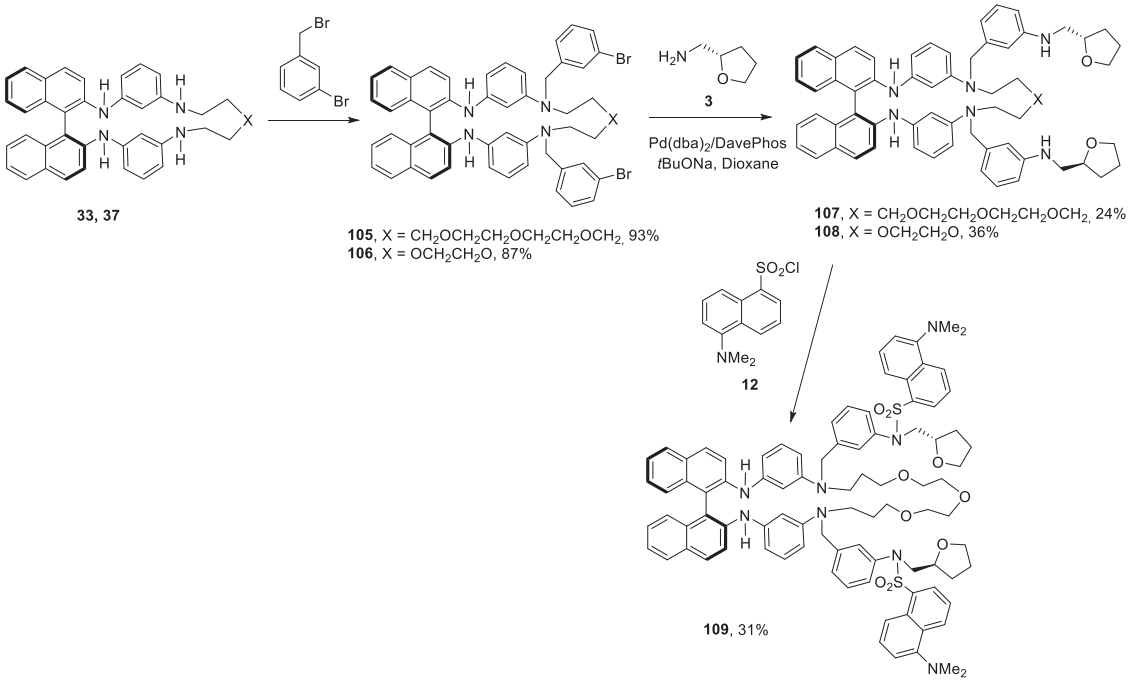
Scheme 12: Synthesis of the cryptands on the basis of BINAM and cyclen or cyclam.



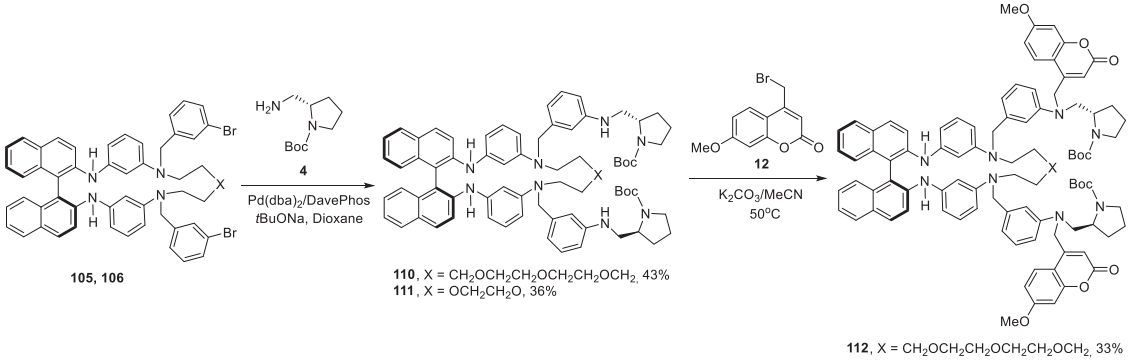
Scheme 13: Synthesis of the cryptands comprising BINAM and calix[4]arene moieties.

Cryptands possessing (*S*)-BINAM moiety

The variety of the structures of macrocyclic compounds incorporating BINAM moiety was expanded to a family of chiral cryptands. It was thought initially that the more rigid organization of the donor sites (nitrogen and oxygen atoms) could provide more selectivity for coordinating certain aminoalcohols. For this purpose, (*S*)-BINAM was reacted with *N*,*N*′-di(bromobenzyl) substituted diazacrown ethers **79–82** to give corresponding macrobicycles **83–86** (Scheme 11) [67]. The yields were obviously higher in the case of diaza-18-crown-6 derivatives **81**, **82**, probably, due to more favorable conformations of these compounds. A similar approach



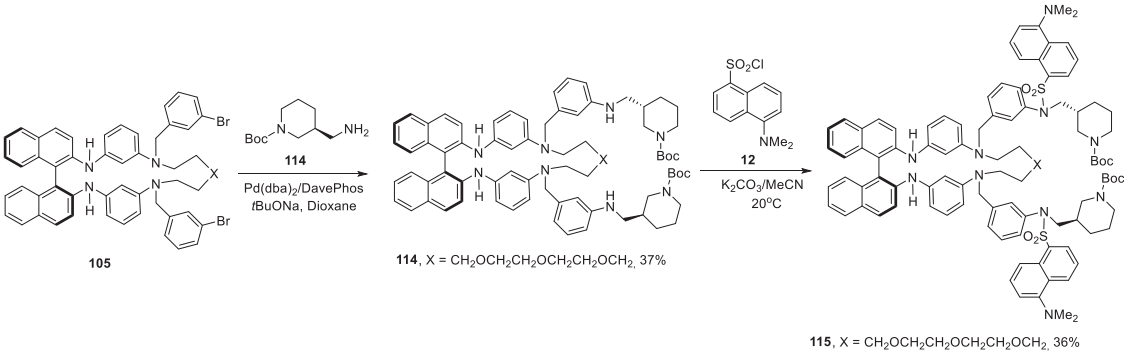
Scheme 14: Modification of the BINAM-containing macrocycles with exocyclic chiral and fluorophore groups.



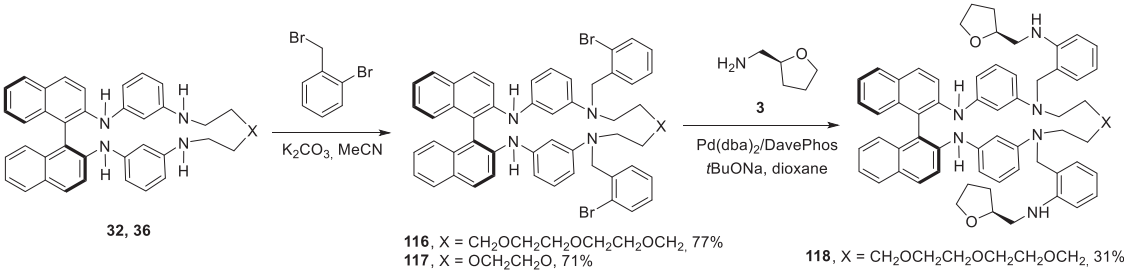
Scheme 15: Modification of the BINAM-containing macrocycles with exocyclic chiral and fluorophore groups.

using *N,N′*-di(bromobenzyl) derivatives of tetraazamacrocycles like cyclen and cyclam **87–90** was also successful and allowed the synthesis of the chiral cryptands **91–94** though the yields were modest (13–34%) (Scheme 12) [68]. These compounds were further converted into didansyl derivatives **95–97**; as in the case of above mentioned macrocycles (*cf*. Scheme 7).

It was possible also to combine BINAM with the calix[4]arene macrocyclic unit (Scheme 13). The catalytic macrocyclization reaction was carried out with diaminocalix[4]arenes **98, 99** and *N,N′*-di(3-bromobiphenyl) substituted BINAM **2** and produced desirable cryptands **100**, **101** in 39 and 27% yields, respectively. After this the macrobicycles were modified with two dansylamide or two 7-methoxycoumarin fluorophore groups to give compounds **102–104** in 41–46% yields (Scheme 13).



Scheme 16: Modification of the BINAM-containing macrocycle with exocyclic chiral and fluorophore groups.



Scheme 17: Modification of the BINAM-containing macrocycles with exocyclic chiral and fluorophore groups.

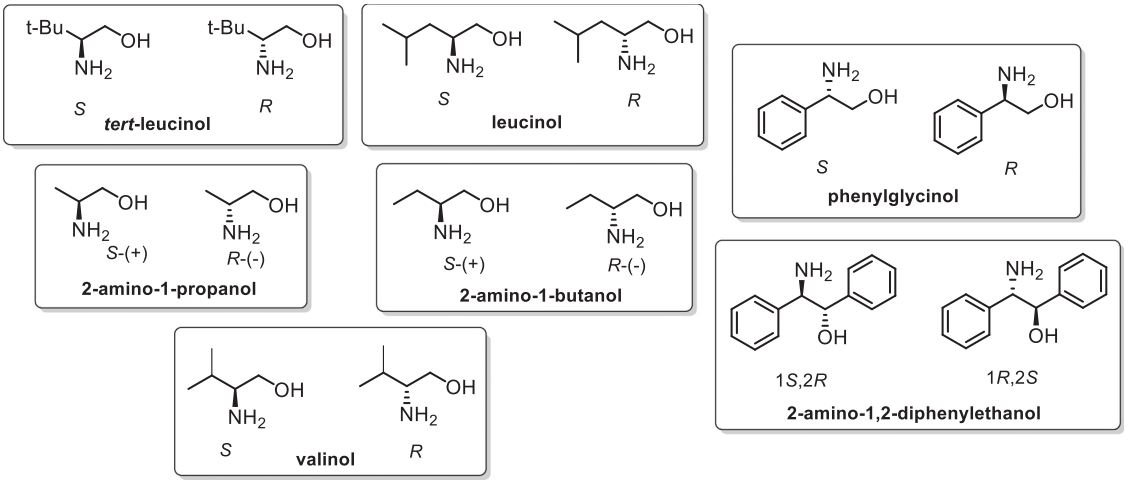


Fig. 1: The panel of amino alcohols employed for the evaluation of the detecting abilities of the synthesized BINAM derivatives.

Introduction of exocyclic chiral groups to macrocyclic derivatives of (S)-BINAM

Not only the additional substituents with fluorescent properties were introduced in the macrocyclic compounds based on (*S*)-BINAM. We also attempted the synthesis of more complex compounds with exocyclic chiral groups in order to alter the ability for complexation with chiral analytes and presumably to enhance stereodiscrimanation by the combination of two types of chirality in one molecule, i.e., *C*2 chirality of the BINAM moiety and central chirality of the *N*,*O*-containing substituents. For this reason, model macrocycles **33**

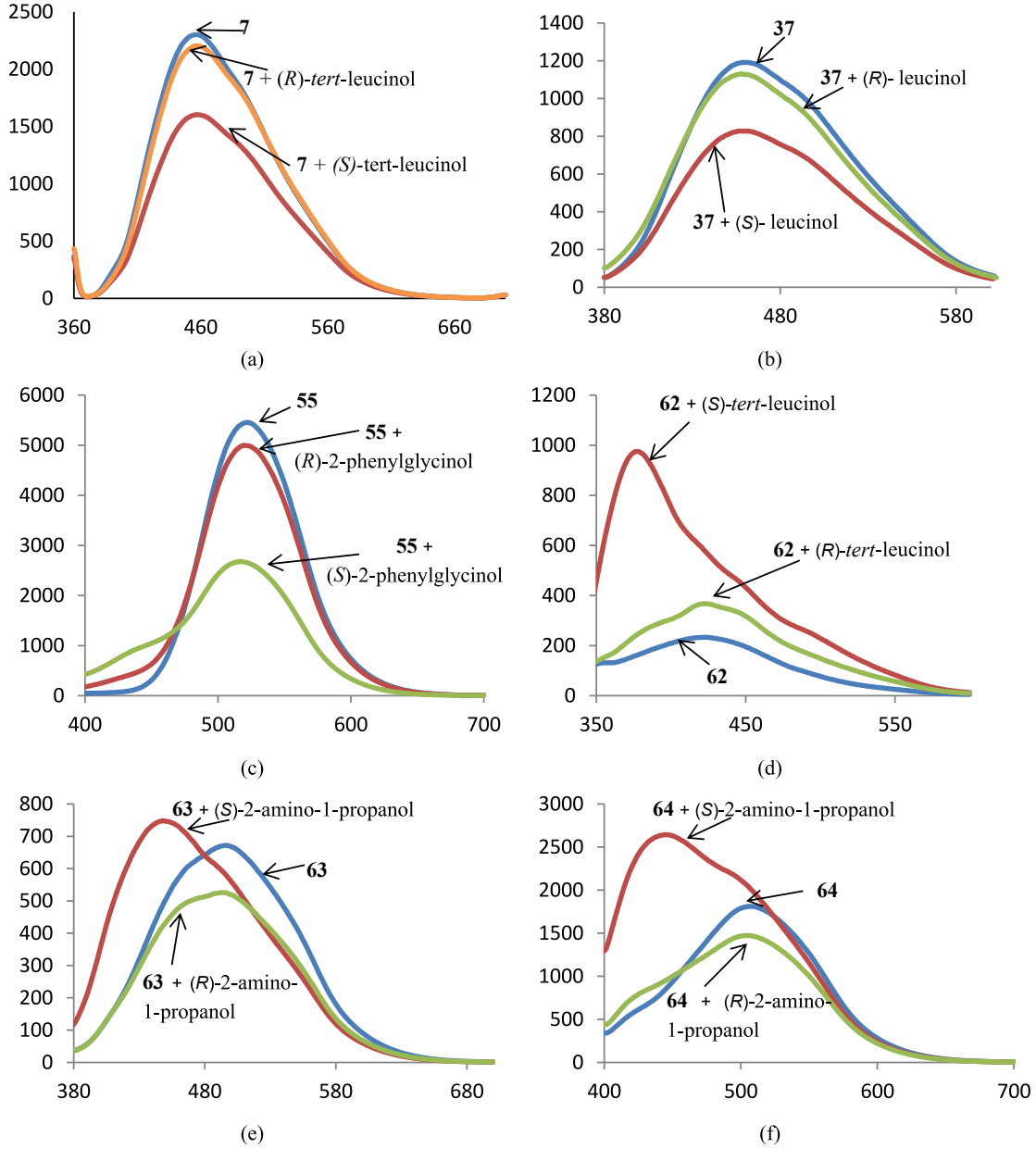


Fig. 2: Spectra of fluorescence of BINAM derivatives **7** (a), **37** (b), **55** (c), **62** (d), **63** (e), **64** (f) in the presence of 1000 equiv. of enantiomers of corresponding amino alcohols; *X*-axis: wavelength, nm, *Y*-axis: relative intensity of emission.

and **37** were transformed into corresponding *N*,*N*′-di(3-bromobenzyl) derivatives **105** and **106**, then the Pd(0)-catalyzed reactions with the optically pure (*S*)-tetrahydrofurfurylamine were accomplished to produce compounds **107** and **108**, and one of them, with the trioxadiamine chain, was converted into didansylated derivative **109** (Scheme 14).

Quite similar procedure was carried out for the modification of the same macrocycles with the chiral *N*-Boc-pyrrolidinylmethyl substituents (Scheme 15). For this purpose, compounds **105**, **106** were introduced in the catalytic reaction with the amine **4** and the resulting product was further modified with the 7-methoxycoumarin fluorophore moiety to produce compound **112**.

In order to diversify the structures of the potential enantioselective receptors, the macrocycle **105** was modified with a chiral substituent featuring *N*-Boc-piperidine moiety using the reaction with the amine **113** (Scheme 16). The resulting compound **114** was further decorated with two dansylamide fluorophore groups to give compound **115**. The same idea of structural diversity governed the synthesis of *N*,*N*′-di(2-bromobenzyl)substituted macrocycle **116**, **117** (Scheme 17). Only the compound with a larger macrocyclic cavity could be further transformed into bis(tetrahydrofurfurylmethylamino) derivative **118**, probably, due to steric demands in such compounds with unpredictable conformational peculiarities. This can also be the reason for modest yields (30–40%) both in catalytic and non-catalytic reactions of the macrocycles **105**, **106** described here.

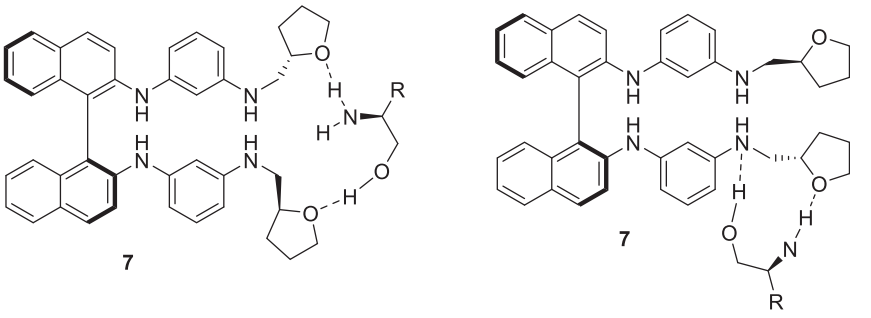


Fig. 3: Plausible coordination patterns for amino alcohols with the BINAM-based ligands.

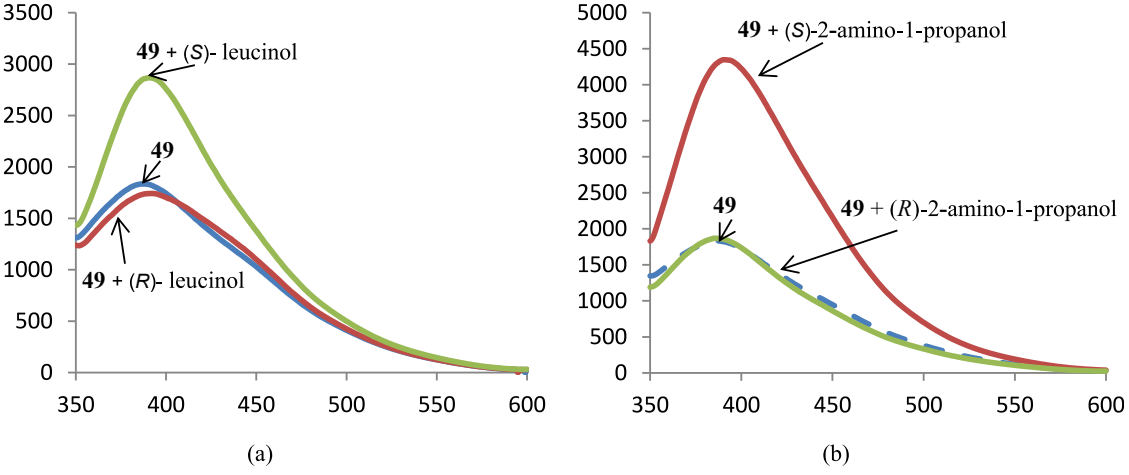


Fig. 4: Spectra of fluorescence of BINAM derivative **49** in the presence of 1000 equiv. of enantiomers of leucinol (a) and 2-amino-1-propanol (b); *X*-axis: wavelength, nm, *Y*-axis: relative intensity of emission.

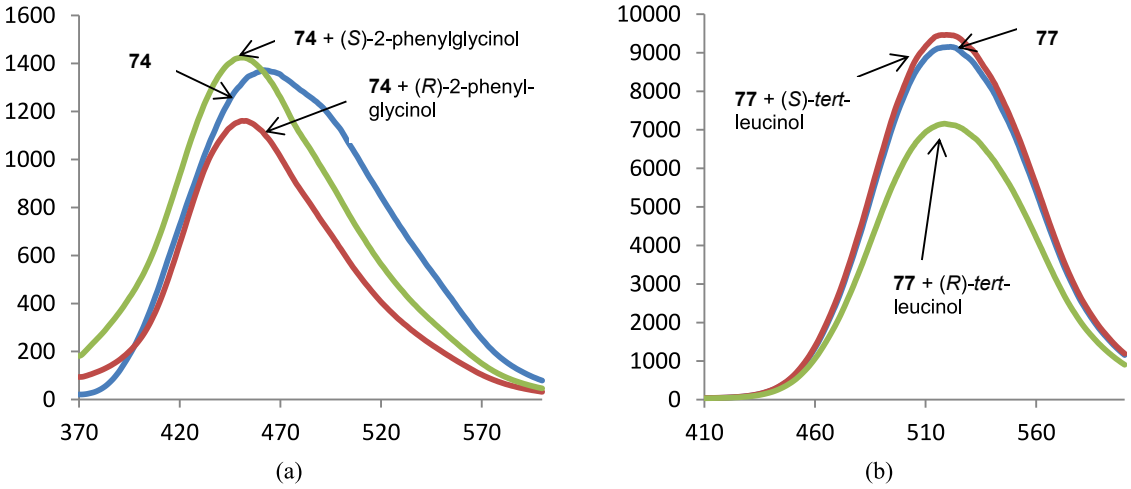


Fig. 5: Spectra of fluorescence of BINAM derivative **74** (a) and **77** (b) in the presence of 1000 equiv. of enantiomers of 2-phenylglycinol (a) and *tert*-leucinol (b); *X*-axis: wavelength, nm, *Y*-axis: relative intensity of emission.

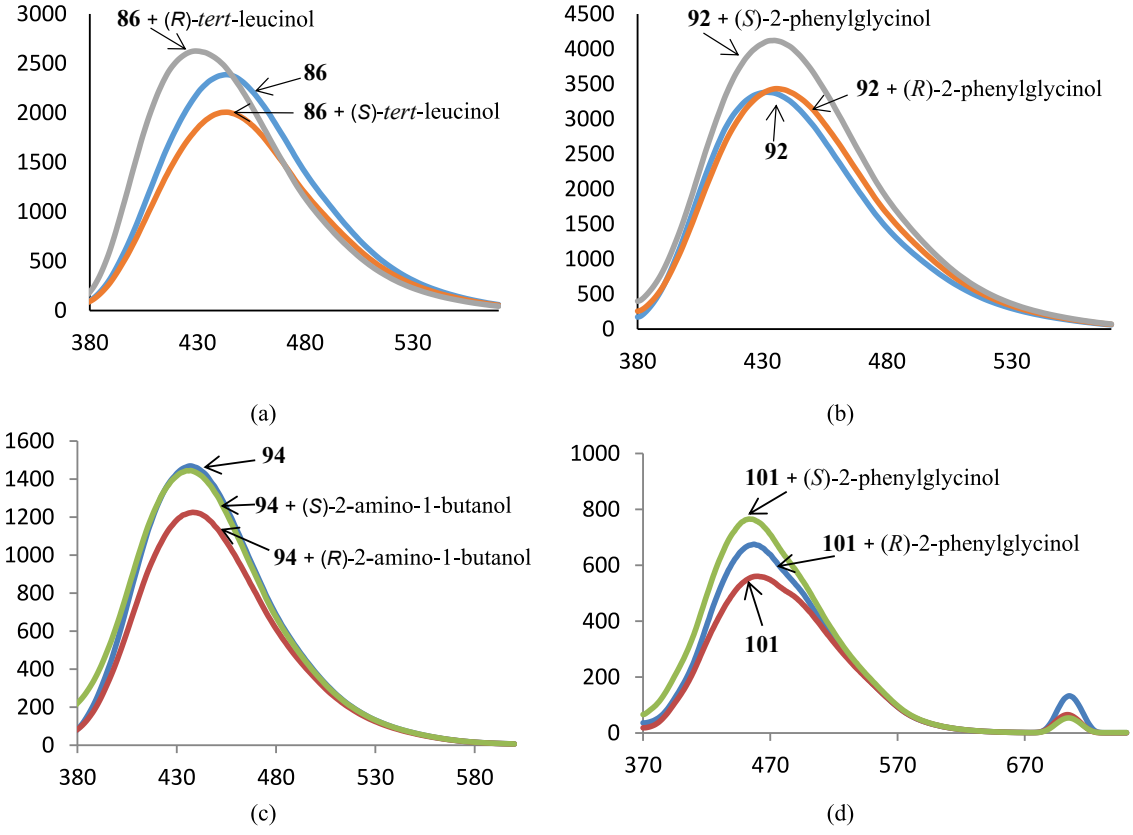


Fig. 6: Spectra of fluorescence of BINAM-containing cryptands **86** (a), **92** (b), **94** (c), **101** (d) in the presence of 1000 equiv. of enantiomers of corresponding amino alcohols; *X*-axis: wavelength, nm, *Y*-axis: relative intensity of emission.

Detection properties of (*S*)-BINAM derivatives

The majority of the BINAM derivatives described above were tested as potential enantioselective fluorescent detectors using a panel of amino alcohols taken as individual enantiomers (Fig. 1). These compounds were chosen as model analytes in view of their structural similarity to corresponding amino acids, perfect solubility in various organic solvents and because they do not form ionic species and thus their coordination properties are not sensitive to pH of the media. Standard experiments included measurements of the emission spectra of the free BINAM derivatives in MeCN and after successive addition of 100, 200, 500 and 1000 equiv. of analytes. In the case when the change of the fluorescence was quite different for two enantiomers, or when in the presence of one enantiomer no change was observed while the second enantiomer led to emission quenching or enhancement, the compound can be judged as a detector for this certain pair of amino alcohols. It is obvious that the comprehensive description of the significant fluorescence changes for each BINAM derivative and each amino alcohol is going far beyond the scope of this mini-review, and we demonstrate here some characteristic examples for various types of BINAM derivatives to assess and compare their usefulness.

The fluorescence of many non-macrocyclic derivatives of BINAM was found to be less sensitive to the addition of the amino alcohols, in many cases the changes were either insufficient or of the same sign for both enantiomers. However, in some cases the compounds do behave as real detectors, e.g., the BINAM derivative **7** can distinguish between two enantiomers of *tert*-leucinol (Fig. 2a). Macrocyclic compounds were more sensitive and cyclic dimer **37** can be used for the recognition of leucinol enantiomers (Fig. 2b). Macrocycle **55**

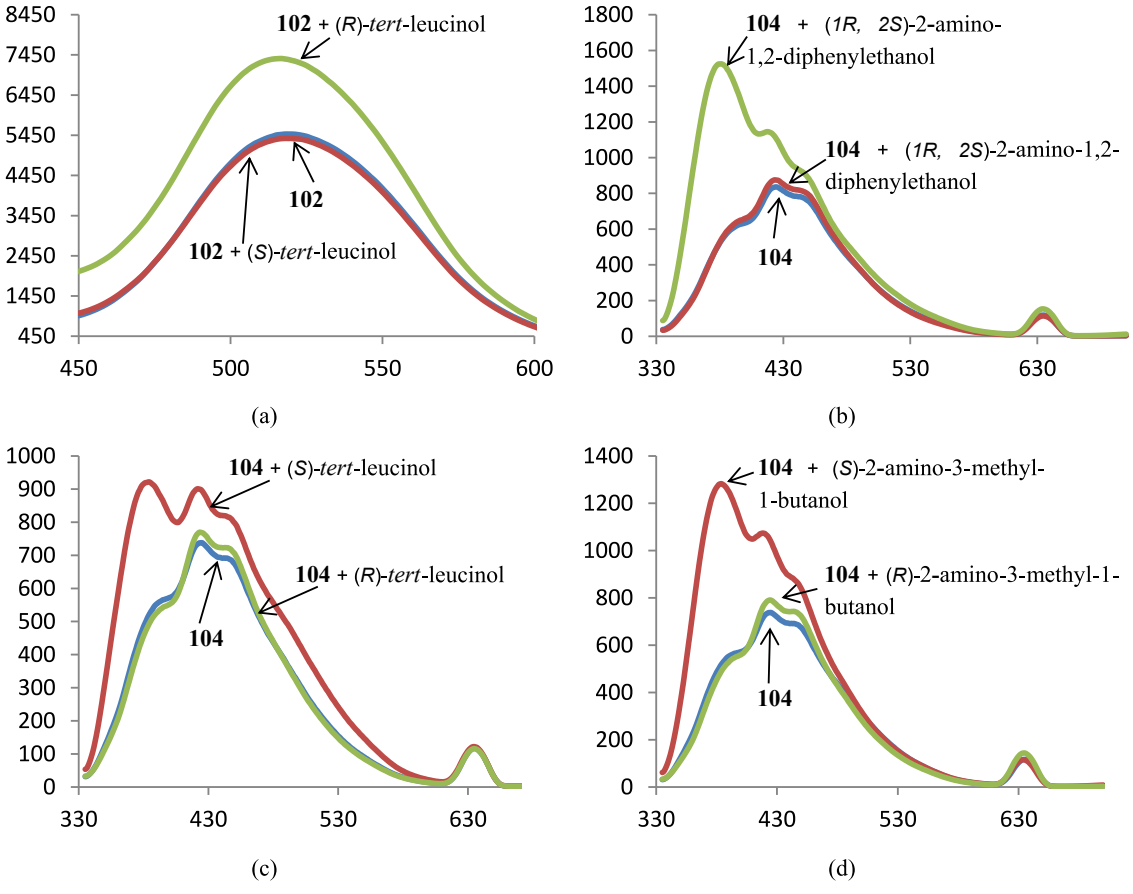


Fig. 7: Spectra of fluorescence of BINAM-containing cryptands **102** (a), **104** (b-d) in the presence of 1000 equiv. of enantiomers of corresponding amino alcohols; *X*-axis: wavelength, nm, *Y*-axis: relative intensity of emission.

bearing two dansyl amide fluorophore groups is able to distinguish between 2-phenylglycinol isomers (Fig. 2c). In all these cases one enantiomer leads to the emission quenching while another one does not change the spectrum. In the case of 7-methoxycoumarin-substituted macrocycle **62** the enhancement of the emission was observed, and in the case of *tert*-leucinol the difference caused by two enantiomers was the most pronounced. Also, in the presence of the enantiomer which led to more significant increase in the emission notable hypsochromic shift was noted (Fig. 2d). As for quinolinyl-substituted macrocycles **63**, **64**, the signs of the fluorescence changes were different for the enantiomers, and again the hypsochromic shift was evident in the case of the emission enhancement (Fig. 2e,f). We may propose the scheme of the plausible coordination patterns for amino alcohols with an exemplary ligand 7 (Fig. 3).

Figure 4 shows the possibilities of the anthraquinone-containing macrocycle **49** to recognize the enantiomers of leucinol and 2-amino-1-propanol, in both cases one enantiomer did not change the fluorescence while the second led to an increase in the fluorescence intensity.

Different behavior of the spectra of fluorescence after the introduction of additional fluorophore groups is demonstrated by Fig. 5. The parent tetraazamacrocycle **74** changes its emission in different ways upon the addition of 2-phenylglycinol enantiomers, and the fluorescence of its tetradansylated derivative **77** quenches in the presence of (*R*)-*tert*-leucinol while the addition of (*S*)-isomer does not lead to any change of the emission.

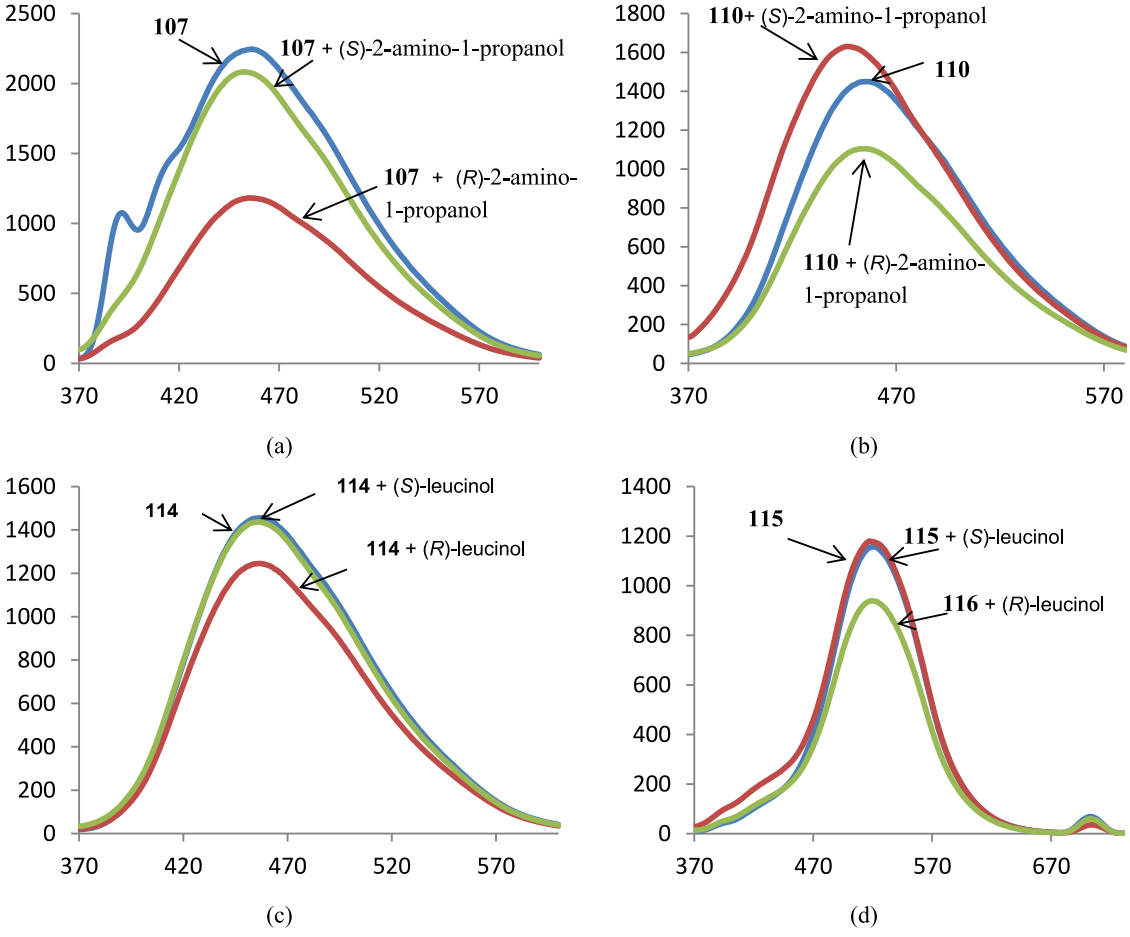


Fig. 8: Spectra of fluorescence of BINAM-containing macrocycles **107** (a), **110** (b), **114** (c), **115** (d) in the presence of 1000 equiv. of enantiomers of corresponding amino alcohols; *X*-axis: wavelength, nm, *Y*-axis: relative intensity of emission.

BINAM-derived cryptands can detect certain amino alcohols, as it is depicted on Fig. 6, however the changes in fluorescence are often not important. In some cases the addition of only one enantiomer leads to the change of the emission intensity (Fig. 6b,c), in other cases the signs of the changes are opposite (Fig. 6a,d).

The decoration of the cryptands on the basis of cyclen or cyclam with dansylamide fluorophores was useless, on the other hand, this procedure enhanced the sensititvity of the calix[4]arene-based cryptands in comparison with the parent cryptand **101**. In the case of dansylamide- and 7-methoxycoumarin-modified macrobicycles **102** and **104** the fluorescence notably enhanced in the presence of one enantiomer of amino alcohols and did not change upon the addition of the another enantiomer (Fig. 7). The introduction of the additional exocyclic chiral substituents in the BINAM-containing macrocycles modified their ability to recognize amino alcohol enantiomers. In many cases only one enantiomer led to emission quenching while the second one did not alter the fluorescence intensity (Fig. 8a,c,d), but also there are examples when both enantiomers changed the intensity with opposite signs (Fig. 8b).

In the majority of experiments, except for the titrations with the compounds **62**–**64** (Fig. 2d–f), we observed the changes in the intensities of fluorescence without any notable shift of the emission maxima. Such behavior is usual in the case when PET mechanism of fluorescence is applicable [69]. In the cases of detectors **62**–**64** the hypsochromic shifts of the emission maxima were noted upon the addition of the amino alcohols what may imply that in these cases the PCT mechanism might be considered. This mechanism is well documented for such fluorophore groups like coumarin (present in **62**) or quinoline (present in **63**, **64**) which possess electron donor and electron withdrawing sites to achieve the charge transfer in the fluorophore moiety. PCT mechanism demands that an interaction of the detector with the analyte takes place which alters this intramolecular charge transfer. Somewhat smaller hypsochromic shifts were also noted for compounds **74** (Fig. 5a) and **86** (Fig. 6a) though they possess only aminonapthyl moieties less prone to act as PCT fluorophores.

Conclusions

As a result of our investigations in the field of the synthesis of perspective enantioselective fluorescent detectors we obtained several families of compounds on the basis of *C*2-chiral BINAM: non-cyclic derivatives of BINAM comprising chiral *N*,*O*-substituents, macrocyclic compounds with oxadiamine and polyamine linkers which also may contain additional exocyclic chiral and fluorophore moieties, BINAM-based cryptands. Optically active amines were used to modify the BINAM derivatives with chiral substituents while the following fluorophore groups were introduced to enhance emission of the detectors: dansylamide, 7-methoxycoumarin, 6- and 3-aminoquinolines. Moreover, these substituents also could change the coordination properties of the detectors thus modifying their recognition abilities. The crucial steps in the syntheses of all these compounds were accomplished using Pd(0)-catalyzed amination reactions. Many of the synthesized BINAM derivatives were tested as potential enantioselective fluorescent detectors with a series of amino alcohols and many of them were found to be able to distinguish between two enantiomers of such analytes. The addition of amino alcohols caused either quenching or enhancement of the emission of the detectors, in some cases hypsochromic shifts of the maxima of fluorescence were also noted. BINAM-containing macrocyclic compounds in general were found to be more suitable for the fluorescent enantioselective detection of amino alcohols.

Funding: This research was funded by the Russian Foundation for Basic Research (RFBR grant N 18-03-00709).

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