Recent Developments in Chiral Polynitrogenated Synthetic Receptors for Anions

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Abstract: In this mini-review, recent chiral receptors bearing polyamine and/or polyamide functional groups are reported. Two main features for their synthesis are the source of the enantiopure nitrogenated synthons and the strategy to assemble the building blocks within the receptor architecture. Combined solutions to both problems have been carried, ranging from chemoenzymatic methods to combinatorial approaches. Topics like conformational control or templation procedures are highlighted. Applications in chiral anion molecular recognition will be also discussed.

Keywords: Molecular recognition, anion, chiral receptor, stereoselective, nitrogen, template.

I. INTRODUCTION

Molecular recognition is present in Nature at many different levels and in varied forms. Many biologically important processes are intimately related to the specific interaction between a receptor and a substrate, or to the self-assembling ability of a given molecular entity. Accordingly, chemists have pursued the design and synthesis of abiotic receptors able to emulate the degree of selectivity (and specificity) displayed in the biological world [1]. The most difficult selectivity to carry out is, by far, that performed between two enantiomers of the same chiral molecule. This stereoselectivity is very common in biology, as many bio-molecules present only one enantiomeric form in nature and are able to exclusively interact with one enantiomer from a racemic mixture of potential substrates [2]. However, the synthesis and study of chiral enantioselective receptors is still a difficult problem facing modern chemists [3].

On the other hand, although most of the enzymatic substrates and cofactors are negatively charged at physiological conditions, anion coordination chemistry is still in its infancy compared to the cationic or neutral non-covalent binding [4]. Apart from some historical reasons, the intrinsic physicochemical properties of anions make this type of molecular recognition especially challenging. Anions usually present many different molecular shapes, showing higher solvation energies and larger sizes than similar cations of comparable net charge and molecular weight [5].

Due to all these facts, an increasing number of papers dealing with the enantioselective chiral anion recognition using abiotic receptors have come out in the last couple of years. Thus, a representative revision of the some important contributions to this field, from my own research and from others', is proposed in this mini-review. I did not pretend to cover all the literature in a comprehensive manner as it will, for sure, overcome the intended length of this mini-review. A general view will be given, highlighting the newest synthetic approaches, as well as the most interesting and promising applications. Besides, I will focus on receptors bearing nitrogen atoms implicating the main functional groups for the binding. Nitrogen containing molecules have been, by far, the most widely explored in anion binding and, as a result, for chiral receptors too. This N atom can be part of an amine, ammonium, amide, urea, thiourea, guanidinium or pyrrole functional group. The presence of net charges (ammonium and guanidinium) or the different H-bonding abilities finely tune the strength of the anion binding.

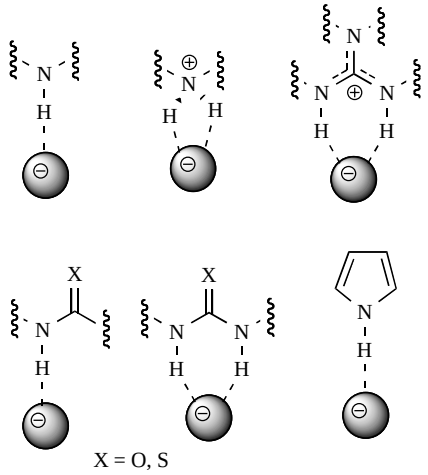

Fig. (1). Anion binding using different nitrogen-containing functional groups.

Electrostatic *vs*. Hydrogen Bond Interactions

The driving force for the binding of an anion to a receptor must be designed taking into account the high solvation energy and the large polarizability of anionic species. Thus, historically, cationic receptors were expected to display the strongest interaction, especially in polar and protic solvents. Ammonium [6] and guanidinium [7] containing molecules have been accordingly studied with this aim (Fig. **1**). However, purely electrostatic interaction shows poor directionality in the binding and, very often, this is not the best option when pursuing selectivity. For that reason, hydrogen bonding donor receptors have been described in the last couple of

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years. Nitrogen containing H-bond donors are amine, amide [8], urea [9], thiourea [10] and pyrrole [11] functional groups. I will focus this review on the most recent examples based on amine/ammonium or amide binding motifs. Obviously, a very good option to obtain strong binding and good selectivity could be to combine two or more different functions in the structure of the receptor [12] Examples of receptors of this type will be also given.

II. THE SOURCE FOR THE ENANTIOPURE NITROGENATED BUILDING BLOCKS

One of the key topics when designing new chiral receptors is the source of the chirality to be implemented in the molecule. Synthons from the chiral pool are especially useful, due to their availability and for environmental reasons. Amino acids are the most popular source of chiral nitrogenated starting materials, as both enantiomers of different orthogonally protected derivatives are commercially available. In some specific examples, alkaloids and other naturally occurring amino compounds can be also used [13]. If non-natural derivatives are considered, cyclic (**1**) and aromatic chiral (**2,3**) diamines are, by far, the most interesting and successful starting points (Fig. **2**). However, new synthetic methodologies leading to enantiopure nitrogenated molecules are still necessary in order to prepare receptors with increasing selectivity.

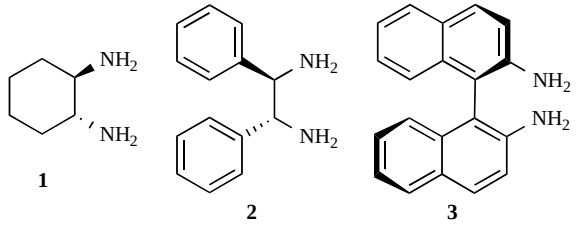


Fig. (2). Structures of diamines deeply used for building chiral receptors.

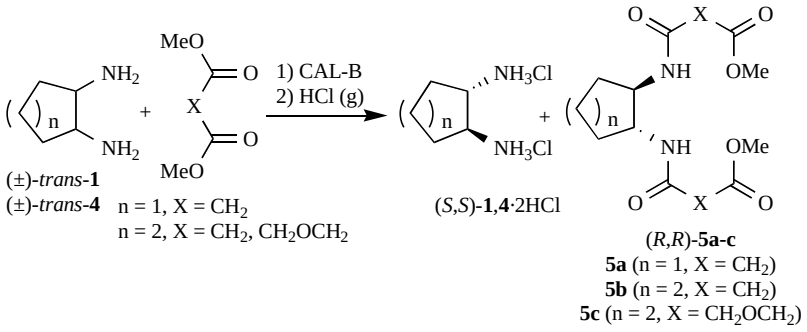
Among the most successful and simple methodologies to obtain chiral amines and diamines is the enzymatic resolution of the corresponding racemate, which has been highly developed in the last couple of years [14]. The main advantage of this approach is the possibility of obtaining both enantiomers of the substrate in high enantiopurity from the same reaction and using mild and simple experimental conditions. For instance, we have used *Candida antarctica* lipase for the sequential kinetic resolution of *trans*-cylohexane-1,2-diamine (**1**) [15] and *trans*-cyclopentane-1,2-diamine (**4**) [16]. The final ee largely depends on the size of the cycle, although the complete resolution of both enantiomers can be achieved for the six-membered ring. In the case of the cyclohexane derivative, both the obtained enantiopure substrate (**1**) and products (**5b-c**) have been used for the synthesis of chiral polyazamacrocycles with applications in chiral anion binding (see below). On the other hand, an improved alternative for the resolution of the cyclopentanediamine counterpart has been described very recently [17].

III. POLYAMINE RECEPTORS

The versatility of polyamine compounds arises from their acid-base properties. Polyamines are basic compounds which are able to accept a determined number of protons, depending on a combination of their structure and the environment (polarity of the solvent and pH). The obtained poliamine/poliammonium species strongly interact with anions, even in very competitive media, like aqueous solution with high ionic strength [18]. Thus, these compounds have been used for anion binding from the beginning of this research field. For a clearer organization of the data, we have classified the selected examples attending to the open chain or macrocyclic nature of the polyamine binding moiety.

Open-Chain Receptors

The main disadvantage of open chain receptors is that the binding unit is too flexible to be pre-organized for the interaction with the anion. This will disfavor selectivity by both enthalpic and entropic reasons. In order to overcome this problem, some clever approximations have been successfully carried out. For instance, Zheng *et al*. appended chiral aminoalcohols to the lower rim of calixarenes leading to semi-rigid polyaminoalcohols (**6a**,**b**) able to enantioselectively recognize chiral carboxylates in chloroform [19]. Although the enantioselectivity of the binding is moderate, this receptor can be used as a chiral solvating agent (CSA) [20] for the NMR determination of the enantiomeric excess (ee) of chiral acids. A more surprising example was later reported by Pericás *et al*., in which a simple design of two receptors (**7a,b**) bearing a pyridine ring led to good selectivity (up to $\Delta\Delta G$ = 1.67 kJ/mol) and large chemical shift splittings on NMR (up to 0.25 ppm), also with an interesting potential as CSA [21]. The main advantage of these receptors are their structural simplicity and easy synthesis. Very recently, Zhang and co-workers reported on two new and simple



Scheme 1. Enzymatic resolution of *trans*-cyclohexane-1,2-diamine and *trans*-cyclopentane-1,2-diamine.

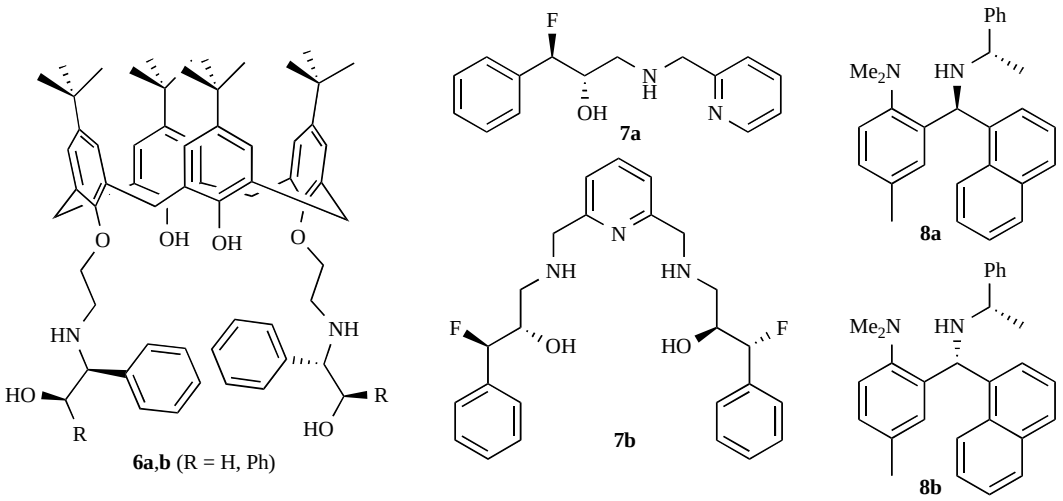
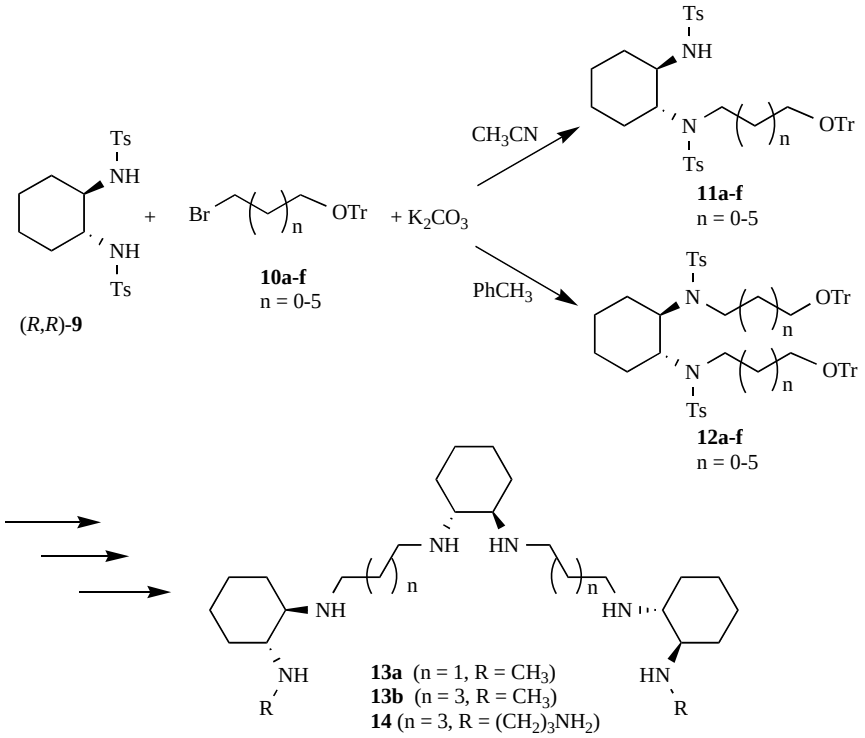


Fig. (3). Open-chain oligoamino anion receptors used as CSA.

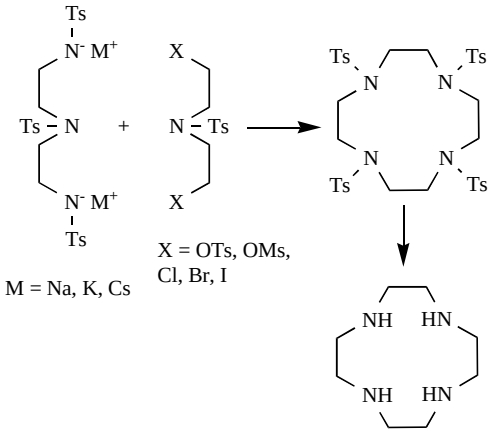
chiral diamines (**8a,b**) able to bind different chiral carboxylic acids, but only in a slightly stereoselective manner ($K_{ass}(S)/K_{ass}(R)$ = 1.2-1.8) [22]. However, they split the NMR signals of the substrates more efficiently than α-phenylethylamine, the chiral building block used for the synthesis of (**8a,b**). On the other hand, both compounds (**8a,b**) were synthesized together in the same reaction and had to be separated by chromatography.

We have also prepared several chiral polyamines bearing *trans*-cyclohexane-1,2-diamine in their structures. The key step for this synthetic strategy was the solvent dependent selective alkylation of the corresponding bis(sulfonamide) (**9**) (Scheme **2**) [23]. In this case, the conformational constriction of the cyclohexane ring, as well as the selection of the right combination of protecting groups and reaction solvent allowed the mono- (**11**) or dialkylation (**12**) of the cyclohexanediamine frame [24]. Both intermediates were successfully used for the modular synthesis of a family of polyamines (**13a-b**, **14**), changing their structural variables, such as the spacer (n), configuration of the chiral centers or substitution of the terminal amino groups (R). Some of these polyamines have shown to bind DNA molecules in a stereoselective manner at physiological conditions [25]. Melting studies with model oligonucleotides showed that polyamines (**13a**) having *all-R* configuration of their chiral centers bind stronger to the AT-rich oligonucleotide ($\Delta\Delta T_m \approx 1.5$ °C), while the *all-S* enantiomer clearly preferred the CG-rich sequence ($\Delta\Delta T_m \approx 5$ °C). Interestingly, this selectivity is prac-



Scheme 2. Synthesis of enantiopure open-chain polyamines.

tically eliminated with the more flexible derivatives (**13b**). A reasonable explanation for this trend could be the different helix handness of the oligonucleotides in the presence of a charged electrolyte, giving rise to left- or right-handed helix depending on the CG-base content.



Scheme 3. Ritchman-Atkins synthesis of macrocyclic polyamines.

Macrocyclic Receptors

Macrocyclic polyamines have been also used as enantioselective receptors for anions, since the constraint due to the cyclic structure very often gives better results in terms of selectivity. There are two main synthetic paths for the preparation of these compounds: reductive amination and the Richman-Atkins procedure (Scheme **3**) [26]. In the first case, a rigid preorganization of the building blocks is required for the success of the method [27]. However, in the case of the Richman-Atkins approach, the preorganization leading to the macrocyclization is obtained thanks to the sulfonamide protecting group, which makes the linear precursor to fold in polar solvents (typically acetonitrile or DMF). Besides, the sulfonamide group increases the acidity of the terminal nitrogen atoms and protects the secondary amine of the linear polyamine precursor.

We have used a chemo-enzymatic approach to synthesize different polyaza [28] and oxaazamacrocycles [29] in enantiopure forms (Fig. **3**), combining enzymatic aminolysis resolutions with the Richman-Atkins procedure. Some of these macrocycles have shown to be enantioselective receptors for dicarboxylates in aqueous solution [29,30] For instance, protonated hexaazamacrocycle (**14**) showed moderate D-selectivity towards tartrate anion, whereas (**15**·H_6^{6+}) exhibited a good preference for *N*-Ac-D-aspartate (K_{ass}(D)/K_{ass}(L) = 5.89). The most surprising results were obtained with the *N*-Ac derivative of glutamate anion, which forms very stable complexes with both (**15**) and (**16**). The stoichiometry of these complexes can be 1 : 1 or 1 : 2 (receptor/anion), depending on the number of the protons and the enantiomer of the anion. For this last anion, both azamacrocycles exhibited a very good D-preference. Regarding the oxaazamacrocycles, the triprotonated species of (**17**) showed a moderate L-enantioselectivity with malate and tartrate (bearing OH groups). On the other hand, the receptor (**16**) displayed a good D-selectivity towards *N*-Ac-aspartate ($\Delta\Delta G$ = 3.83 kJ/mol). Despite the lack of enantioselectivity of this compound with hydroxiacids, a very good diastereopreference towards the *meso* form of tartrate was observed ($\Delta\Delta G$ = 7.5 kJ/mol), which helped us to propose a reasonable mode of binding, based on electrostatic and H-bonding interactions.

In the last couple of years, an effort has been made in order to translate the binding selectivity into useful applications, such as the development of fluorescent sensors able to yield differential signal depending on the enantiomeric composition of the substrate [31]. For instance, Pu *et al*. prepared the fluorescent macrocycles (**22**-**24**) using the reductive amination synthetic approach as both precursors, diamine and dialdehyde, are conformationally constrained [32]. These

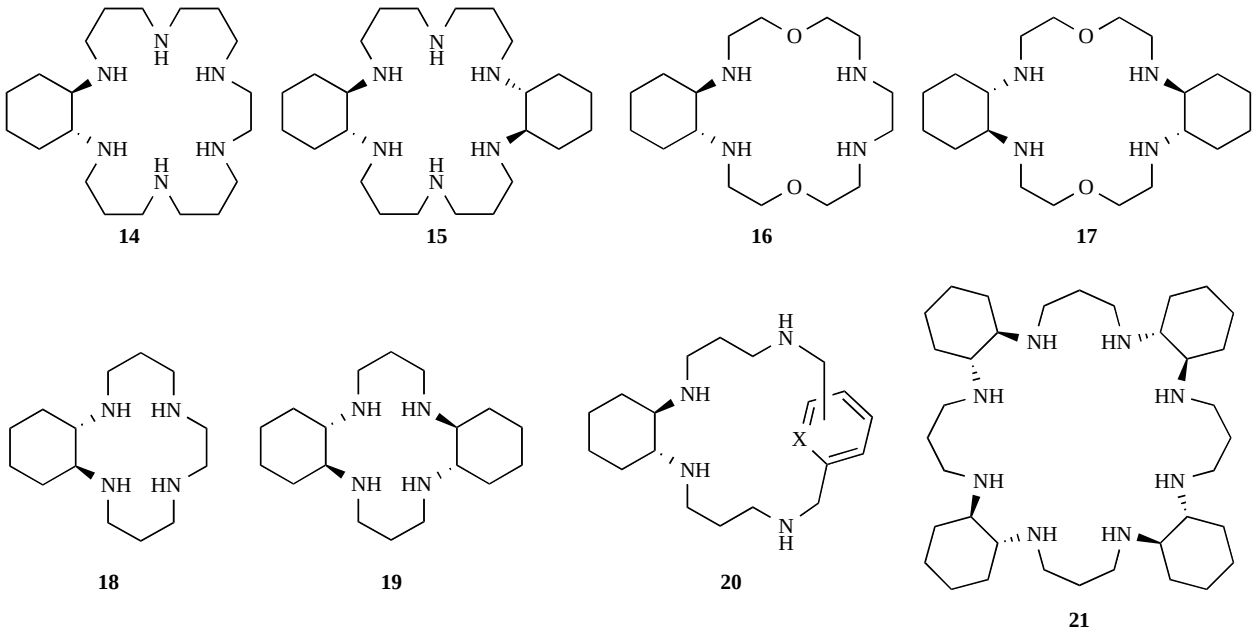


Fig. (4). Molecular structures of enantiopure macrocyclic polyamines prepared by the Richman-Atkins procedure.

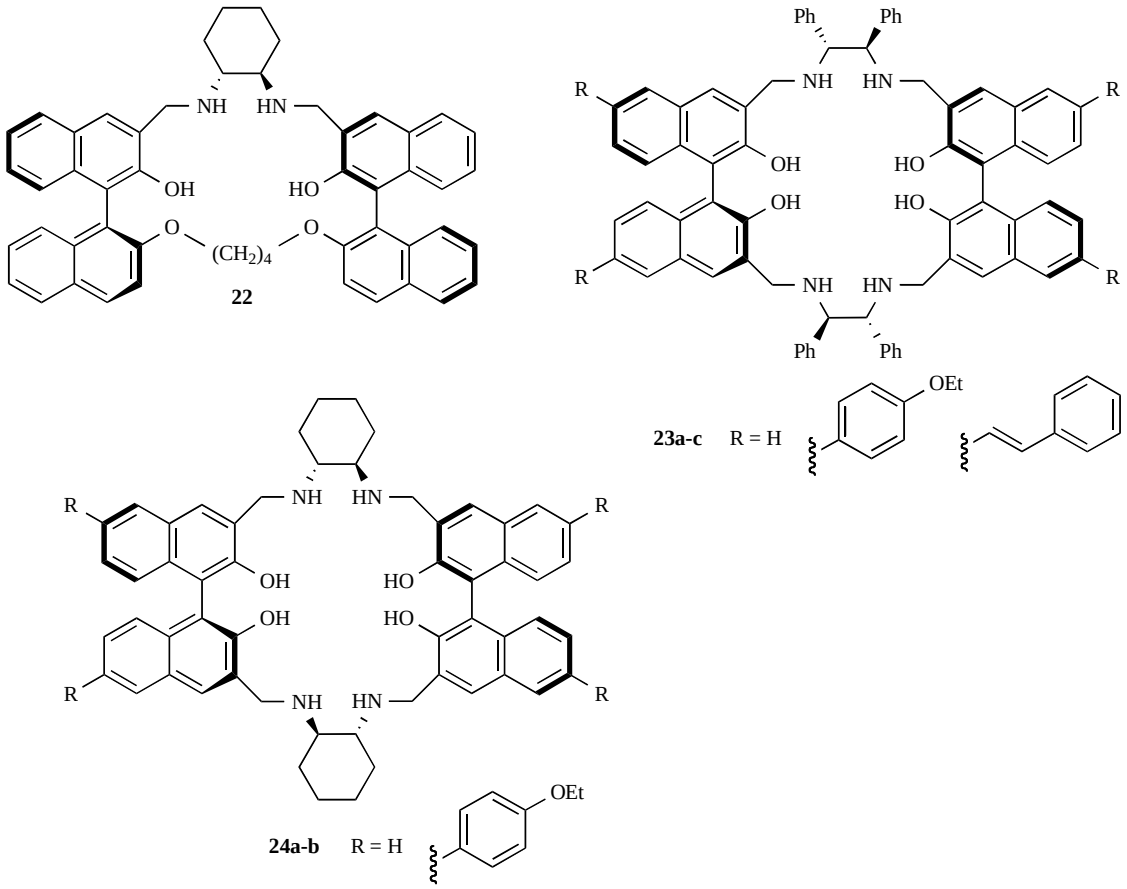


Fig. (5). Macrocyclic polyamines used as enantioselective fluorescent sensors.

macrocycles share a 1,1'-binaphthyl moiety which acts as a chiral reporter and also as fluorescent antenna. The obtained receptors are able to display a highly enantioselective fluorescent response to mandelic acid derivatives.

Very recently, a conceptually different methodology for the discovery and synthesis of new receptors has been proposed: the dynamic combinatorial chemistry (DCC) approach [33]. We wondered if we could use this procedure to prepare new chiral azamacrocycles [34]. Thus, the condensation between diamine (**1**) and dialdehyde (**25**) in methanol led to an equilibrium mixture containing different cyclic and linear oligomers (Scheme **4**). Inspection of many different cationic templates rendered interesting results. Thus, the system is shifted to the dimeric species (**26**) in the presence of Ba(II) but to the trimer (**27**) in the presence of Cd(II), although cadmium ion is smaller than barium. Deep NMR, mass spectrometry, UV and modeling studies demonstrated the formation of dinuclear metal complexes between the trimeric oligoimine (**27**) and Cd(II). In situ reduction of these complexes led to the selective and efficient preparation of either the dimeric (**28**) or trimeric (**29**) polyazamacrocyclic compound, both in very high isolated yields. Besides, assays performed with the racemic mixture of the diamine showed that the cadmium templated reaction is completely diastereoselective to the formation of the corresponding heterochiral stereoisomer [35].

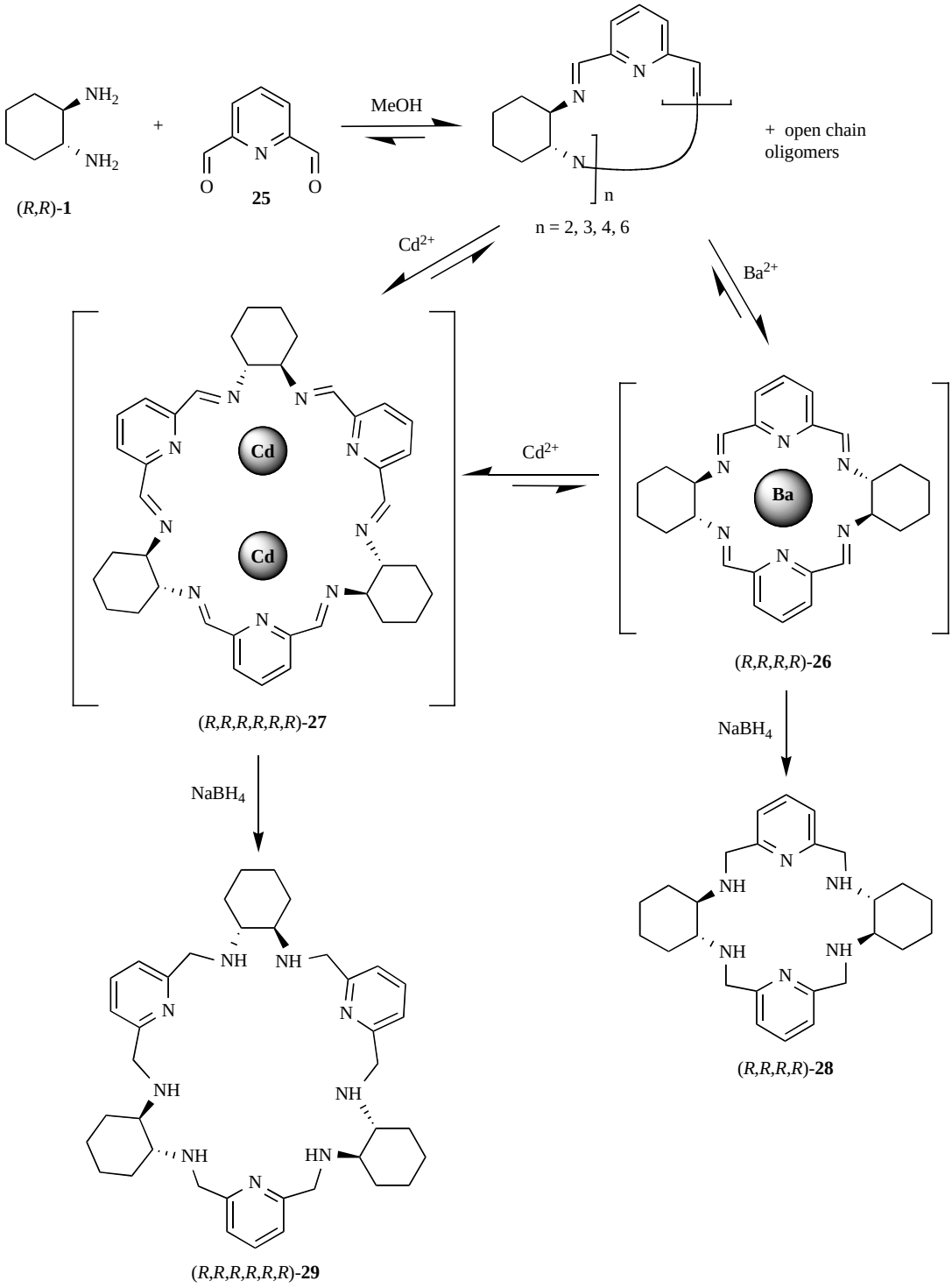
These compounds have been also used as receptors for biologically interesting chiral dicarboxylates at physiological conditions. Interestingly the large macrocycle (**29**) displayed complicated equilibrium pattern, but with weak interaction, probably due to a poor size complementarity. On the other hand, (**28**) showed to be a highly enantioselective receptor (up to $\Delta\Delta G$ = 6.12 kJ/mol) for malate dianion in water, over a wide pH range and in the presence of the competing chloride anion, as in biomolecular media [36]. Further studies with other dicarboxylates and using a multidisciplinary approach allowed proposing a model for the selectivity displayed, in which the twisted helical conformation of the receptor plays a fundamental role [37]. Besides, on the other hand, compound (**28**) has proved to be an excellent CSA for chiral carboxylic acids in $CDCl_3$ [38].

IV. POLYAMIDE RECEPTORS

Amide bond is also able to interact with anions by hydrogen bonding [39]. Although the obtained complexes are usually weaker than those formed with charged species, the selectivity is often higher. Actually, this binding motif is commonly found in the binding pockets of proteins able to interact with anions [40]. Inspired by these observations, chemists have designed chiral receptors having amide bonds as the recognition group.

Open Chain Receptors

Also in the case of amidic receptors, the open chain derivatives usually bear a conformationally constrained chiral



Scheme 4. Syntheses of enantiopure macrocyclic polyamines from a DCL of oligoimines.

reporter. That is the case of the bis(amide) appended binaphtol derivatives (**30a-c**) depicted in Fig. (**6**) [41]. Their syntheses from the adequately protected amino acid derivatives are simple and quite straightforward. Fluorescence and NMR binding studies showed that receptor (**30a**) displayed an extremely large stereoselectivity (K_{ass}(D)/K_{ass}(L) = 17.35) in the interaction with dibenzoyl tartrate. Surprisingly, the most enantioselective receptor resulted from the less sterically demanding compound (R = Me).

Other interesting examples have been reported from the same group [42,43], in which the conformational restriction is imposed by a calix[4]arene molecular frame, while the chiral reporter is an amino acid (Fig. **7**). Once again, their preparation using conventional procedures is simple and efficient. In the case of the tryptophane derivatives (**31a–c**) [42], a wide screening for the binding with chiral species was carried out, performed by both NMR and fluorescence spectroscopy. Receptors (**31a–c**) showed different chiral

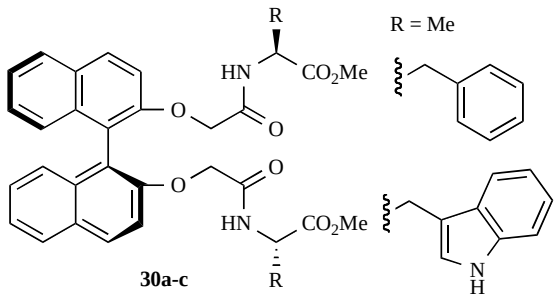


Fig. (6). Amino acid derived diamide used as fluorescent enantioselective receptor of dicarboxylates.

recognition abilities with the guest molecules. For instance, receptor (**31a**) exhibits excellent enantioselective fluorescent recognition ability towards the *N*-Boc-protected alanine anion and (**31b**) reveals good enantioselective recognition ability towards the enantiomers of mandelate. In both cases, the receptor formed strong 1 : 1 complexes with the D enantiomer of the anion, while the L isomer was not bound. Although no deep structural studies on the supramolecular complexes were reported, a relatively good structural preorganization and multiple hydrogen bonds must induce the enantioselective recognition. Besides, the different fluorescent responses that result from complexation reveal that (**31a**) and (**31b**) could be used as fluorescent chemosensors. On the other hand, the receptors (**31d-e**) were designed using other amino acids (Ala or Phe) as building blocks [43]. In these examples, the fluorescent moiety was introduced with the antracene rings and they were also tested as fluorescent sensor towards malate dianion in chloroform. Both structures formed strong 1 : 1 complexes also displaying a good enantiodiscrimination with this dicarboxylate, being $K_{ass}(D)/K_{ass}(L) = 4.34$ for (**31d**) and 10.41 for (**31e**).

Another building block able to preorganize the binding groups in open chain receptors is the pyridine-2,3-bis(carboxamide) moiety. The two intramolecular H-bonds between the pyridine nitrogen and both NH atoms organize

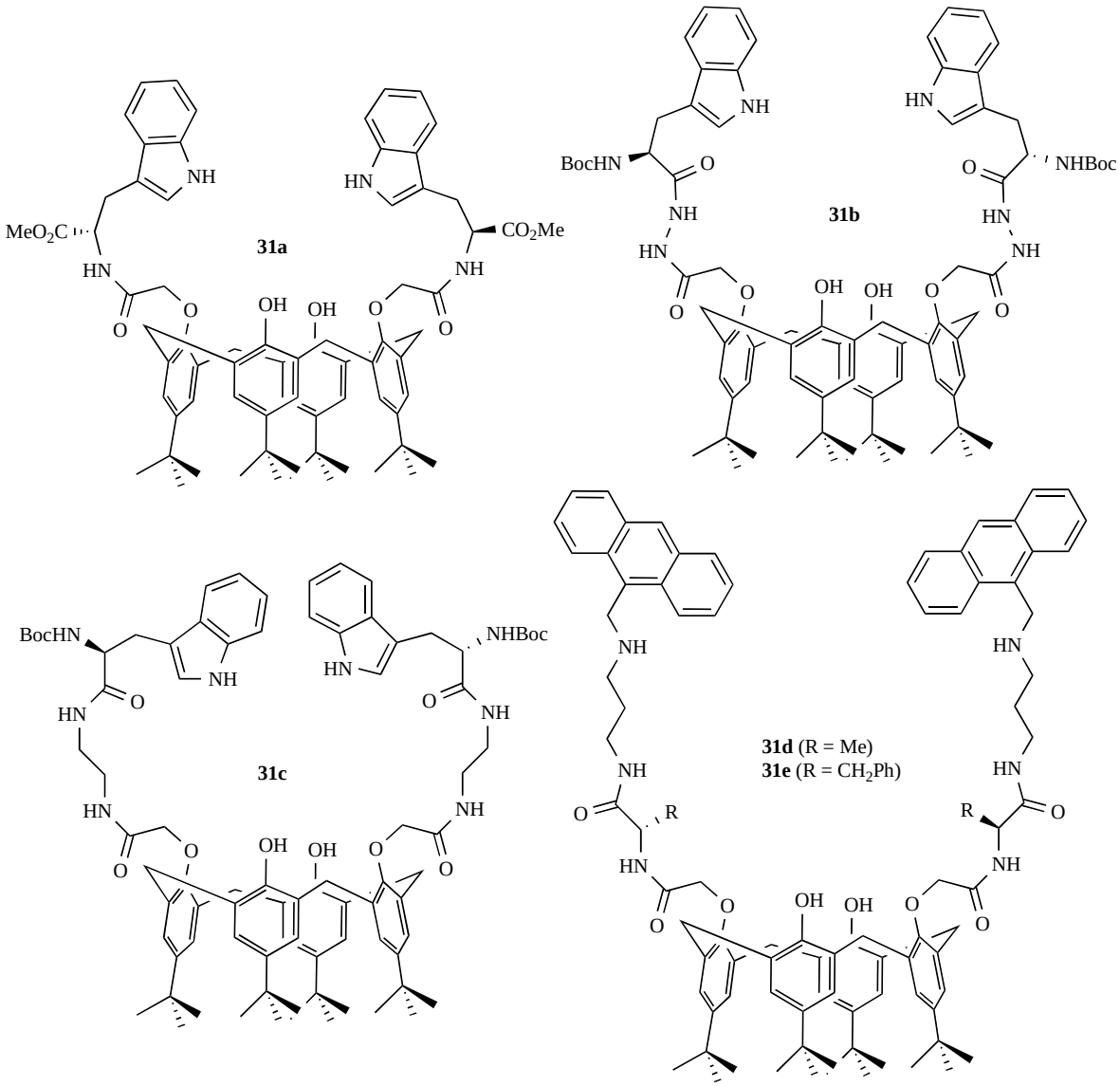


Fig. (7). Calixarene-appended bis-amide used as fluorescent sensor of carboxylates.

the system in a U-shape conformation [44]. This is the approximation recently described by Yang *et al*. [45] who prepared a receptor of this type (**32**), using an α-aminoxyacid amide binding motif (Fig. **8**). The H-bonding ability of α-aminoxyamide moiety is higher than that of a comparable amide group, due to the electron-withdrawing effect of the O atom. Thus, the obtained binding constants in $CDCl_3$ are larger. This compound was able to discriminate between the enantiomers of mandelate anion ($\Delta\Delta G$ = 1.6 kJ/mol) and a precise NMR study (2D NOESY) allowed the authors to propose a structural explanation of this selectivity. Besides, the diastereomeric complexes formed with many chiral carboxylates showed a large chemical shift splitting, demonstrating the potential application of (**32**) as CSA for chiral carboxylates.

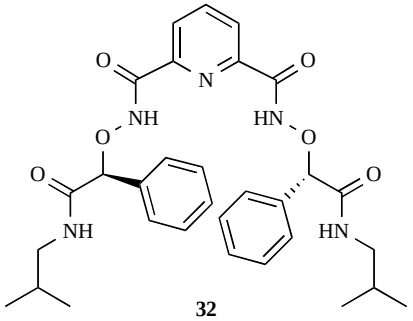


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Fig. (8). An enantioselective receptor based on the α-aminoxyacid amide binding motif.

We have also taken advantage of the pyridine-2,6-bis(carboxamide) structural behavior for designing a pincer-like receptor for chiral carboxylates (Fig. **9**) [46]. The synthesis of (**33**) is simple and highly efficient, starting from the enantiopure enzymatically obtained synthon. In this case, the introduction of two tertiary amine groups permitted the direct use of carboxylic acids, instead of the quaternary ammonium salt. Thus, the proton transference from the substrate to the receptor is produced, leading to a strong interaction within the diastereomeric supramolecular salt complex. This system proved to be useful as CSA for chiral α-arylcarboxylic acids, such as the pharmacologically active α-arylpropionic acids. A deep structural study (NMR and modeling) suggested the formation of 1 : 2 receptor : substrate complexes and the vital importance of the H-bonding pattern and the aryl-aryl interactions. Moreover, this is the first report on the use of chiral cyclopentane-1,2-diamine in molecular recognition.

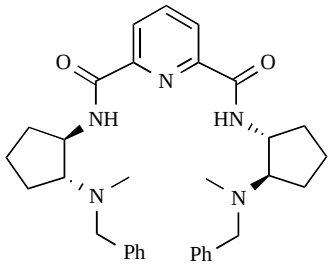

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Fig. (9). Pincer-like amino-amide receptor used as CSA for carboxylic acids.

A similar rationale was used by He and co-workers [47] for the preparation of enantioselective sensors, bearing a dipeptide moiety as the chiral source and two diaminoantracene arms as the fluorescence groups (Fig. **10**). The two receptors (**34a-b**) were studied by both fluorescence and NMR spectroscopy, showing some degree of enantioselectivity towards the tetrabutylammonium salts of mandelate. As expected, the selectivity was higher using the more rigid proline derivative (**34a**) (K_{ass}(D)/K_{ass}(L) = 8.96) than the phenylalanine (**34b**) counterpart (K_{ass}(D)/K_{ass}(L) = 4.01). Apart from the utility as chemosensors, these compounds were tested as CSA of the mentioned carboxylate, displaying very good splitting of the NMR signals.

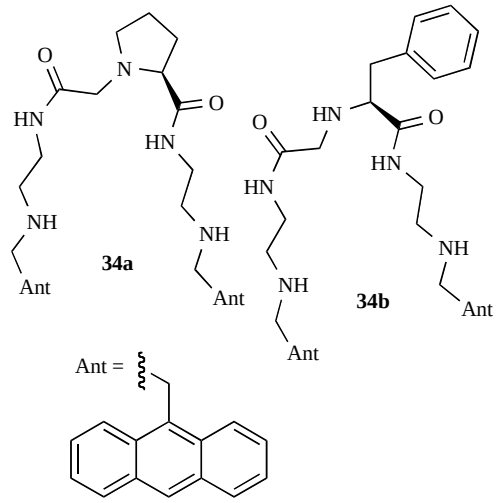


Fig. (10). Enantioselective fluorescent sensors and CSAs based on open-chain polyaminoamides.

Kilburn and co-workers reported an interesting design which was successfully used for the binding of *N*-Cbz-protected amino acids and dipeptides (Fig. **11**) [48]. Their syntheses were performed in solid phase by conventional peptide coupling conditions. The receptors are symmetrical tweezers bearing a carboxylic binding site (CBS) and two chiral arms. The CBS is a 2,6-diamidopyridine unit. The arms are two pseudopeptidic open chains, in which some of the amide bonds have been replaced by sulfonamide groups. In this function, the NH is better H-bond donor, while the SO_2 is weaker H-bond acceptor. This design minimizes the collapse of the arms by self-complementary H-bonding interactions, and maximizes the binding with the substrate. A little apparent enantioselectivity was observed by NMR titration in $CDCl_3$ between the short receptor (**35a**) and the enantiomers of *N*-Cbz-Ala-OH. The longer derivative (**35b**) displayed a high enantioselectivity towards the dipeptide *N*-Cbz-D-Ala-D-Ala-OH (>20 : 1, comparing with its enantiomer) although the absolute binding constants were weak. Anyway, it is particularly noteworthy to observe such stereoselectivity from a receptor lacking a preorganization for binding. Based on a similar design and using strategies of combinatorial chemistry, the optimization of the polypeptide sequences on the arms of the tweezer has been also performed [49]. Thus, libraries of resin bound receptors (**36**) prepared by the split-and-pool technique were tested against fluorescent-labeled peptides with a carboxylic terminus. The best receptor for a given carboxylic-peptide can be detected

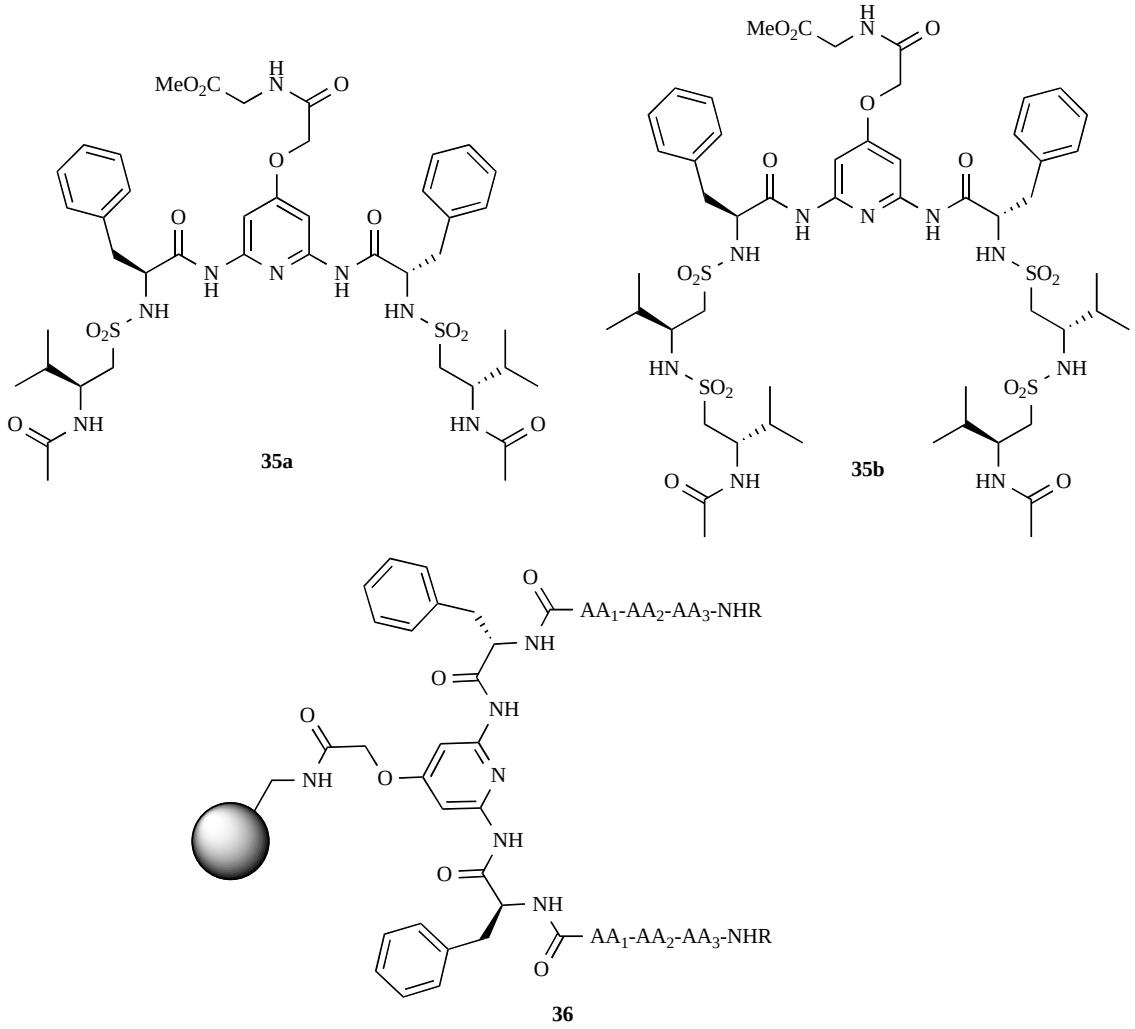


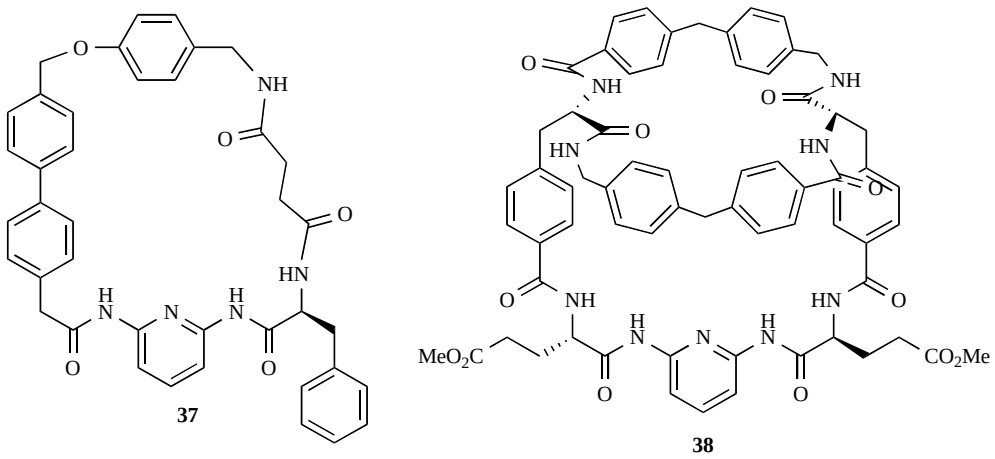
Fig. (11). Tweezer receptors based on 2,6-diamidopyridine as the carboxylic binding site.

in that way, although the necessary re-evaluation of the lead receptor showed experimental problems in some cases.

Macrocyclic Receptors

The 2,6-diamidopyridine binding motif has been also implemented in macrocyclic and macrobicyclic receptors (Fig. **12**). The synthesis of both racemic and homochiral cyclic derivative (**37**) has been accomplished in a multi-step pathway, leading to the desired compound in low overall yields [50]. This compound showed to be an effective receptor for dipeptides with a carboxylic acid terminus in $CDCl_3$, showing selectivity for *N*-Cbz-β-alanyl-L-Xxx-OH dipeptides. The stereoselectivity largely depends on the nature of the amino acid on the carboxylic terminus (Xxx) of the substrate. For instance, the difference in the binding energy ($\Delta\Delta G$) of diastereomeric complexes is 3.3 kJ/mol for Ala, 2.2 kJ/mol for Phe and 4.1 kJ/mol for Val. Interestingly, when this position is changed to lactate, both the selectivity and the interaction with the receptor dramatically dropped, implying a vital role of the H-bonding of the replaced amide. Detailed structural analyses by NMR and modeling suggested a somehow flexible conformation in solution and gave some clues about the source for the observed selectivity. One attempt to rigidify the structure of the receptor was also carried out by setting the CBS at the base of a bowl-shaped cavity. Based on previous reported data [51], macrobicyclic receptor (**38**) was designed and synthesized, although in moderate overall yield and after many reaction steps [52]. NMR titration studies showed that (**38**) preferentially binds to the L-enantiomer of the *N*-Cbz-Ala-OH substrate ($\Delta\Delta G$ = 4.8 kJ/mol). Increasing the length and complexity of the substrate also increased the strength of the binding by a factor of 6, and retained the observed stereoselectivity. Thus, the binding constants measured for *N*-Cbz-L-Ala-L-Ala-OH and *N*-Cbz-D-Ala-D-Ala-OH rendered a $\Delta\Delta G$ = 4.8 kJ/mol favorable to the L isomer.

The same binding unit has been recently used by Ema *et al.* [53] for the synthesis of a family of macrocycles (**39-41**) with multiple H-bonding sites (Fig. **13**). The synthesis seems to be easy and quite straightforward. The NMR titration data in $CDCl_3$ showed a moderate enantioselectivity of receptor (**39**) towards (*S*)-mandelic acid ($\Delta\Delta G$ = 1.46 kJ/mol), although for receptor (**40**) this selectivity is lower ($\Delta\Delta G \approx 0.6$ kJ/mol). Interestingly, in both cases, the aromatic proton in *para* to the NO_2 groups also participates by H-bonding with the substrates. Despite the moderate stereoselectivity, the



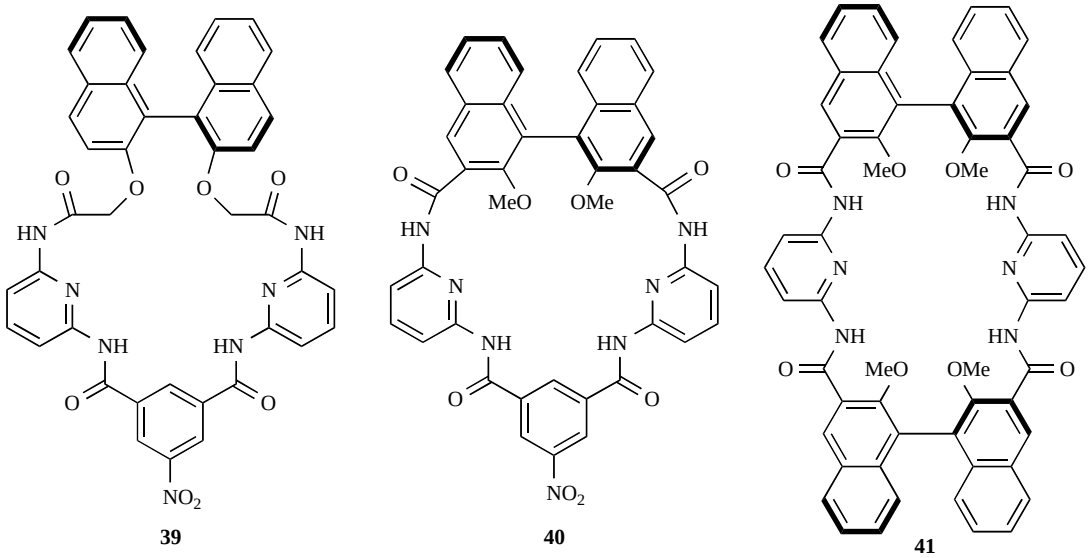
37 **38**

Fig. (12). Macrocyclic and macrobicyclic oligoamides as stereoselective receptors.

macrocycles are able to largely split (up to $\Delta\Delta\delta$ = 0.55 ppm) the NMR signals of many different H-bonding acceptor substrates, even using only 5% mol of the receptor. Thus, these compounds have a tremendous practical utility as CSA for the determination of the ee of chiral compounds.

Also for the case of the macrocyclic receptors, the combination of both amide and amine functional groups allows to directly use the carboxylic acid substrates. Thus, the anion is formed in solution by the proton transference from the substrate to the receptor amino nitrogen atoms. This has been the strategy followed by Fu and co-workers during the last couple of years. For example, they described the preparation of chiral dioxocylens (**42a-e**) by the cyclization between diethylenetriamine and the methyl esters of different *N*-(methoxycarbonylmethyl)-α-amino acids [54]. A similar synthetic strategy was also used to prepare the larger C_2 symmetrical macrocycles derived from proline (**43**) [55] or tartaric acid (**44a-b**, **45**) [56]. The method is rather simple although requires long reaction times (7-10 days) and leads to moderate or low overall yields. The obtained macrocyles were tested for NMR enantiodiscrimination (CSA) with many different chiral carboxylic acids. Some interesting trends were observed. In general, the receptors bearing the proline moiety produced larger splitting than those deriving from other amino acids, probably due to a more rigid conformation in solution. Besides, the C_2 symmetrical derivative (**43**) is much better than the C_1 symmetrical one (**42e**). Additionally, the stoichiometry of the complexes is also different, as expected from the different size and number of basic nitrogen atoms. For instance, compound (**43**) formed 1 : 2 receptor : substrate complexes with mandelic acid, while the stoichiometry was 1 : 1 in the case of compound (**42e**). Regarding the macrocycles derived from tartaric acid, compound (**44b**) behaved especially well as CSA, probably due to the shielding effect produced by the benzylic arms attached to the amines. Moreover, (**44b**) displayed slight enantioselectivity towards mandelic ($K_{ass}(R)/K_{ass}(S)$ = 1.40) and α-methoxyphenylacetic ($K_{ass}(R)/K_{ass}(S)$ = 1.63) acids.

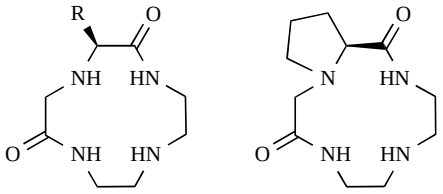
Pseudopeptidic macrocycles bearing both amine and amide functional groups have been also reported by Luis *et al.* [57-62] The key step for the synthesis of these compounds is the macrocyclization reaction, which is favored by the fold-



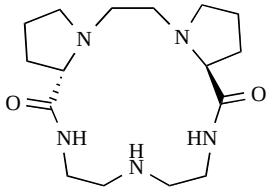
39 **40** **41**

Fig. (13).

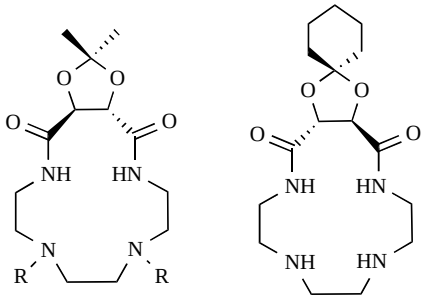
ing of the open-chain precursor in a U-turn conformation [57]. Thus, naphthalene-containing macrocycles can be obtained in reasonable yields, showing interesting fluorescence [58] and conformational [59] properties. One of these compounds has been used as a fluorescent ratiometric chemosensor for Cbz-protected phenylalanine [60]. Additionally, the receptor showed a moderate preference for the L-enantiomer of the substrate.



42a-d (R = Me, Bn, iPr, sec-Bu) **42e**

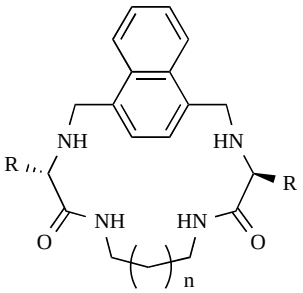


43



44a-b (R = H, Bn) **45**

Fig. (14). Macrocyclic polyaminoamides used as CSA for NMR enantiodiscrimination.



46a,b (n = 0, R = i-Pr, Bn)
47a,b (n = 1, R = i-Pr, Bn)
48a,b (n = 2, R = i-Pr, Bn)

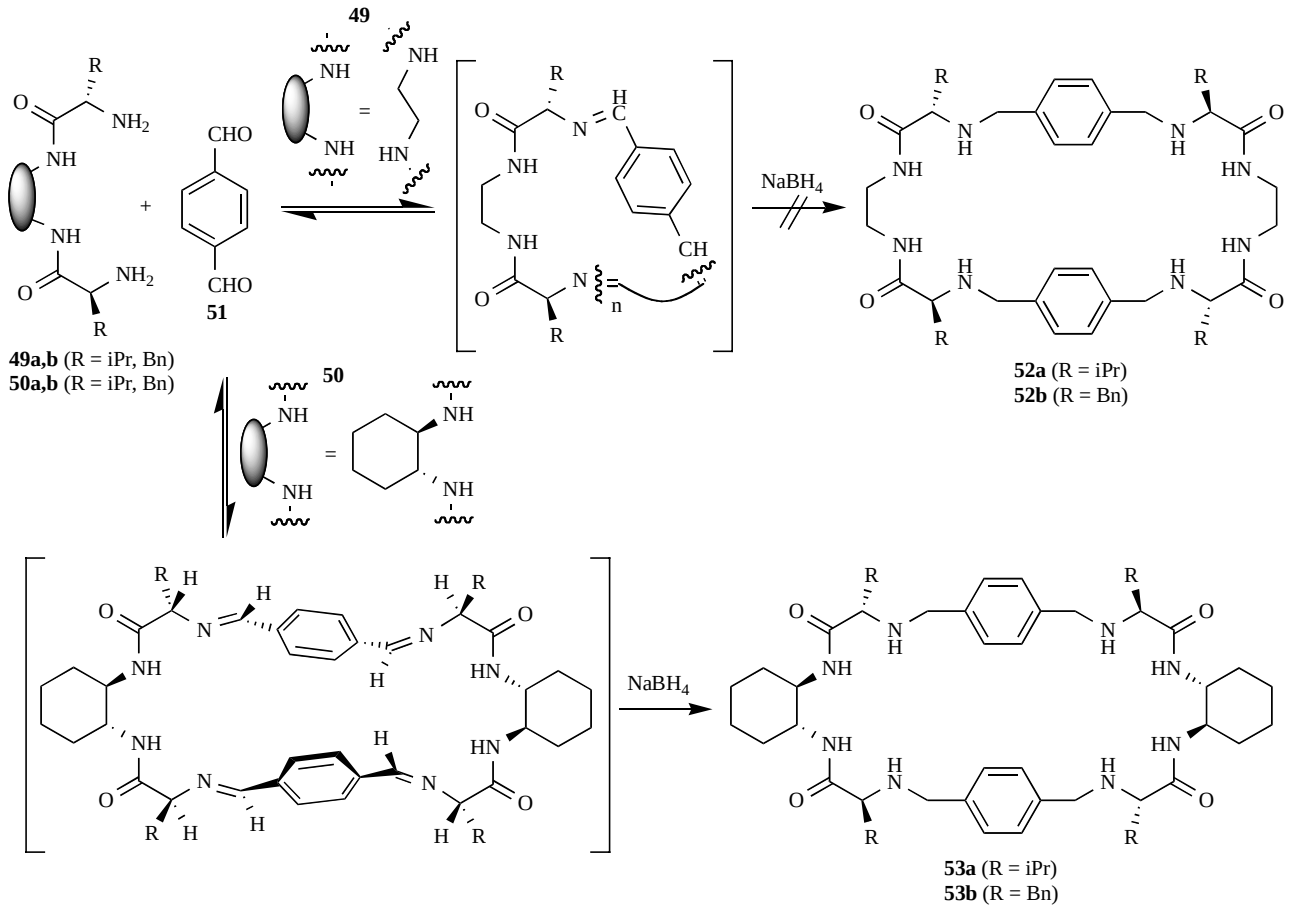
Fig. (15). Macrocyclic pseudopeptidic naphthalenophanes.

Probably the main problem to prepare macrocyclic receptors is the low selectivity often found for the cyclization step. This usually leads to low yields and tedious purification steps, as shown in some examples of this review. Considering the potential applications of macrocycles derived from amino acids in the chiral anion recognition field, we envisioned to carry out a reductive amination reaction between the corresponding open-chain pseudopeptidic bis(amidoamine) (**49-50a,b**) and an aromatic dialdehyde (**51**) (Scheme **5**). When the reaction was performed with the flexible ethylenic spacer (**49a,b**), it always led to a complicated mixture of open chain oligomers, with no formation of the intended macrocycle (**52a,b**) [61]. However, when the (*R*,*R*)-cyclohexane-1,2-diamine derivatives (**50a,b**) were used, the process nicely led to the desired [2+2] macrocyclic product (**53a,b**), easily isolable in high yield after the in situ reduction. The tetraimine intermediate (Scheme **5**) was thoroughly studied by NMR, circular dichroism and theoretical calculations. Interestingly, the observed preorganization for the cyclization is highly configurationally driven, as it is shown by the match/mismatch relationships between the absolute configurations of both the chiral diamine and the amino acid.

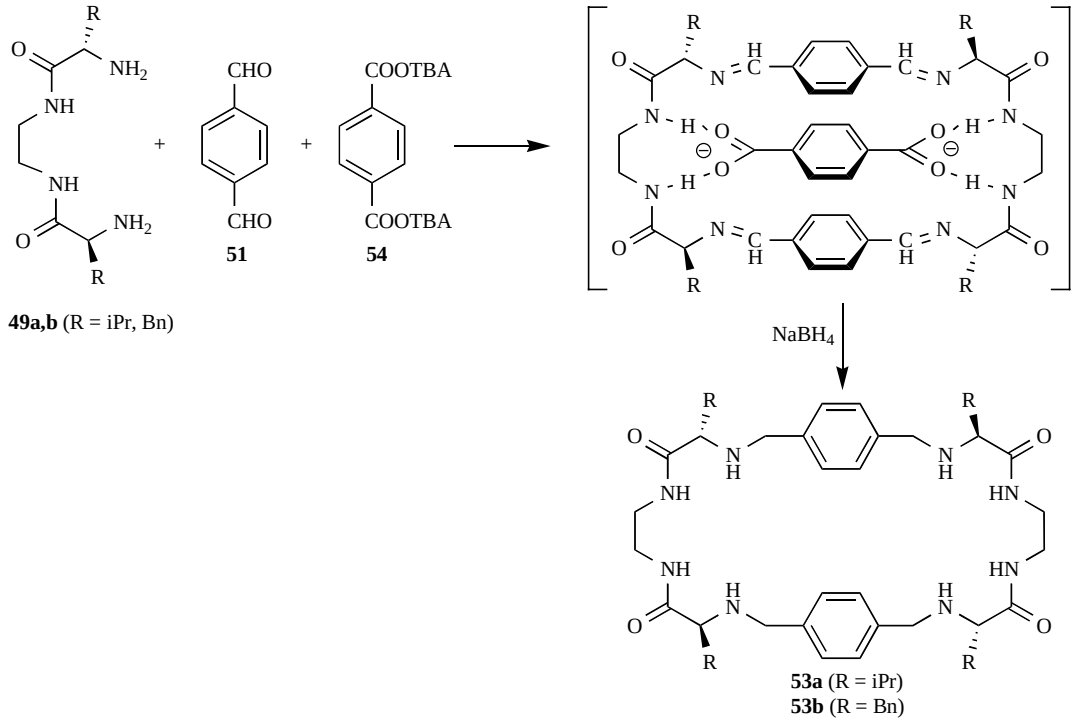
Considering these results, we used a conceptually different approach to promote the [2+2] macrocyclization. Taking advantage of the amide-anion strong interaction, we envisioned to use an anion to produce the necessary preorganization in the case of the more flexible derivatives (**49a,b**) [62]. After a preliminary structural design by molecular modeling, we decided to use the complementary therephthalate dianion as a template [63]. Satisfyingly, the presence of the template led to the formation of a macrocyclic tetraimine-dianion supramolecular complex (Scheme **6**) which could be fully characterized by NMR, ESI-MS and circular dichroism. Besides, these supramolecular complexes can be in situ reduced to the desired macrocycles (**53a,b**) in a one pot two steps procedure comprising the condensation of four components in a highly selective manner. The final overall yields were very high (60-65% from the starting **49a,b**). Therefore, chiral macrocyclic compounds can be efficiently prepared through anion templation, which emerges as an interesting new application of anion molecular recognition.

VII. CONCLUSIONS AND OUTLOOK

Molecular recognition of chiral anionic species is an emerging area for research, but still a challenging task in modern chemistry. Amine and amide containing receptors have proved to be successful in terms of both strength and selectivity of the interaction. Although many researchers are intensively working in this field, the efficient synthesis of new receptors usually comprises multi-step strategies with low yields and many purification processes. Besides, there is a need for a deeper structural knowledge of the supramolecular species in order to better design new compounds. The preorganization of the receptor is essential for both its preparation and efficacy. New synthetic approaches based on combinatorial (conventional and dynamic) chemistry and templated procedures have recently shown a tremendous potential within this research field.



Scheme 5. Synthesis of chiral pseudopeptidic macrocycles through a configurationally driven preorganization.



Scheme 6. Anion templated synthesis of pseudopeptidic macrocycles.

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