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REVIEW

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Upper rim-bridged calixarenes

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Calix[*n*]arenes represent a very attractive family of macrocyclic compounds with many potential supramolecular applications. Due to their well-established chemistry and many different synthetic strategies, enabling practically any derivatization of the basic skeleton, calixarenes are among the very popular building blocks used for the design and construction of various receptors, sensors and other sophisticated supramolecular systems. Regio- and/or stereo-selective derivatization of calixarenes currently represents a very extensive set of reactions, the overview of which would fill many thick books. Therefore, this review deals with only a small part of the above-mentioned reactions, specifically describes possible ways of bridging the upper rim of calixarenes, often leading to interesting rigidified structures, and also briefly mentions the potential use of these compounds.

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Preface

Although modern supramolecular chemistry uses a wide range of macrocyclic compounds due to their increased preorganization compared to noncyclic analogues, calixarenes occupy an absolutely essential position in this context.[1] Above all, they enable a simple multigram preparation from cheap starting materials (Fig. 1), while providing the option of choosing the size of the cavity depending on the reaction conditions. The resulting macrocycles (calix[4]arene to calix[8]arenes) then show considerable variability in terms of their subsequent derivatization, enabling the introduction of suitable functional groups into selected positions on the basic skeleton.

Calixarenes are therefore almost ideal candidates for the design and synthesis of various receptors intended for catching cations, anions or neutral molecules (depending on the substitution of the macrocycle).[2] If we focus on the smallest of them, calix[4]arene, we have a unique possibility to "tune" the three-dimensional structure of the molecule by simple alkylation/acylation of phenolic hydroxyls. It is the possibility to fix the basic skeleton in one of the four basic conformations (atropisomers) that makes these molecules indispensable as molecular scaffolds in the design of new receptors and building blocks. It is precisely the *cone* conformation of calix[4]arene, with a shape reminiscent of the ancient calix crater vase (Fig. 2), to which we owe the general name of this family of macrocycles.[1b]

Calix[4]arenes in particular have become very popular building blocks for the design and synthesis of new receptors, with an extensive literature on "shaping" their cavity through conformational immobilization. In this context, by far the most common methods are simple alkylation/acylation (including bridging) of the phenolic functions of calixarenes (the so-called lower rim). As the title suggests, this review is only focused on derivatives with a bridged upper rim, a topic that, to the best of my knowledge, has not been covered before.

Although the introduction of substituents into the lower rim of the macrocycle leads to immobilization of the system (in the case of calix[4]arenes derivatives), at the same time it excludes the possibility of targeted use of free phenolic groups, either for subsequent derivatization or for relevant supramolecular

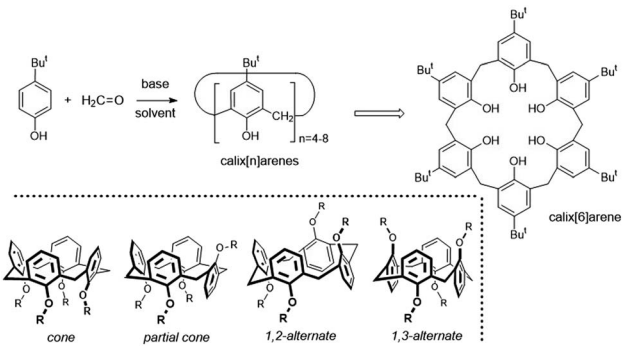

Fig. 1 Preparation of calix[*n*]arenes; calix[8]arene as an example of the structure; four basic conformations (atropisomers) of calix[4]arene.

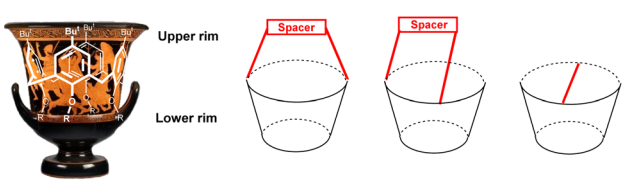

Fig. 2 Lower rim and upper rim of calix[*n*]arenes and the upper rim-bridged derivatives (schematically).

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applications. In addition, alkylation of the lower rim only works for calix[4]arene, whereas higher macrocycles cannot be fixed in this simple way. Therefore, it may be interesting to turn attention to the opposite side of calixarenes – the aromatic part of the molecule, usually called the upper rim (Fig. 2).

This part is primarily amenable to various types of aromatic electrophilic substitution, such as halogenation, acylation, nitration, sulfonation, *etc.* The chemistry of the upper rim of calixarenes therefore offers a much more diverse range of downstream derivatizations than that of the lower rim. A suitable bridging of the upper rim therefore leads to a rigidification of the molecule without the need for the substitution of phenolic groups, which are thus still available.

Furthermore, dimerization of calixarenes by linking their upper rims leads to larger cavities that are preorganized for various predominantly supramolecular applications. The combination of suitable functional groups together with aromatic cavities of macrocycles gives rise to interesting receptors capable of complexation using a whole range of non-covalent interactions. Simple bridging of calixarene leads to confined spaces, enabling complexation of the guest species within the rigidified cavity. Last but not least, upper-rim *meta*-bridging of calixarenes gives rise to a new class of (often inherently chiral) calixarene derivatives with an extremely rigid and distorted cavities, with possible applications in chiral recognition of suitable guests.

Because the number of reports dealing with calixarenes is huge, only selected examples of upper rim-bridged systems are described in this review. As shown schematically in Fig. 2, these are systems with different aromatic subunits arbitrarily connected by a spacer(s) or by a direct bond. In addition, selected systems based on bis-calixarenes, which are connected to each other by upper rims, are also included (see *e.g.* Fig. 4). However, it should be noted that this overview is not an exhaustive summary of all existing systems. Instead, it is intended to serve more as a guide, showing possible approaches to the synthesis of this interesting subgroup of calix[*n*]arene derivatives. The review is focused on demonstrating numerous synthetic approaches leading to bridging of the upper rim, so emphasis is placed on synthetic procedures and the selection of suitable starting systems, rather than on the actual use of compounds prepared in this way. Potential applications of bridged systems are usually only briefly indicated, if interested, the reader is referred to the original primary literature for a full description.

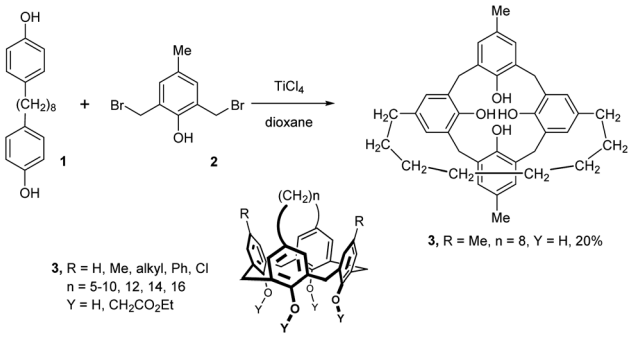

Fig. 3 The first example of upper rim-bridged calix[4]arene.

20% yield when the reaction was carried out at normal concentrations (30 h at 100 °C). Alkali metal ions transport experiments (from an alkaline source – phase through a liquid membrane to a neutral receiving phase) with Cs^+ ions showed a sharp maximum of the transport ability for this compound ($n = 8$), suggesting complexation of the caesium inside the cavity.

The conformational behaviour of similar systems **3** possessing different bridges (Fig. 3) was studied by CIDNP NMR technique[4] and by single crystal X-ray analysis.[5] Both techniques confirmed that the macrocycles adopt a *cone* conformation both in the solid state and in solution. A wide range of derivatives bearing various substituents on the unconnected phenolic units (**3**, R = methyl, octyl, dodecyl, octadecyl, *tert*-butyl, cyclohexyl, phenyl and chloro groups) was prepared[6] by the aforementioned synthetic approach to show its general applicability. The yields of products were usually in the range of 5–25%, occasionally reaching 35–40%.[7] The lower limit for the length of the bridge seems to be $n = 5$.

On the other hand, a unique cage molecule **4** was isolated in very low yield[8] by the condensation of bisphenol **1** possessing a shorter spacer ($n = 4$) with bis-bromomethyl derivative **2** (Fig. 4).

A similar approach based on the tetrakis-bromomethylated compound **2a** gave a fully bridged cage system **5**, but again only in very low yield. In this case, a longer spacer was used for both reaction components **1** and **2a** ($n = 10$) – see Fig. 4.[8] Using the aforementioned strategy, even calix[4]arenes with bridged neighbouring aromatic groups have been reported, yet without any experimental details.[7]

Overview of possible strategies

Condensation of suitable fragments

The oldest approach to the upper rim-bridged calix[4]arenes is based on the condensation of suitably substituted starting phenols as indicated in Fig. 3.[3] The condensation of bisphenol **1** with 2,6-bis(bromomethy)-4-methylphenol **2** under Lewis acid ($TiCl_4$) catalysis led directly to macrocycle **3**. Interestingly, the authors found that it is not necessary to use high dilution conditions for the macrocyclization reaction as the desired calixarene **3** (R = Me, $n = 8$, Y = H) was isolated in

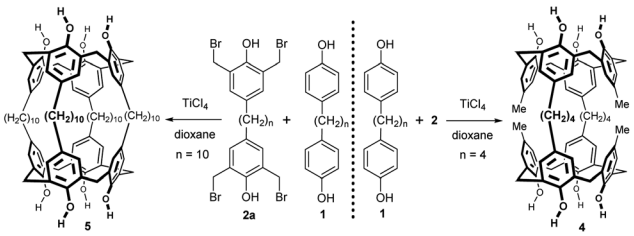

Fig. 4 Calixarene cages by fragment condensation.

Intramolecular linking *via* ether/thioether or ester functions

While bridging of lower rim with polyether chain is very common procedure in calixarene chemistry (giving rise to so called calixcrowns), analogous derivatives bridged on the upper rim are very rare. One of the examples is the alkylation of oligoethylene glycols **7** with the bis-chloromethyl compound **6** in refluxing THF in the presence of NaI and NaH which gave the corresponding bridged products **8a–e** in 11–95% yields (Fig. 5), strictly depending on the length of the glycol.[9] As the lower rim was alkylated with methyl groups, the resulting macrocycles are not conformationally rigidified and the upper rim crowns **8a–e** were used for study of conformational interconversions between the individual conformers (*cone – partial cone – 1,3-alternate*) formed by the rotation of unbridged aromatic subunits.

Tetrachloromethylated calix[4]arene **9b** was transformed into a double calix-crown **13** in 50% yield by reaction with ethylene glycol in DMF/NaH (Fig. 6).[10] The reverse approach relied on the bis-hydroxymethyl derivative **9a**, which was allowed to react with α,α′-dibromo-*p*-xylene **10** or its anthracene analogue. The corresponding bridged products **11** and **12** were obtained in 30 and 35% yields, respectively.[10] The absolute and relative ability of these compounds to undergo host–guest complexation with neutral molecules (AcO-*i*Pr, AcOEt, AcO-*t*Bu, AcO-*n*Pr *etc*) was investigated in the gas-phase using a mass spectrometric technique.

Bis(hydroxymethylated) calixarenes **14a** and **14b** (obtained by reduction of the corresponding dialdehydes) were reacted with tosyl chloride under basic conditions (Fig. 7). The main products **15a** (30%) and **15b** (40%), representing the results of an intramolecular cyclization, possess very short bridge chain (only three atoms). The ^{1}H NMR spectra of these compounds are in an agreement with a highly distorted flattened *cone* conformation of these products.[11] Interestingly, the coupling between the calixarene **14c** and thioethyl tetrabenzoyl-β-D-galactopyranoside in the presence of Cu(OTf) in MeCN provided compound **15c** (2%) as a byproduct to the expected bis-β-galactosyl calixarene (not shown).[12] The ^{1}H NMR properties of compound **15c** were studied both experimentally and computationally.[13]

Bis(hydroxymethylated) calixarenes **14a** and **14b** were also reacted with bis(chloromethyl) derivatives **16a** and **16b** in different conditions (Fig. 7). The best results were achieved using CsOH in DMF leading to bis-calix[4]arene product **17a** and **17b** in 42 and 38% yield, respectively.[11]

The new upper rim bridged hosts **18a–d**, bearing pyridine or benzene rings within the cavity, were synthesized from diol **14a** and the corresponding diacid chlorides under high dilution conditions (Fig. 7). The shape, rigidity, and chemical structure of the bridge control the host–guest complexation properties of these cavitands. The ^{1}H NMR titrations suggested the formation of *endo*-complexes with selected neutral guest molecules having acidic C–H bonds (CH_3CN, CH_3NO_2, $CH_2(CN)_2$).[14]

An interesting approach to bridging the upper rim using an ether bond is shown in Fig. 8. The initial bis(hydroxymethyl) derivative **14a** was first alkylated using propargyl bromide to form the corresponding diether **19** in 70% yield (Fig. 8).[15] The triple bonds were then oxidatively coupled using $Cu(OAc)_2$ to provide a butadiyne-bridged compound **20** in 60% yield. The ability of this cavitand to undergo host–guest complexation with neutral molecules was investigated in the gas-phase using a MS technique.

The reaction of **14c** with bromochloromethane in the presence of NaH in THF (Fig. 9) provided intramolecularly bridged compound **21** (30%), 2 + 2 reaction product **22** and some higher cyclic oligomers.[16] The chloroform solutions of pure monomer **21** or pure dimer **22** were treated with a catalytic amount of triflic acid (TfOH) at 25 °C. Under these conditions, both cyclic products were cleaved to form the short bridged calix[4]arene **15c** as the main product (up to 60%).

Chloromethyl derivative of calix[6]arene **24** (available by direct chloromethylation of starting **23**) was reacted with thiourea at room temperature in DMSO followed by the treatment with aqueous NaOH solution (Fig. 10). This reaction afforded the mercaptomethyl calix[6]arene **25** in 52% yield. Equimolar amounts of **24** and **25** were then mixed in *N*-methylformanilide-THF mixture containing Cs_2CO_3 and $NaBH_4$ under high dilution conditions to give "carcerand" **26**.[17] The MS and elemental analysis showed that **26** possesses a molecular cavity in which *N*-methylformanilide is trapped noncovalently as a guest.

Calix[4]arene-tetrathiafulvalene (TTF) conjugates were prepared by reaction of TTF dithiolates generated *in situ* from 2-

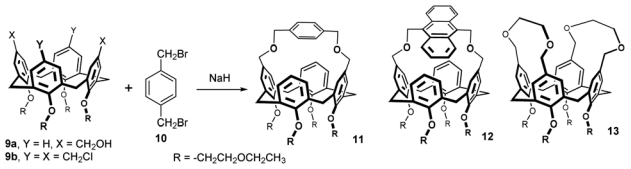

Fig. 6 Upper rim calix[4]arene ethers.

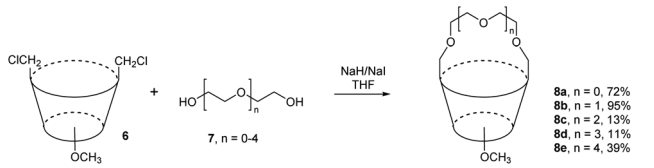

Fig. 5 Upper rim calix[4]arene crowns.

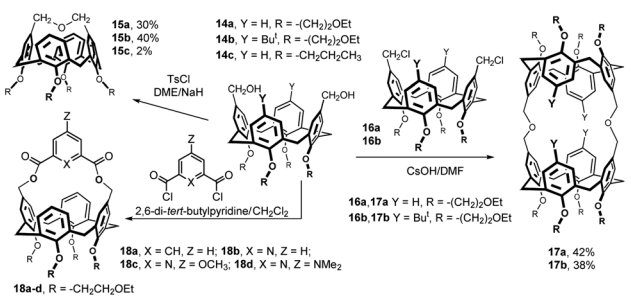

Fig. 7 Upper rim calix[4]arene ethers.

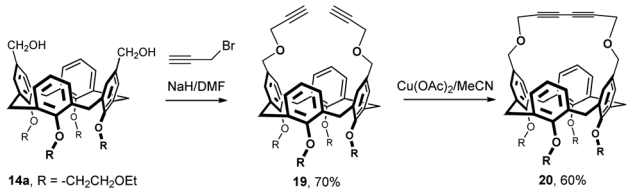

Fig. 8 Upper rim calix[4]arene ethers *via* coupling of terminal alkynes.

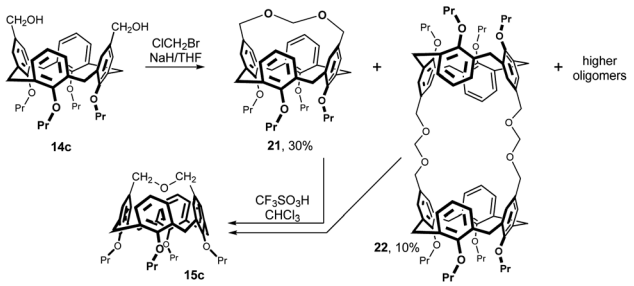

Fig. 9 Upper rim calix[4]arene ethers *via* coupling of terminal alkynes.

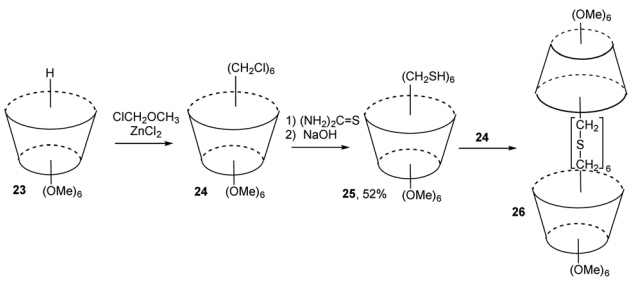

Fig. 10 Molecular capsule based on calix[6]arene.

cyanoethylthio TTF derivatives **27a–d** (Fig. 11).[18] The corresponding dithiolates were then alkylated by tetrakis(chloromethyl) calixarene **9c**. The upper rim TTF-calixarene conjugates **28a–d** were obtained in good yields (59–64%) as bright orange-yellow solids showing moderate binding with pyridinium cations in solution. Interestingly, the same reaction with calix[4]arene in the *1,3-alternate* conformation (analogous to **9c**), completely failed and no trace of the expected product **28e** was observed in the reaction mixture.[19] A binding study (^{1}H NMR) in $CDCl_3$ using compound **28b** as a host and *N*-methylpyridinium derivatives as guests revealed poor binding efficiency under fast-exchange conditions due to the cation–π interactions.

Calix[4]arene-TTF conjugates **(*Z*)-30** and **(*E*)-30** were prepared using a similar strategy (Fig. 11) – the cyclisation of 2,6 (2,7)-TTF dithiolates (generated from **(*Z*)-29** and **(*E*)-29**) with bis-bromomethylated calix[4]arene **16c**.[19] The (*Z*)-isomer **(*Z*)-30** was found to be a stable compound. On the other hand, the (*E*)-isomer **(*E*)-30** isomerised rather fast in solution, affording predominantly the thermodynamically more stable **(*Z*)-30**, as well as minor amounts of decomposition products. The 2 + 2 cyclisation product **(*Z*/*E*)-31** was isolated as a mixture of four possible

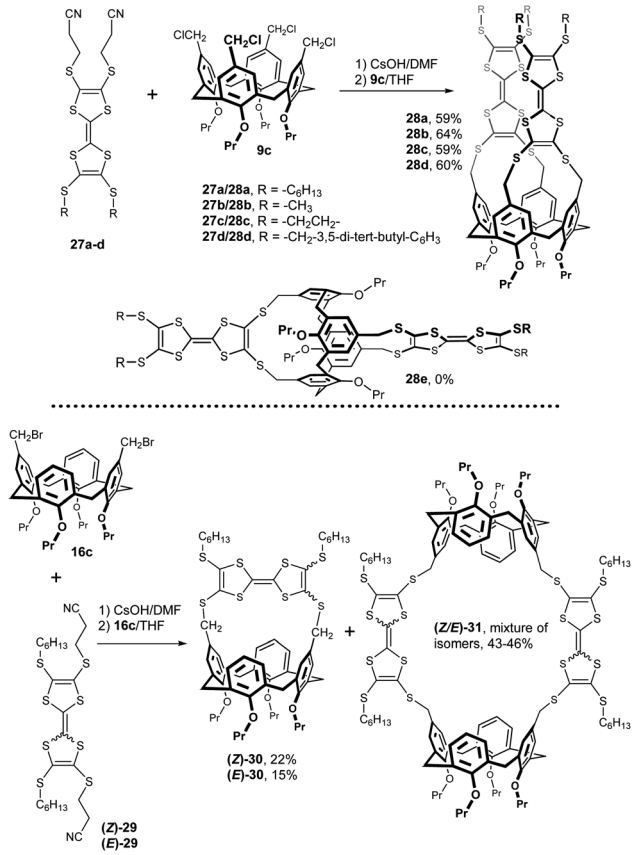

Fig. 11 Calix[4]arene-TTF conjugates.

(*Z*/*E*)-stereoisomers. Redox properties of new calix[4]arene-TTF conjugates were characterised using cyclic voltammetry.

The octathiabis(calixarene) cage **31a** was isolated in 30% yield from the reaction of tetrathiol **9d** with methylene diiodide in DMA under high-dilution conditions using Cs_2CO_3 as a base (Fig. 12).[20] An analogous bis(calixarene) cage **31b** was prepared from the tetrakis(chloromethyl) derivative **9b** and 1,2-ethanedithiol using K_2CO_3/DMF in 20% yield. Moreover, when **9d** was reacted with α,α-dibromo-*o*-xylene, only a basket-shaped molecule **32** was formed.

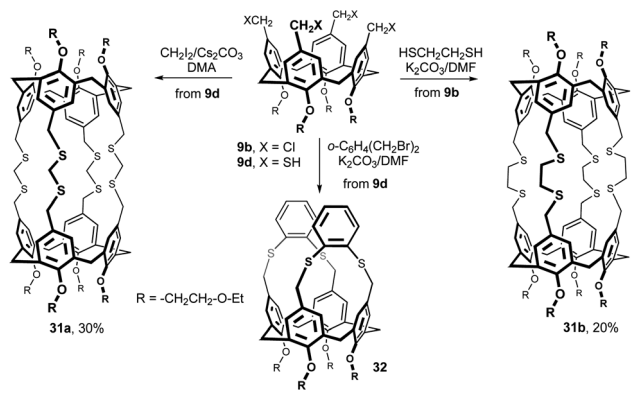

Fig. 12 Molecular capsules based on thioether functions.

Bridging *via* a hydrocarbon spacer

The reaction of dialdehydes **33a** and **33b** in THF with low-valent titanium species generated from Mg/Hg amalgam and $TiCl_4$ (McMurry reaction) was studied[21] (Fig. 13). In both cases, the intramolecularly bridged alkenes **34a** and **34b** were obtained as the main products in relatively low yields (25–30%).[22] To verify the general applicability of intramolecular reductive coupling, the reactivity of the tri- and *tetra*-aldehydes **33c** and **33d** was also studied. As expected, only the aldehyde groups on the opposite aromatic subunits were coupled to yield the ethylene bridged products **34c** (27%) and **34d** (15%). The remaining aldehydes were at the same time reduced to methyl groups. Interestingly, in the case of starting calixarenes with four substituents on the upper rim (**33b** and **33d**) the alkene bridged products **34b** and **34d** were accompanied by small amount of alkane analogues **35b** (10%) and **35d** (15%). A short reaction time also led to the isolation of the corresponding diol **36** as a mixture of two diastereomers.

The McMurry coupling of tetrapropoxydialdehyde **33e** was carried out under different reaction conditions ($TiCl_3$/Zn in refluxing THF).[23] The resulting ethylene bridged product **34e** was obtained in 30% yield (Fig. 12). The same reaction carried out at room temperature yielded two diastereomeric structures **36e** in 43% yield. Since the aforementioned reaction always connects aldehydes on the opposite aromatic subunits, the use of tetraaldehyde in the *1,3-alternate* conformation could lead to bridging on both sides of the molecule. Indeed, the reaction of starting compound **33f** provided double bridged cage product **34f** in 30% yield.[23]

Cyclization of suitable building blocks afforded calix[5]arene derivative which was transformed in multiple step procedure into diethynyl calix[5]arene **35** (Fig. 14). Eglinton coupling with copper acetate in pyridine at 60 °C, and the following deprotection of the acetyl groups provided the desired double calix[5]arene **36** in excellent yield (75%).[24] Two sets of signals in ^{1}H NMR spectra revealed a mixture of two conformational isomers

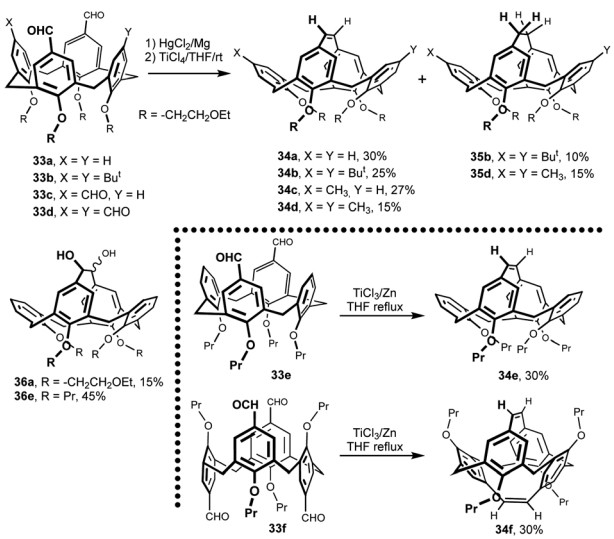

Fig. 13 McMurry reaction of calix[4]arenes.

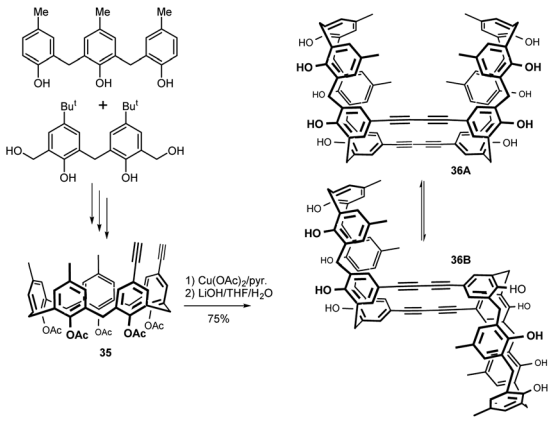

Fig. 14 Upper rim bridged calix[5]arenes.

syn **36A** and *anti* **36B** in a ratio of 7 : 3. At 130 °C, the relative population of the two isomers became almost equal and remained unchanged after cooling to room temp., indicating high energy barrier of interconversion between the isomers. Both atropisomers were finally isolated and the complexation ability of isomer **36A** toward commercially available fullerenes (C_{60}, C_{70}, C_{76}, C_{78} and C_{84}) was studied. The *syn* isomer **36A** showed very strong binding abilities for higher fullerenes and even precipitated as host–guest complexes. The captured fullerenes were released by heating the complex to afford the *anti* isomer **36B**.[24]

Although the Claisen rearrangement is quite often used in the chemistry of calixarenes for upper rim derivatization, its application for bridging is really rare. Thus, when tetrabutylammonium iodide (1 equiv.) was added to the reaction mixtures containing 1 equiv. of calix[4]arene and 0.5 equiv. of the alkylating agent (1,4-dichloro-2-butene or 3-chloro-2-chloromethyl-1-propene) in CH_2Cl_2 solution with NaH as the base, the bis-ethers **37a** and **37b** were obtained in yields of 84% and 51%, respectively (Fig. 15).[25] A subsequent study of the tandem Claisen rearrangement revealed that the addition of bis-(trimethylsilyl)urea (BTSMU) (2 equiv. per phenolic unit) is a key prerequisite for a successful reaction. By heating the starting compounds in *N*,*N*-diethylaniline (DEA), the doubly bridged derivatives **38a** and **38b** were isolated in 15 and 22% yield, respectively. The same strategy was applied to analogous calix[6]arene derivatives (not shown here), where the Claisen rearrangement was performed in even higher yields (33% and

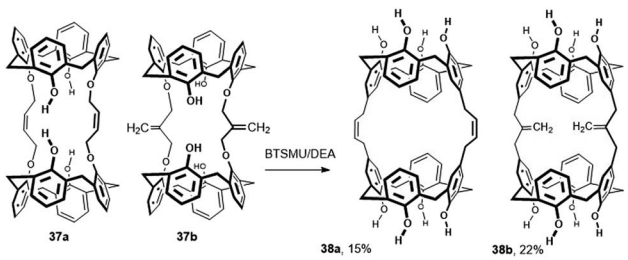

Fig. 15 Tandem Claisen rearrangement of calix[4]arenes, BSTMU = 1,3-bis(trimethylsilyl)urea, DEA = *N*,*N*-diethylaniline.

70%) than those reported for calix[4]arene derivatives.[25] The complexation behaviour of these bis-calixarenes toward fullerenes C_{60} and C_{70} has been studied.

As shown in Fig. 16, ring-closing metathesis study within the calixarene series was carried out with Grubbs catalyst (Cl_2-$Ru(PCy_2)_2$ = CHPh). Diallyl calix[4]arene **39a**, obtained by Claisen rearrangement of its lower rim counterpart, provided small amount of a cyclic dimer **38** (5%) accompanied by linear dimer **40a** and trimer **40b** in 25% and 20% yields in benzene. Surprisingly, the same reaction performed in DCM gave the cyclic trimer **42** as the only product that was obtained in virtually quantitative yield.[26] While the ring-closing metathesis of the lower rim-unsubstituted compound **39a** gave no intramolecularly bridged product, the ester group-bearing analogue **39b** (–CH_2COOMe) led smoothly to the cage structure **41** (84%).

Bridging *via* imine or hydrazone moiety

Because the introduction of the amine function (reduction of nitro group) or the direct formylation of the upper rim are well-established synthetic procedures in the chemistry of calixarenes, the application of the imine bonds in the construction of bridged systems is offered.

The condensation of diamines **43a** and **43b** with dialdehydes **44a–c** (reflux in DCM in the presence of molecular sieves) allowed for the isolation of the corresponding bis-calix[4]arenes **45a–c** in good yields (74–92%) (Fig. 17). The two imine bridges were then easily reduced with an excess of $NaBH_4$ at rt (EtOH-THF mixture) to the more flexible amines **46a** and **46b**, in good yields (87% and 95%, respectively).[27] The presence of short bridges (2 atoms) results in a relatively rigid head-to-head arrangement of the two calix[4]arene groups and compounds **45a** and **45b** showed a very high affinity for Ag^+ ions, with the complexation constants up to 9.5×10^5 M^{-1} (^{1}H NMR titration) in $CDCl_3$. Membrane transport experiments and CHEMFET studies revealed the selective transport and complexation of silver(I) ions.

A very similar synthetic strategy was used for the preparation of molecular containers **47** and **48**. The Schiff base derivative **47** was obtained in 69% yield by condensation of diamine **43b** with

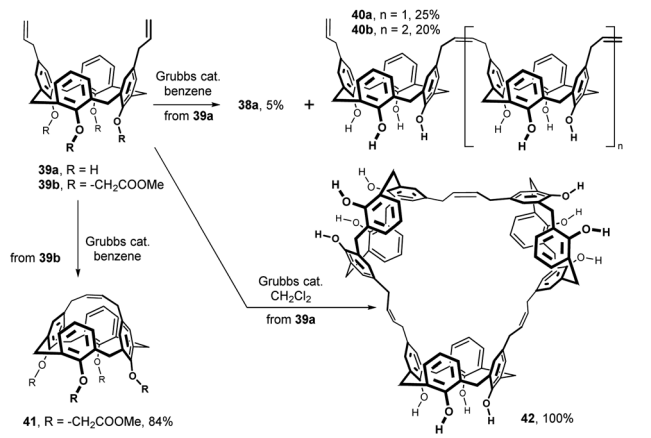

Fig. 16 Upper rim-bridged calix[4]arenes by ring closing metathesis.

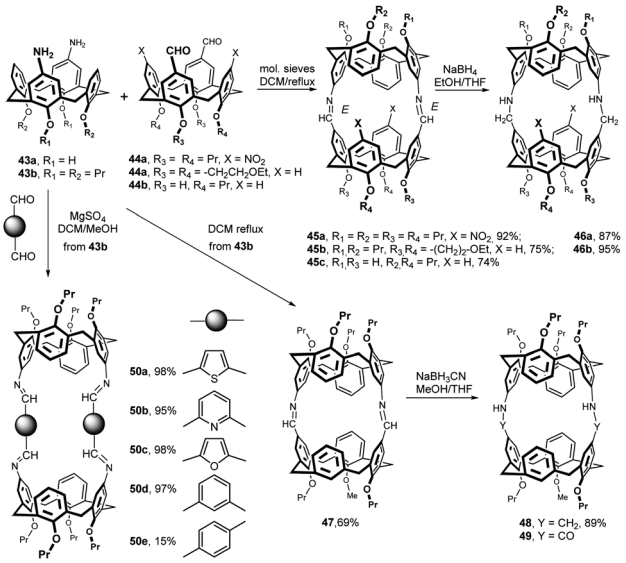

Fig. 17 Bridging of calix[4]arenes *via* Schiff base formation.

the corresponding dialdehyde (Fig. 17). Subsequent reduction with $NaBH_3(CN)$ afforded amine **48** in 89% yield.[28] A series of thermodynamic and structural studies on the host–guest complexation between molecular containers **48** and **49** (amide analogue) and the *N*-methylpicolinium salts were carried out. It has been shown that in these systems the organic cation is encapsulated within the molecular containers and therefore is separated from its counter anion.

The condensation reactions of diaminocalix[4]arene **43b** with various aromatic dialdehydes (24 h reflux in DCM:MeOH) in the presence of $MgSO_4$ provided the corresponding bis-calix[4]arenes **50a–d** in excellent yields (>95%; Fig. 17). Interestingly, in the case of terephthalaldehyde, the yield of bis-calixarene **50e** was only 19%. This indicates that the macrocyclization *via* imine bonds strongly depends on the geometry of the starting aldehyde (compare the *meta-vs. para*-substitution, **50d** *vs.* **50e**).[29] The binding studies between the bis-calix[4]arenes and viologen-type guest molecules revealed that thiophene-based derivative **50a** exhibited good binding affinities toward biologically interesting viologen guests even in relatively polar media ($CDCl_3 : CD_3OD = 2 : 1$ v/v).

An extension of this strategy to the chemistry of higher calixarenes is shown in Fig. 18. A 1,3,5-trisubstituted triamine **51** and the corresponding trialdehyde **52** were prepared by a multistep synthesis from the starting *tert*-butylcalix[6]arene. Their mutual condensation in boiling toluene (Dean–Stark trap) led to the cage-like structure **53** in 26% yield. Similarly, the aldehyde **52** was reacted with *para*-phenylenediamines to give double calix[6]arenes **54a** and **54b** with extended cavity in 50% and 40% yield, respectivelly.[30] The binding studies towards *N*-methylpyridinium, *N*-methyl-2-picolinium and *N*-methyl-4-picolinium iodides as guests were carried out in $CDCl_3/CD_3CN = 9 : 1$ v/v. While cages **53** and **54b** did not show any complexation ability, compound **54a** was found to complex pyridinium salts with association constants up to 890 M^{-1}.

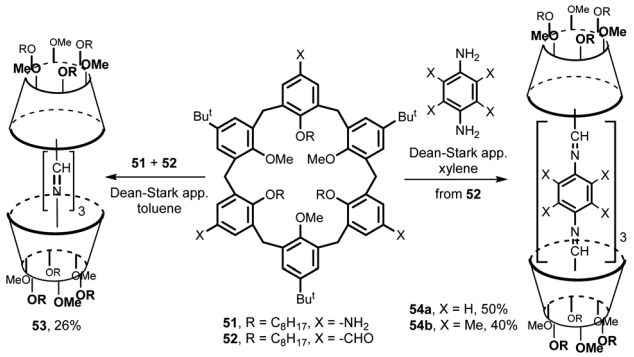

Fig. 18 Bridging of calix[6]arenes *via* Schiff base formation.

Calix[4]arene with intramolecularly bridged upper rim was prepared by reaction of dialdehyde **55a** with 1,8-diamino-3,6-dioxaoctane (Fig. 19). The resulting macrocycle was isolated in 59% yield. Subsequent alkylation with ethyl bromoacetate afforded ionophore **57** (68% yield), which was studied using extraction experiments for its ability to bind/extract the dichromate anion.[31]

Dialdehyde **55b** was bridged by reaction with carbohydrazide (reflux in EtOH) to give the corresponding carbohydrazone-based bis-calixarene **58** (72% yield) (Fig. 19).[32] According to the authors, this compound shows a selective enhancement of fluorescence intensity in response to Fe^{3+} ions suggesting its application as an iron selective chemosensor. The hydrazone structural motif can also be found in compounds **60a–c**, formed by the condensation of dialdehyde **33e** with the corresponding bis-acyl hydrazides **59a–c** (Fig. 19).[33] The biological activity screening showed that these compounds exhibit high antimicrobial activity against both Gram-positive and Gram-negative bacteria.

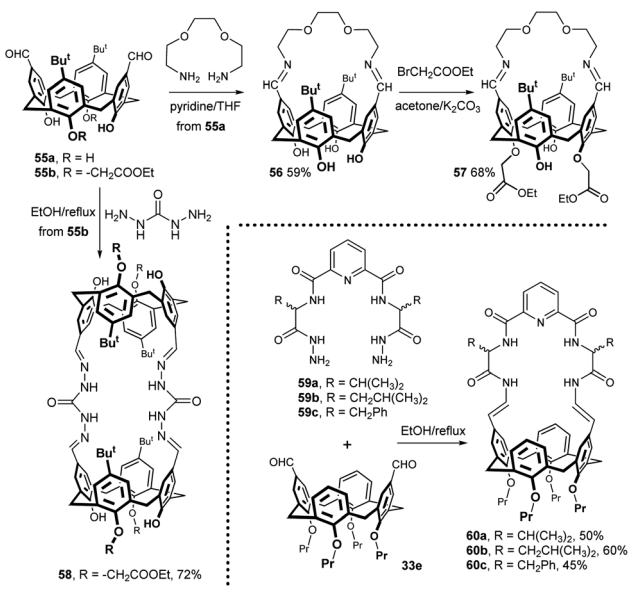

Fig. 19 Imine- or hydrazone-bridged calix[4]arenes.

Intramolecular cyclization *via* amidic function (from aminocalix[*n*]arenes)

As already mentioned, introduction of an amino group into the upper rim of calixarenes is a well-established synthetic procedure in calixarene chemistry. It is therefore not surprising that a substantial part of the derivatives with a bridged upper rim is based on the use of the amide bond.

In this context, the first example shown in Fig. 20 is somewhat unusual, since the authors used an amide functional group for alkylation reactions at the nitrogen atom. The key intermediate bis(acetamino) derivative **62** was obtained in 50% yield by the acylation of starting diamine **61**. Di-sodium salt of **62** formed by deprotonation with NaH was reacted with α,α′-dibromo-*p*-xylene **10** to provide an intramolecularly bridged cavitand **63** (20%).[15] A similar alkylation with propargyl bromide led to dialkynyl derivative **64** in essentially quantitative yield. Oxidative coupling of acetylene functions with $Cu(OAc)_2$ provided cavitand **65** in 20% yield. All these cavitands, together with the structurally related compounds from Fig. 8, were studied for the complexation of neutral substances in the gas phase.

Treatment of **66a** and **66b** with aliphatic diacid dichlorides containing four to eight methylene groups between the carboxyl moieties resulted in intramolecular bridging of calix[4]arene diamines. Reaction carried out under high dilution conditions yielded the corresponding *cone* conformers **67a–c** and **68a–d** in very good yield (Fig. 21). The *1,3-alternate* congeners **69a–c** were obtained analogously from **66c**.[34]

Starting from diamino derivative **43b**, the L-alanine moiety was introduced into the upper rim to form compound **70** in high yield. The following reaction with aromatic diacyl dichlorides then gave compounds **71a** and **71b** in 40 and 30% yields.[35] The formation of expected products was accompanied by [2 + 2] condensation leading to giant byproducts **71a′** and **71b′** in small amounts (Fig. 22). ESI-MS and ^{1}H NMR experiments revealed that **71a** and **71b** behaved as macrocyclic receptors for carboxylate anion recognition in acetone solution. The combination of HB interactions and π–π stacking resulted in high complexation constants towards benzoate anion ($K_c = 4 \times 10^4$ mol^{-1}).

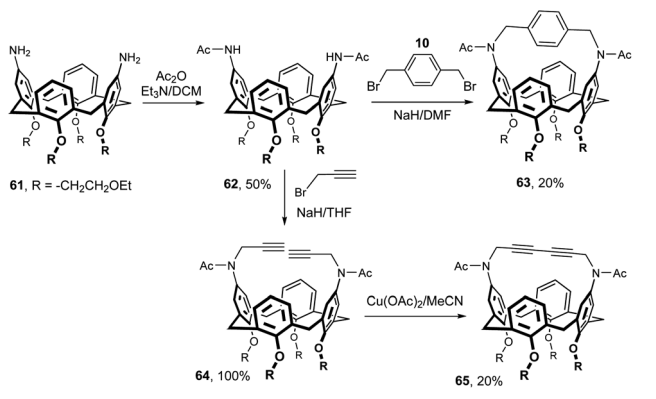

Fig. 20 Upper rim-bridged calix[4]arenes *via* alkylation of amidic functions.

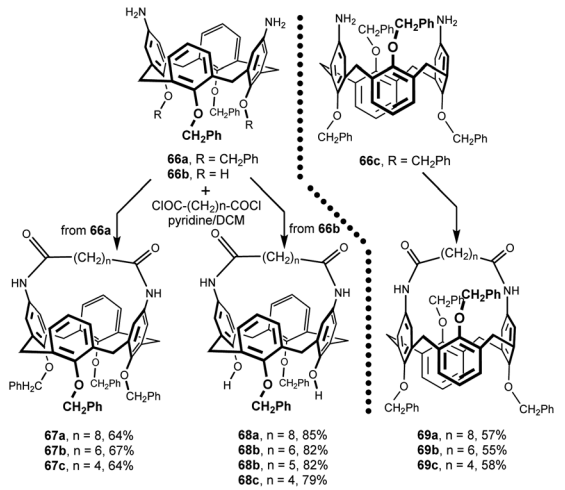

Fig. 21 Upper rim calix[4]arene *via* alkylation of amidic functions.

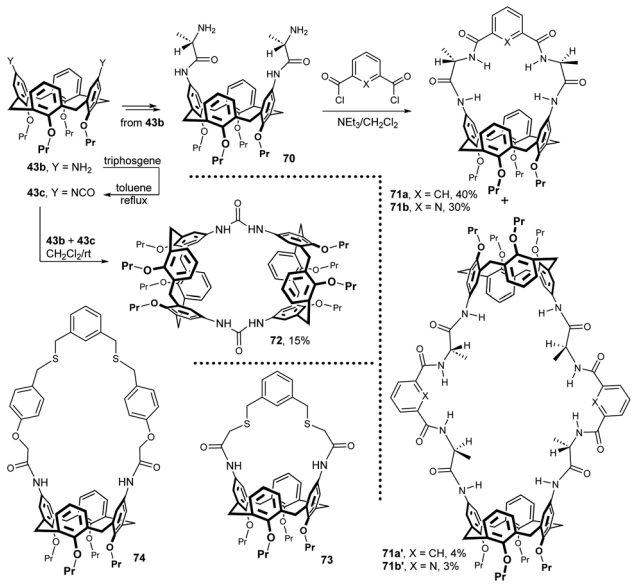

Fig. 22 Upper rim-bridged calix[4]arenes *via* amidic functions.

Calixarene **43b** was also transformed into the corresponding isocyanate **43c** by reaction with triphosgene ($CCl_3OC(O)OCCl_3$) in toluene under reflux. The reaction between difunctional compounds **43b** and **43c**, carried out under high dilution conditions, afforded the bridged bis-calixarene **72** in 15% yield.[36] Again, titration experiments showed the ability to complex selected anions (benzoate) in solution. The preparation of bis-amide analogue of **72** (not shown, 10% yield) by reacting the corresponding diacid dichloride with diamine **43b** was also reported.

A similar general approach (bridging of amidic intermediates) was used in the synthesis of ligands **73** and **74** (Fig. 22). However, in this case, the last step was the dialkylation of the corresponding chloromethyl derivatives using *α*,*α*′-*meta*-xylene dithiol.[37]

The synthesis of macrocyclic peptido-calixarene derivatives was carried out by the application of the azide or mixed anhydride coupling methods (Fig. 23). Thus, the reaction of bis-aminomethyl calix[4]arene **75** with free diacid derivative in the presence of ethyl chloroformate (mixed anhydride method) afforded the corresponding chiral calix[4]arene **77** bearing L-tyrosine moieties in 65% yield.[38] The same product was also obtained with diacyl diazide in 45% yield. Analogous procedures were used for the synthesis of the structurally related compound **78** starting from diaminocalixarene **61**. A series of similar compounds containing valine or leucine residue was also reported.[33] While the aminomethyl derivative **75** was easily bridged with 2,6-pyridinedicarboxylic acid to give compound **76**, calixarene **61** bearing amino groups directly on the upper rim does not react in this way because the distance and geometry do not match the amide bonds in the intended product **79**.[38]

Carcerand **85** based on a combination of calix[4]arene and resorcin[4]arene structural motifs was prepared by a very complex multi-step approach (Fig. 24). The key step was the reaction of the two building blocks **80** and **81** leading to diamide **82** in 40% yield.[39] Subsequent deprotection of the phthalimide groups (Phth) with methylhydrazine provided the diamino derivative **83**, which was acylated with chloroacetyl chloride to give intermediate **84** in essentially quantitative yield. The final carcerand **85** was formed quantitatively by the intramolecular alkylation of **84** induced by Cs_2CO_3/KI in DMF at 80 °C.

The ^{1}H NMR spectrum confirmed that molecule of DMF is incarcerated within the inner space of the carcerand (dramatic upfield shifts of DMF signals by up to 3.5 ppm), thus forming so called carceplex **85** DMF. The following study of formation of similar carceplexes[40] with different guest molecules[41] led eventually to the discovery that, due to the non-symmetrical cavity, two different orientations of the guest molecule with respect to the host are possible (Fig. 24). For this new type of isomerism the name carceroisomerism was proposed.[42] A slightly modified synthetic strategy also led to the synthesis of hemicarcerands represented by formula **86**.[43] Using a synthetic strategy similar to that employed for the preparation of compound **85**, a 2 + 1 system **87** (ref. 44) or even a huge 2 + 2 macrocycle[45] (not shown) were obtained.

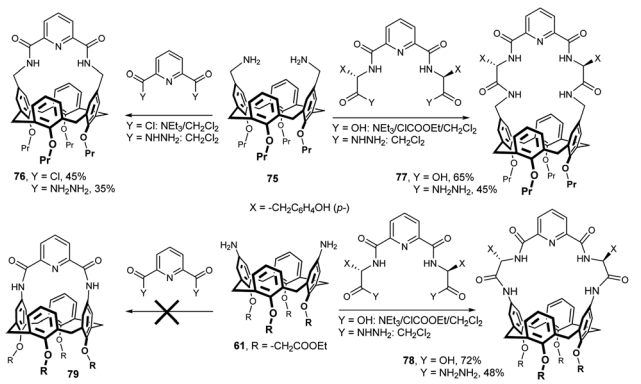

Fig. 23 Synthesis of peptidocalix[4]arenes.

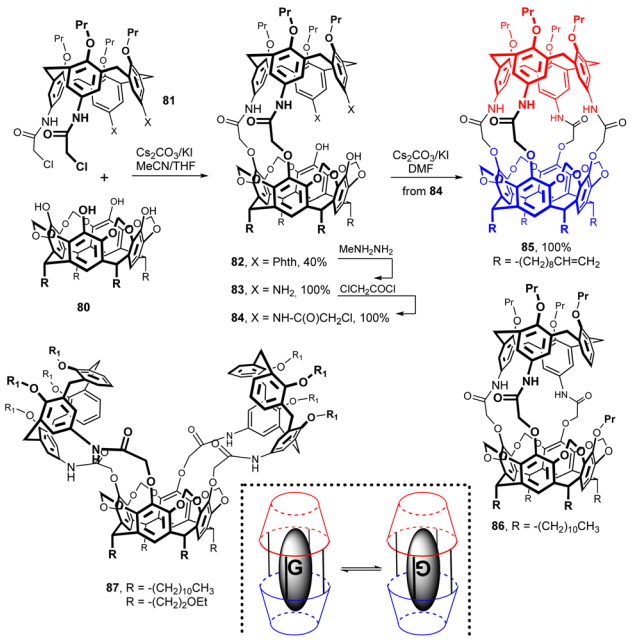

Fig. 24 Synthesis of carcerands and hemicarcerands, the example of carceroisomerism.

Calix[4]arenes containing ferrocene moiety bonded *via* amidic function across the upper rim have been synthesized. As shown in Fig. 25, coupling of diamino derivatives **88a**, **88b** and **61** with freshly synthesized 1,1-bis(chlorocarbonyl)ferrocene in the presence of NEt_3 gave the corresponding products **89a–c** in good yields (42–50%).[46] ^{1}H NMR anion-binding studies in $CDCl_3$ showed some selectivity of **89b** for the chloride anion (over Br^- and I^-) and the ability to bind carboxylates for all three mentioned receptors. Moreover, the presence of ferrocene unit enabled the application of cyclic voltammetry and square wave voltammetry for anion recognition.[47]

5,15-Bis(7-carboxyl-1-naphthyl)-10,20-diphenylporphyrin **91** possessing the *syn* arrangement of two naphthalene moieties was used for bridging diaminocalix[5]arene **90** (Fig. 25). The resulting rigidified receptor **92** was transformed into Zn-porphyrin derivative and studied for binding ability towards various pyridine derivatives.[48] A similar motif, *i.e.* porphyrin bridged with diaminocalix[4]arene **43b**, was studied as a receptor for various nitrogenous ligands. The confined rigid cavity showed high selectivity towards imidazole (*versus* pyridine).[49]

The coupling reaction of **94** with calix[5]arene derivative **93** furnished a chiral receptor **95** in 32% yield.[50] The ^{1}H NMR titration study confirmed some enantioselective recognition of chiral ammonium guest molecules. Regarding chiral bridged calixarene systems, the reaction of permethylated $6^A,6^D$-diamino-β-cyclodextrin with calix[4]arene derivatives immobilised in the *1,3-alternate* conformation was reported (not shown).[51] The application of succinylamido spacer enabled the preparation of 1 : 1 or 1 : 2 (calixarene : cyclodextrin) upper rim-bridged conjugates.

An interesting synthetic route to bis-calixarene is shown in Fig. 26 and relies on multiple cycloadditions between bifunctional dipoles and bifunctional dipolarophiles. The starting diamine **43b** was acylated with acryloyl chloride or methyl propiolate to give the corresponding amides **96** and **97**, both in 79% yield. The quadruple cycloaddition with bifunctional hydroxamic acid chloride then provided bis-calix[4]arenes **98** (27%) or **99** (26%).[52] The conformational studies of these

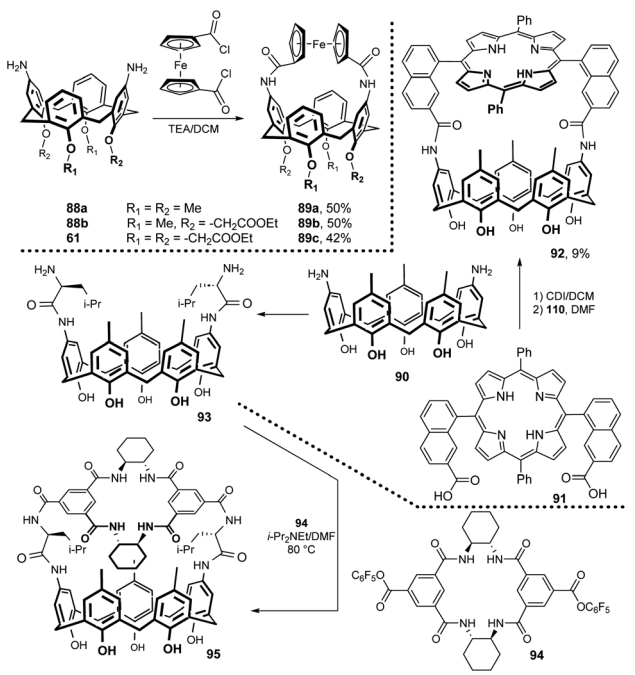

Fig. 25 Intramolecularly bridged calix[4]- and calix[5]arenes.

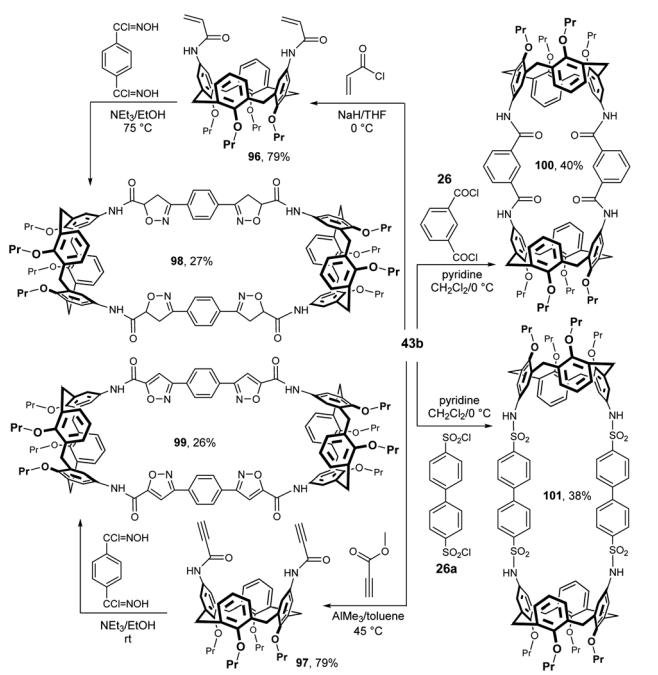

Fig. 26 Synthesis of peptidocalix[4]arenes.

compounds were carried out by solution NMR experiments and X-ray crystallography.[53]

When isophthaloyl dichloride **26** was treated with diaminocalix[4]arene **43b** in DCM in the presence of pyridine, biscalix[4]arene **100** was obtained in 40% yield.[29b] A similar reaction of biphenyl-4,4′-disulfonyl chloride **26a** provided biscalixarene **101** (38%), which also demonstrates the overall utility of the starting diamine **43b** in the synthesis of this type of compounds.

A calix[6]arene-based ligand possessing a tren unit capping the upper rim was prepared from triamino derivative **102** (Fig. 27). The macrocyclization with nitrilotriacetic acid in the presence of PyBOP and NEt_3 led to tris-amide **103** in 45% yield. The reduction of amide bonds with $BH_3 \cdot THF$ finally gave the ligand **104** in good yield (75%).[54] The corresponding Zn^{2+} complex **105** was studied both in solution and in the solid state. A similar synthetic strategy also led to the corresponding Mo analogues of **105** or to Mo complex **106**, where the three MeO moieties are replaced with hydrogens. These complexes possessing trigonally symmetric, sterically protected, and rigid substrate-binding pocket were studied for their ability to reduce the molecular nitrogen N_2.[55]

Cyclization *via* amidic function (from calixarene carboxylic acids)

While aminocalixarenes are readily available *via* nitration and subsequent reduction of intermediate nitro compounds, the corresponding calixarene-carboxylic acids are much less frequent. Several examples of amide bond formation are given in Fig. 28. The starting dicarboxylic acid **107a** was activated *via* pentafluorophenol (PFP) ester (85% yield) and treated with the corresponding amine moiety (2-(4-(2-azidoethoxy)phenoxy)-ethanamine) in the presence of TEA. The intermediate bisazide (isolated in 50% yield) was then reduced to diamine **108** in overall 42% yield. Reaction with pyridine-3,5-dicarbonyl chloride under high dilution conditions gave the macrocycle **109** in 50% yield. The N methylation of pyridine moiety provided macrocycle which was able to form pseudorotaxane with isophthalimide-derived thread and finally led to rotaxane (not shown).[56]

Diacid **107a** was converted to chloride using $SOCl_2$ and then coupled with anthracene based diamine to give the fluorescent anion receptor **110** in 30% yield (Fig. 28). The fluorescence spectroscopy showed that this compound can selectively

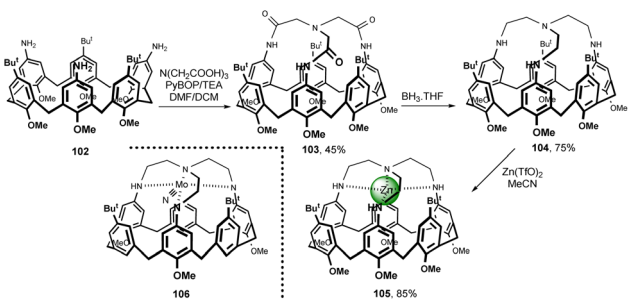

Fig. 27 Calix[6]arene derivatives bridged *via* tren moiety.

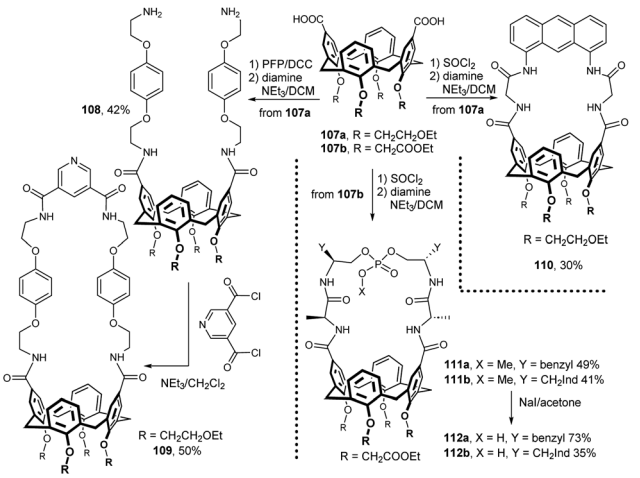

Fig. 28 Amidic bridges starting from calix[4]arene carboxylic acids.

recognise AcO^- anion over other anions examined (F^-, Cl^-, Br^-, $H_2PO_4^-$ and HSO_4^-).[57]

Diacid **107b** (available by oxidation of the corresponding aldehyde) was transformed into diacyl dichloride ($SOCl_2$) and reacted with pseudopeptides possessing two terminal NH_2 functions (Fig. 28). The cyclization reaction carried out under high dilution conditions provided the L-Phe and L-Thr derivatives **111a** and **111b** in 50 and 42% yield. Selective hydrolysis of the phosphoric methyl ester gave macrocycles **112a** and **112b**. These compounds were studied as carbohydrate receptors with good selectivity for β-glucosides.[58]

A rare example of a bridged calix[6]arene derivative is shown in Fig. 29. The starting tricarboxylic acid **113**, prepared by a multistep procedure, was treated with $SOCl_2$ under reflux and reacted with 2-aminopyridine in the presence of DMAP to afford **114** in 50% yield.[59] Highly selective recognition of this receptor towards fluoride ion was demonstrated by fluorescent and ^1H NMR titration experiments. A calix[6]crown-derived hydroxamic acid **115** (no synthetic details reported) was studied for the liquid–liquid extraction and sequential separation of some selected metal cations Cr(III), Mo(VI) and W(VI).[60]

Template synthesis of bridged calixarenes using tetraurea dimers

Tetraurea derivatives of calix[4]arenes in the *cone* conformation are known to spontaneously form dimeric capsules in nonpolar solvents. These supramolecular self-assemblies are held together by a cyclic array of hydrogen bonds (Fig. 30). It was

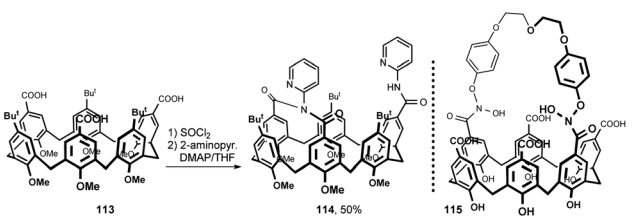

Fig. 29 Calix[6]arene derivatives bridged *via* amidic bonds.

shown that the tetratosylurea **116** cannot form homodimers, but instead exclusively forms heterodimers[61] with the corresponding tetraarylurea calix[4]arene **117**. This heterodimer, where **116** plays the role of template, can be used for preorganisation of alkenyl moieties of **117** in such a specific way, that the metathesis reaction between its double bonds proceeds in very high yields.[62] Application of this procedure to a mixture of **116** + **117a** and **117b** (benzene, Grubbs catalyst) followed by the hydrogenation of alkene intermediate (H_2/PtO_2) gave macrocyclic compounds **118a** and **118b** in high yield (>90% according to the ^{1}H NMR). The analogous reaction without the presence of template **116** was unsuccessful which indicates the essential role of the template for the correct preorganization of the respective functional groups.

This approach proved so effective that it was used to synthesize a number of calixarene derivatives with unusual topologies. Thus, the heterodimerisation of tetraarylurea calix[4]arenes **119** with tetratosylurea **116** followed by metathesis and hydrogenation were used to provide products **120** bearing huge macrocycles on the upper rim (Fig. 31). Incredibly, the respective multimacrocyclic calix[4]arene derivatives **120** were the only identifiable products (yields of 60–95% after purification).[63]

This behaviour of tetratosylurea **116** has been shown to be general and it always forms only heterodimeric structures with other ureas. Based on this general strategy, a number of previously unknown topologies were prepared, such as [8]catenanes,[64] multicyclic bis[2]catenanes,[65] fourfold [2]rotaxanes,[66] combination of structural elements of rotaxanes and catenanes,[67] bis- and trisloop tetraurea calix[4]arenes,[68] self-assembled dendrimers,[69] multiple catenanes based on tetraloop calix[4]arenes,[70] or molecular capsules consisting of calix[4]arene and calix[4]pyrrole moieties.[71]

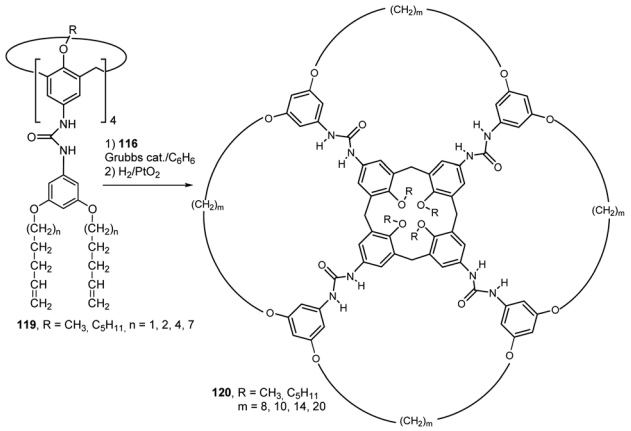

Fig. 31 Synthesis of calixarene-based huge macrocycles.

Direct bridging of the upper rim

As a part of ongoing effort to develop novel derivatisation procedures of basic calixarene skeleton, we reported the first example calix[4]arenes with intramolecularly bridged *meta* positions at the upper rim.[72]

The starting iodocompound **121** was transformed into sulfide **122** (55%) employing the reaction with 2-pyridine disulfide and a CuI/Mg/2,2-bipyridine/DMF system (Fig. 32). Subsequent oxidation to sulfoxide **123** was smoothly accomplished by *meta*-chloroperoxybenzoic acid in chloroform (87% yield). The presence of the 2-pyridyl moiety then enabled Pd-catalyzed double C–H activation offering an access to unprecedented derivatives with intramolecular single bond bridge between the *meta* positions of the two neighbouring aromatic subunits. Thus, the reaction of **123** in the presence of $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 + benzoquinone (oxidants) in a DCE–benzene mixture provided a mixture of two products. As the introduction of a single bond leads to inherently chiral system, the combination with a stereogenic centre on sulfur atom results in the mixture of diastereomers **124a** and **124b** which were isolated in 43 and 29% yield, respectively.[72] Interestingly, the replacement of the pyridine group with phenyl or pyrimidin-2-yl moieties did not give any bridged product. Only in the case of the ethyl sulfoxide derivative the bridged compound was obtained in 13% yield (not shown).[73]

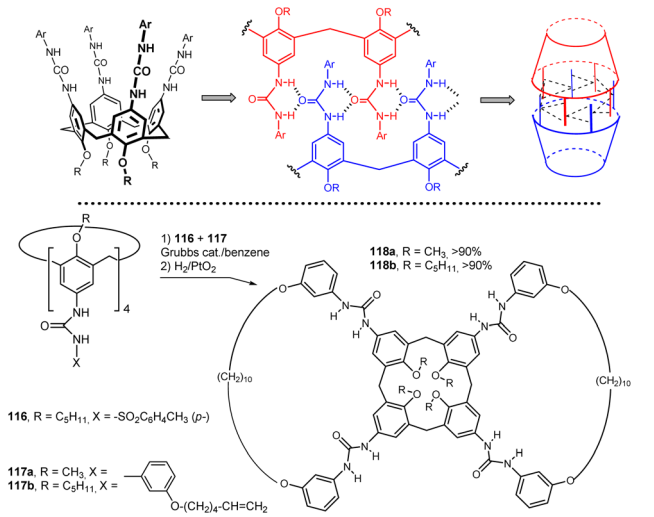

Fig. 30 Macrocyclization *via* metathesis of tetraurea dimers.

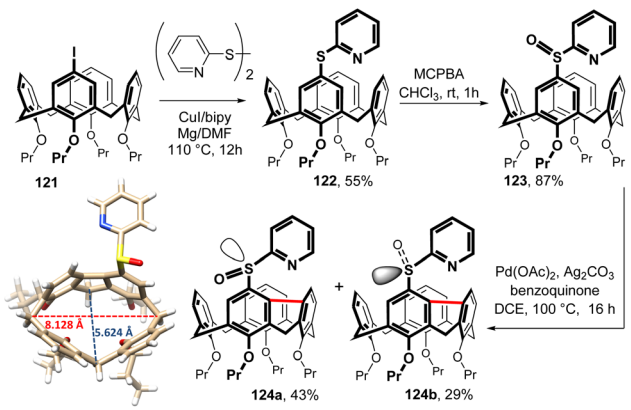

Fig. 32 Direct bridging of calix[4]arenes *via* a single bond bridge, X-ray structure of **124a**.

As shown in Fig. 32, the cavity of **124a** is substantially distorted from the symmetrical square arrangement typical for calix[4]arene derivatives. While the distance between two opposing CH_2 bridges is typically around 7.15 Å, the lengths of the corresponding diagonals in **124a** are dramatically different, 5.6 Å and 8.1 Å.[72]

Very recently, a synthesis of inherently chiral calixarenes by a catalytic enantioselective cross dehydrogenative coupling was reported.[74] The Friedel–Crafts reaction of alkylated calix[4]arenes with (substituted) 2-bromobenzoyl chlorides afforded starting compounds **125** (Fig. 33). The application of Pd chemistry did not lead to the expected product **126**, but the upper rim-bridged calix[4]arene was obtained instead. The enantioselective desymmetrization reaction of **125** was initially investigated by varying the Pd-sources, the ligands, the solvents, and the temperature to find the optimised reaction conditions. As shown in Fig. 32, under optimized conditions [$PdBr_2$ (10 mol%), ligand L (20 mol%), Rb_2CO_3 (3.0 equiv.), THF/110 °C in a sealed tube] compounds **125** were successfully transformed into series of compounds **127** bearing different substituents on benzoyl moiety with *ee* values of up to 93%. The exclusive formation of **127** instead of **126** indicates that the 1,5-palladium migration (from intermediate **A** to intermediate **B**) takes place during the reaction (Fig. 33), eventually leading to the transannular arylation of B.[74] Compounds **127** represent new family of inherently chiral calixarenes possessing unique chiroptical properties due to their highly rigid structure, induced by the 9*H*-fluorene segment, and they were found to be useful scaffolds for the fabrication of CPL materials.

Bridging *via* organomercurial derivatives

Due to their structure, calixarenes are subject to a number of electrophilic substitutions on the upper rim. The electronic effects of the lower rim alkoxy groups (or free OH groups) result in regioselective substitution into the *para* position of aromatic subunits, including the *ipso*-substitution of *tert*-butyl groups.[1]

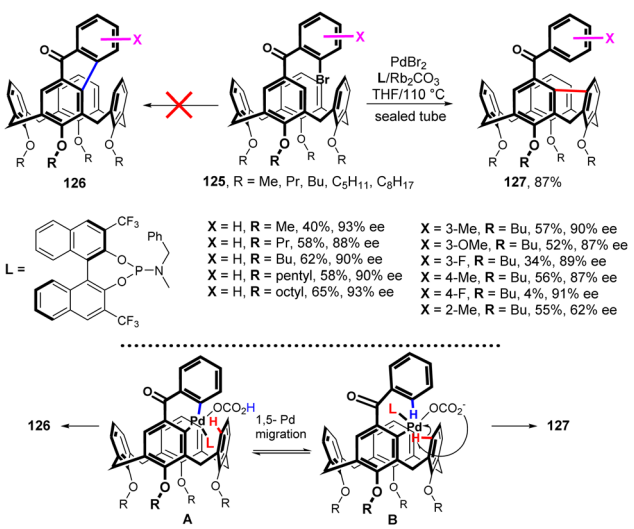

Fig. 33 Direct bridging of calixarenes, 1,5-palladium migration in Pd complex.

However, about a decade ago, a reaction leading to selective substitution of the *meta* position (relative to the OR group) of the aromatic skeleton of calix[4]arene was discovered – the mercuration of calix[4]arenes. In this way, the *meta* position of calixarenes, which was practically unavailable at that time, was made available and a number of previously unfeasible derivatizations and substitution patterns were made possible.

As shown in Fig. 34, reaction of the starting di-*tert*-butyl derivative **128a** with 1 equiv. of Hg(II) trifluoroacetate ($Hg(TFA)_2$) afforded the unexpected *meta*-substituted isomer **129a**, which was isolated in 44% yields (after conversion to chloromercurio derivative) as the only substitution product.[75] The same reaction with two equiv. of $Hg(TFA)_2$ provided *meta*,*meta*-disubstituted product **130a** in 45% yield. Analogously, the reaction of a simple tetrapropoxy derivative **128b** gave under similar condition even higher yield of monochloromercurio derivative **129b** (70%) without any *para*-substituted isomer. The disubstitution of compound **128b** resulted in the isolation of two main products, *meta*,*meta*-isomer **130b** and *meta*,*para*-isomer **131b**, both in 20% yields.[76]

The corresponding quantum-chemical calculations revealed that the *meta*-substitution product **129b** is favored over the *para* analogue by more than 3.5 kcal mol^{-1}. This indicates that the regioselectivity is thermodynamically driven. Moreover, the X-ray analysis confirmed[75,77] the stabilization of the *meta* product by neighbour aromatic subunit *via* intramolecular Hg···π interactions – see Fig. 34 for the X-ray structure of **130a** (TFA form). It is clear that the corresponding *para*-analogue could not provide similar stabilization effect.

The unexpected regioselectivity of mercuration laid the foundation for an entirely new type of substitution in calixarene chemistry. Thus, the *meta*-chloromercurio derivative **129b** was subjected to an intramolecular cross-coupling under Pd catalysis. The best reaction conditions [$Pd(OAc)_2/AsPh_3/Cs_2CO_3$ in DCM] provided a bridged product **132b** in 64% yield (Fig. 35). In order to ascertain the general applicability of this synthetic approach, the conformationally mobile derivatives **128c** and **128d** were also reacted in the same way. Both compounds were successfully converted to bridged systems **132c** and **132d** *via* the HgCl intermediates **129c** and **129d**.[78] The VT ^1H NMR study revealed that methoxy derivative **132d** exists as a dynamic mixture of two conformations at rt (*cone* – *1,2-alternate*). A similar equilibrium

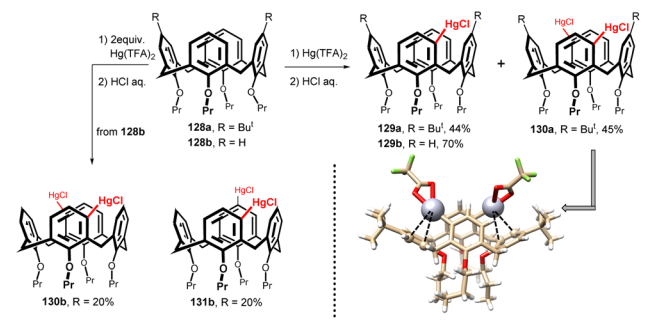

Fig. 34 Mercuration of tetrapropoxycalix[4]arenes (*cone*), X-ray structure of compound **150a** (HgTFA form).

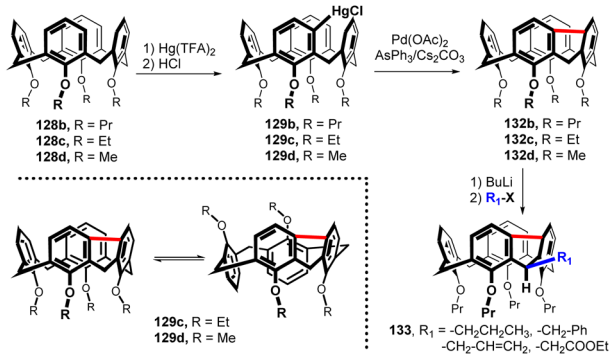

Fig. 35 Synthesis of single bond-bridged calix[4]arenes.

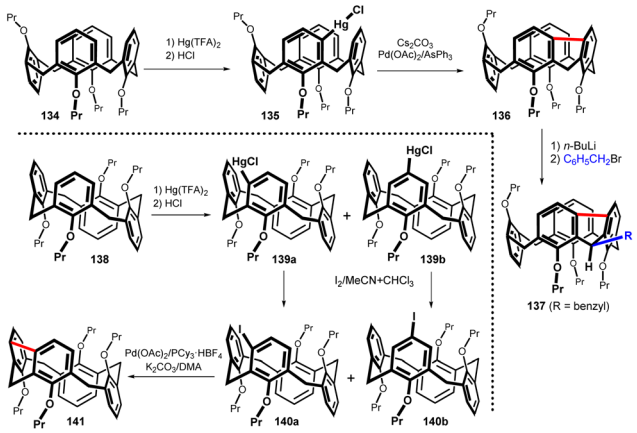

Fig. 36 Regioselective mercuration of the partial *cone* **134** and *1,2-alternate* **138** including the subsequent bridging reactions.

was observed for Et derivative **132c** at 130 °C. On the other hand, the increased rigidity of the system enabled the separation of the two conformers at room temperature.

The presence of fluorene moiety within the bridged molecule **132b** enables the regioselective alkylation of calix[4]arenes furnishing compounds **133** in good yield (Fig. 35). As the CH_2 group of fluorene moiety is known for its enhanced acidity, deprotonation of **132b** occurs exclusively at this position. Moreover, based on the X-ray analysis, the alkylation takes place stereoselectively at the equatorial position of the CH_2 bridging unit. The same reaction with **128b** as a model compound does not proceed at all.[79]

These single bond-bridged compounds possess rigidified and highly distorted cavities. Due to the high internal strain, these systems are susceptible to reactions otherwise unknown in calixarene chemistry. Recently, the cleavage of such systems with various electrofiles leading to linear oligophenols was described.[80]

To determine the extent of possible application of *meta*-substitution in calix[4]arenes, the mercuration of all remaining conformers was performed. Thus, the reaction of the *partial cone* conformer **134** using one equivalent of $Hg(TFA)_2$ in $CHCl_3$ at room temperature afforded regioisomer **135** (of seven theoretically possible) as the main product (Fig. 36). Heating the toluene solution overnight at 110 °C in the presence of $Pd(OAc)_2/AsPh_3$ as the catalyst and Cs_2CO_3 as the base provided the *meta*-bridged compound **136** in 88% yield.[81] This compound was also regio- and stereo-selectively alkylated as evidenced by the formation of compound **137** (70%).

The mercuration of the *1,2-alternate* conformer **138** using a standard procedure provided an inseparable mixture of regioisomers **139a** and **139b** (40 : 60) together with 26% of unreacted starting compound (Fig. 36). Conversion of this mixture to iodo derivatives by reaction with I_2 unfortunately led to another inseparable mixture of products **140a** and **140b**. Despite the isolation problems, the final Pd-catalysed cyclization followed by preparative TLC on silica gel afforded the bridged product **141** in 13% overall yield (over three steps from **138**).[82]

The bis-chloromercurio derivative **130b** (*meta*,*meta*) or the corresponding diiodo compound **143**, easily available by the reaction with I_2 (Fig. 37), represent a perfect starting point for the synthesis of double bridged system. Unfortunately, despite our great efforts, compound **142** was never prepared, probably due to the extreme internal strain introduced into the cavity by two short bridges.

On the other hand, diiodo intermediate **143** was smoothly transformed into the corresponding carboxylic acid **144** *via* the lithiation with BuLi and the treatment with CO_2 (Fig. 37). The doubly carbonyl-bridged derivative **145** was obtained in 32% yield (from **143**) by the intramolecular Friedel–Crafts acylation, demonstrating the possibility of double bridging of the cavity using single-atom bridges. The ketone groups react by nucleophilic addition reaction with PhLi or with $LiAlH_4$ to give the corresponding alcohols **146a** and **146b** in good yields. It is

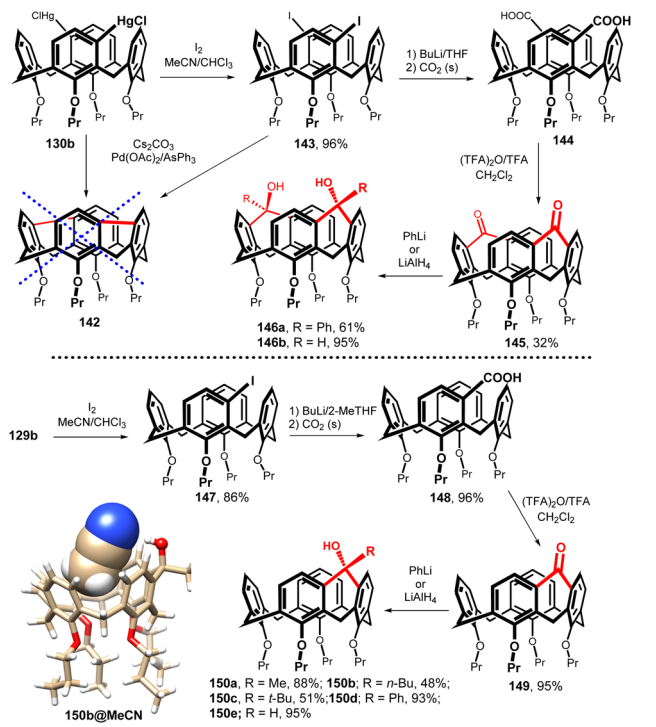

Fig. 37 Synthesis of upper rim single atom-bridged calix[4]arenes.

interesting that in both cases the reaction proceeds stereospecifically with access of the nucleophile from the outside of the cavity.[83]

Diketone derivative **145** with two monoatomic bridges possessing sp^2 hybridization represents an extremely distorted calixarene cavity, as can be demonstrated by the exceptionally short/long main diagonals (distance between the opposite CH_2 bridges) which are 5.43 and 8.27 Å (Fig. 38a). A highly preorganised cavity of **145** was found to form a complex with CH_2Cl_2 molecule (Fig. 38b) held by hydrogen bonding interactions between the phenolic oxygens and the C–H bonds of DCM (C–H···O distance of 2.66 Å). At the same time, the Cl atoms (of DCM) interact with carbonyl oxygens from the neighbouring **145** *via* halogen bonding interactions (Cl···O = 3.183 Å).[83]

The same type of chemistry was carried out starting with monochloromercurio derivative **129b** which was reacted with I_2 to provide the iodo calix[4]arene **147** (86%) and transformed into the corresponding carboxylic acid **148** (96%) *via* the lithiation with BuLi and the reaction with CO_2 (Fig. 37). The final ketone-bridged macrocycle **149** was obtained in high yield (95%) by intramolecular Friedel–Crafts acylation, and subjected to nucleophilic addition (RLi or $LiAlH_4$) to provide the corresponding alcohols **150a–e** in good yields.[84] Rigidified skeleton together with a hydroxyl group pointing into the cavity make these compounds suitable for the interaction with neutral guest molecules (MeOH, MeCN, $MeNO_2$). An example of such a complex is shown in Fig. 37, where MeCN is captured by the CH–π interactions of the methyl group with the aromatic cavity and simultaneously by the HB interaction of the OH group with the nitrile nitrogen (O–H···N distance 2.257 Å).

A similar strategy for the synthesis of single-atom bridges is based on the use of Friedel–Crafts intramolecular alkylation (Fig. 39). The initial iodo derivatives **143** and **147** were lithiated (BuLi/THF, −78 °C) and allowed to react with ketones or aldehydes to give alcohols **151** and **154a–f** in good yields.[85] Final cyclization using Amberlyst® 15 then provided the respective bridged macrocycles **155b–f**.[86] The utility of this approach for double bridged calix[4]arenes was demonstrated by the preparation of derivative **152**, which was smoothly obtained in 63% yield. The methylene-bridged derivative **155a** was prepared from the corresponding carboxylic acid **148** by reduction with borane (to furnish **153** in 83% yield) and subsequent cyclization with Nafion® which, in this particular case, gave higher yield (72%). All the bridged calixarenes **152** and **155a–f** described above

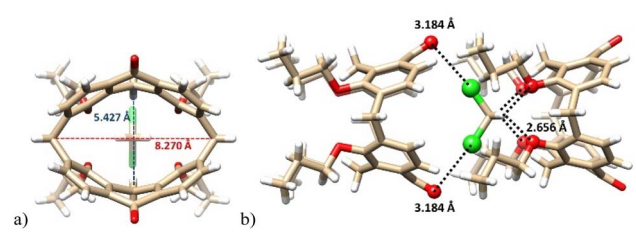

Fig. 38 The X-ray structure of **145** DCM complex (a): highly distorted cavity of **145**, (b) supramolecular interactions of DCM within the complex.

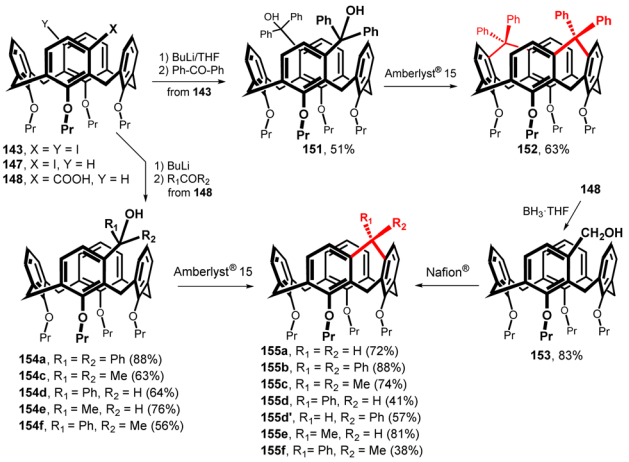

Fig. 39 Upper rim-bridged calix[4]arenes by intramolecular Friedel–Crafts alkylation.

represent highly rigid cavities capable of complexing quaternary ammonium cations or neutral substances by cation–π or CH–π interactions.

When the chloromercurio derivatives **129d** and **130b** were reacted with nitrosyl chloride, generated *in situ* from isopentyl nitrite and HCl at low temperature (0 °C), the corresponding nitroso calixarenes **156** and **160** were obtained in good yields.[87] These key intermediates were then reduced to *meta*-amino derivatives **157** (89%) and **161** (85%) using RANEY® nickel and hydrazine hydrate (Fig. 40). The acylation with various carboxylic acid derivatives (chloride, anhydride, bromide) provided the corresponding monoamides **158a–e** and diamides **162a–d**. The intramolecular Bischler–Napieralski cyclization of monoamides **158** (reflux with $POCl_3$ in toluene) led to a novel type of bridged calixarene containing a seven membered ring (diatomic bridge). The racemic product **159a** was then successfully separated into pure enantiomers on a chiral column (Chiral Art Amylose-SA). The ^1H NMR titration experiments indicated that the cavity of **159a** was preorganised for the complexation of selected guest molecules (*N*-methylpyridinium salts) including some enantioselectivity towards *N*-methylnicotinium iodide.[88] The use of mild reaction conditions for Bischler–Napieralski cyclization of diamides **162a–d** (Tf_2O/2-chloropyridine in CH_2Cl_2 at −78 °C) afforded the double-bridged product **163a–d**. However, it turned out that this type of double bridging does not lead to very stable compounds and their decomposition occurs relatively quickly. A similar strategy starting from the *meta*, *para* isomer **131b** led to the bridged systems **164** (Fig. 40).[89]

A new strategy to bridge the upper rim of calix[4]arene was recently published.[90] The starting ketone **149** (one-atom bridge) was subjected to Baeyer–Villiger reaction (Fig. 41) with *meta*-chloroperoxybenzoic acid in toluene to form a cyclic lactone **165** (58%) (two-atom bridge). Thus, expansion of the bridge led to an inherently chiral product (in the form of a racemate). The attempts to carry out the reaction enantioselectively using enzymes have failed, unfortunately. Conversion of the ketone **149** to the corresponding oxime **166** (74%) and subsequent

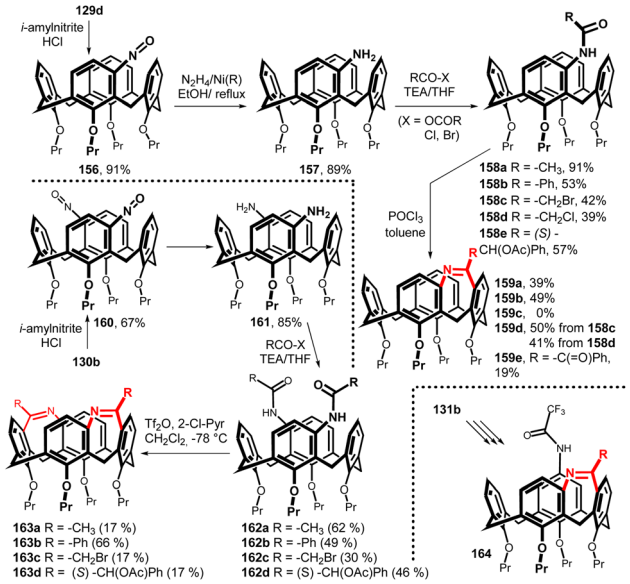

Fig. 40 The intramolecular Bischler–Napieralski cyclization of calix[4]arenes.

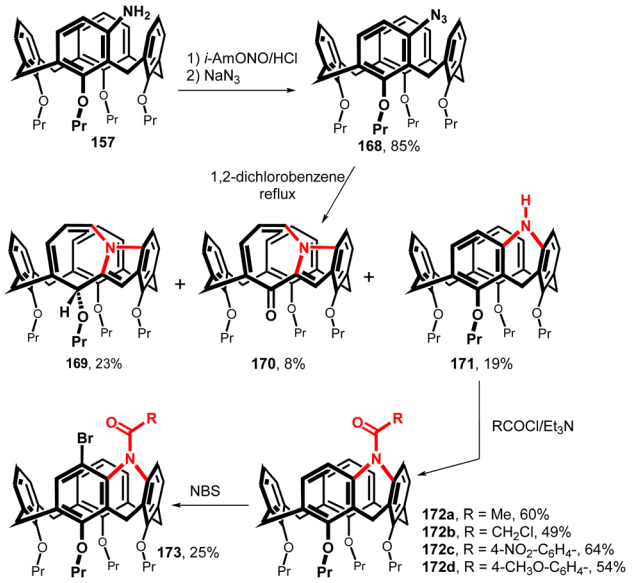

Fig. 42 Synthesis of amine-bridged calix[4]arene derivatives.

Beckmann rearrangement led analogously to lactam **167** (59%). ^{1}H NMR titration experiments with quaternary ammonium salts revealed some unusual complexation stoichiometries depending on the chirality of **167** (racemic mixture *versus* pure enantiomers).

The amine bridged calix[4]arene was synthesised starting from *meta*-amino derivative **157** (Fig. 42). The reaction with isoamyl nitrite in HCl/THF at 0 °C generated a diazonium salt which was immediately reacted with NaN_3 to provide an azide **168** in 85% yield. The thermal decomposition (1,2-dichlorobenzene/reflux) furnished a rather complex reaction mixture from which the three main products **169–171** were isolated. In addition to the expected amine **171** (19%), structures **169** and **170** with a seven-membered ring resulting from the rearrangement of the primary forming nitrene were also obtained.[91] The amine-bridged calix[4]arene **171** was acylated under standard conditions (RCOCl/TEA) to afford the corresponding amides **172a–d.** As shown by ^{1}H NMR spectroscopy, the restricted rotation around the amidic C–N bond led finally to the desymmetrization of the whole molecule (atropisomerism) at low temperatures (slow exchange conditions). The introduction of bromine atom into the *para*-position of the neighbour ring (compound **173**) led to inherently chiral system with hindered rotation at rt.[92]

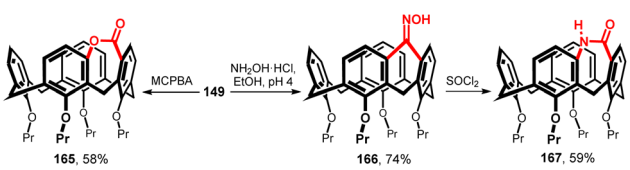

Fig. 41 Transformation of ketone-bridged calix[4]arenes.

Conclusions and outlook

In this review, I have attempted to show the basic strategies leading to the bridging of the upper rim of calix[*n*]arenes. Although a substantial part of the structures comes from the chemistry of calix[4]arenes, where the exceptionally well-developed chemistry of these compounds can be applied, there are also examples showing the successful bridging of larger calixarenes. Using relatively diverse synthetic approaches, many structurally and functionally interesting systems with a rigidified cavity capable of various supramolecular applications (depending on the specific chemistry used) can be prepared.

Much attention has been paid to the synthesis of systems with bridged *meta* positions of adjacent aromatic subunits. Although organomercury compounds are not among the most popular chemicals, their use in calixarene chemistry is proving to have a completely irreplaceable role, as it allows direct access to derivatives that are otherwise essentially unattainable. The bridged derivatives formed in this way show extremely rigid and often inherently chiral structures with many possible applications, *e.g.* in the field of chiral recognition. In addition, the presence of the fluorene moiety within the calixarene skeleton gives us the possibility to apply some procedures known from the chemistry of this compound (*e.g.* regioselective deprotonation of the methylene bridge followed by stereoselective alkylation).

As shown by some recent examples, a similar way of bridging calixarene systems (*meta* bridging) can be achieved by direct C–H activation (intramolecular coupling) using transition metal chemistry. It can be assumed that the further development of this strategy may lead to new macrocyclic systems with a hitherto unknown topology. Especially in the case of larger calixarenes, where system rigidification cannot be achieved by simple alkylation of the lower rim, new methods of bridging the upper

rim could provide conformationally immobilized systems, thereby enabling greater use of these macrocycles in supramolecular chemistry.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, U. K., 1998; (*b*) C. D. Gutsche, *Calixarenes: an Introduction*, RSC Publishing, Cambridge, U. K., 2nd edn, 2008.

2 (*a*) L. Mandolini and R. Ungaro, *Calixarenes in Action*, Imperial College Press, London, 2000; (*b*) V. M. Mirsky and A. Yatsimirsky, *Artificial Receptors for Chemical Sensors*, Wiley, Weinheim, 2010; (*c*) P. Neri, J. L. Sessler and M. X. Wang, *Calixarenes and beyond*, Springer, Cham, Switzerland, 2016.

3 V. Böhmer, H. Goldmann and W. Vogt, The first example of a new class of bridged calixarene, *J. Chem. Soc., Chem. Commun.*, 1985, 667–668.

4 V. Böhmer, H. Goldmann, R. Kaptein and L. Zetta, Photo-CIDNP studies on calixarenes and bridged calixarenes, *J. Chem. Soc., Chem. Commun.*, 1987, 1358–1360.

5 (*a*) V. Böhmer, H. Goldmann, W. Vogt, E. F. Paulus, F. L. Tobiason and M. J. Thielman, Bridged calix[4]arenes; x-ray crystal and molecular structures and spectroscopic studies, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1769–1775; (*b*) E. Paulus, V. Böhmer, H. Goldmann and W. Vogt, The crystal and molecular structure of two calix[4]arenes bridged at opposite para positions, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1609–1615.

6 H. Goldmann, W. Vogt, E. Paulus and V. Böhmer, A series of calix[4]arenes, having two opposite para positions connected by an aliphatic chain, *J. Am. Chem. Soc.*, 1988, **110**, 6811–6817.

7 V. Böhmer and W. Vogt, Calix[4]arenes, bridged at the upper rim, *Pure Appl. Chem.*, 1993, **65**, 403–408.

8 V. Böhmer, H. Goldmann, W. Vogt, J. Vicens and Z. Asfari, The synthesis of double-calixarenes, *Tetrahedron Lett.*, 1989, **30**, 1391–1394.

9 J. D. Van Loon, L. C. Groenen, S. S. Wijmenga, W. Verboom and D. N. Reinhoudt, Upper rim calixcrowns: elucidation of the mechanism of conformational interconversion of calix[4]arenes by quantitative 2-D EXSY NMR spectroscopy, *J. Am. Chem. Soc.*, 1991, **113**, 2378.

10 A. Arduini, A. Casnati, M. Fabbi, P. Minari, A. Pochini, A. R. Sicuri and R. Ungaro, New artificial receptors from selectively functionalized calix[4]arenes, *Supramol. Chem.*, 1993, **1**, 235–246.

11 A. Arduini, S. Fanni, G. Manfredi, A. Pochini, R. Ungaro, A. R. Sicuri and F. Ugozzoli, Direct regioselective formylation of tetraalkoxycalix [4] arenes fixed in the cone conformation and synthesis of new cavitands, *J. Org. Chem.*, 1995, **60**, 1448–1453.

12 A. Dondoni, A. Marra, M.-C. Scherrmann, A. Casnati, F. Sansone and R. Ungaro, Synthesis and properties of O-glycosyl calix[4]arenes (calixsugars), *Chem.–Eur. J.*, 1997, **3**, 1774–1782.

13 H. D. Banks, A. Dondoni, M. Kleban and A. Marra, Computational and experimental studies of Di- and tetrasubstituted calix[4]arenes, *Chirality*, 2002, **14**, 173–179.

14 A. Arduini, W. M. McGregor, A. Pochini, A. Secchi, F. Ugozzoli and R. Ungaro, New Upper Rim Pyridine-Bridged Calix[4]arenes: Synthesis and Complexation Properties toward Neutral Molecules and Ammonium Ions in Organic Media, *J. Org. Chem.*, 1996, **61**, 6881–6887.

15 A. Arduini, M. Cantoni, E. Graviani, A. Pochini, A. Secchi, A. R. Sicuri, R. Ungaro and M. Vincenti, Gas-phase complexation of neutral molecules by upper rim bridged calix[4]arenes, *Tetrahedron*, 1995, **51**, 599–606.

16 R. Cacciapaglia, S. Di Stefano and L. Mandolini, On the 'livingness' of a dynamic library of cyclophane formaldehyde acetals incorporating calix[4]arene subunits, *J. Phys. Org. Chem.*, 2008, **21**, 688–693.

17 T. Arimura, S. Matsumoto, O. Teshima, T. Nagasaki and S. Shinkai, Calixarene-based molecular capsule, *Tetrahedron Lett.*, 1991, **32**, 5111–5114.

18 M. H. Düker, R. Gómez, C. M. L. Vande Velde and V. A. Azov, Upper rim tetrathiafulvalene-bridged calix[4]arenes, *Tetrahedron Lett.*, 2011, **52**, 2881–2884.

19 M. H. Düker, F. Kutter, T. Dülcks and V. A. Azov, Calix[4] arenes with 1,2- and 1,3-upper rim tetrathiafulvalene bridges, *Supramol. Chem.*, 2014, **26**, 552–560.

20 M. T. Blanda and K. E. Griswold, Synthesis of a Symmetric Octathio Bis(calix[4]arene) Cage Molecule, *J. Org. Chem.*, 1994, **59**, 4313–4315.

21 T. Takeda and A. Tsubouchi, Synthesis of alkenes by McMurry coupling and related reductive dimerization reactions, *Sci. Synth.*, 2010, **47a**, 247–325.

22 A. Arduini, S. Fanni, A. Pochini, A. R. Sicuri and R. Ungaro, Highly distorted Cone calix[4]arenes through intramolecular mc murry coupling reaction, *Tetrahedron*, 1995, **51**, 7951–7958.

23 P. Lhotak and S. Shinkai, Structurally unusual calix[4]arene derivatives generated by intra- and intermolecular McMurry reactions, *Tetrahedron Lett.*, 1996, **37**, 645.

24 T. Haino, C. Fukunaga and Y. Fukazawa, A New Calix[5] arene-Based Container: Selective Extraction of Higher Fullerenes, *Org. Lett.*, 2006, **8**, 3545–3548.

25 J. Wang and C. D. Gutsche, Complexation of Fullerenes with Bis-calix[n]arenes Synthesized by Tandem Claisen Rearrangement1, *J. Am. Chem. Soc.*, 1998, **120**, 12226–12231.

26 M. Pitarch, V. McKee, M. Nieuwenhuyzen and M. A. McKervey, Synthesis of bridged, multifunctional calixarenes via ring closing metathesis, *J. Org. Chem.*, 1998, **63**, 946–951.

27 O. Struck, L. A. J. Chrisstoffels, R. J. W. Lugtenberg, W. Verboom, G. J. van Hummel, S. Harkema and D. N. Reinhoudt, Head-to-Head Linked Double Calix[4] arenes: Convenient Synthesis and Complexation Properties, *J. Org. Chem.*, 1997, **62**, 2487–2493.

28 H. Iwamoto, K. Niimi, T. Haino and Y. Fukazawa, Energetics of guest binding to calix[4]arene molecular containers, *Tetrahedron*, 2009, **65**, 7259–7267.

29 (*a*) G. T. Hwang and B. H. Kim, Bis-calix[4]arenes with imine linkages: synthesis and binding study of thiopheno bis-calix [4]arene with viologens, *Tetrahedron Lett.*, 2000, **41**, 5917–5921; (*b*) G. T. Hwang and B. H. Kim, Synthesis and binding studies of multiple calix[4]arenes, *Tetrahedron*, 2002, **58**, 9019–9028.

30 A. Arduini, R. Ferdani, A. Pochini and A. Secchi, Synthesis of Upper Rim Covalently Linked Double Calix[6]arenes, *Tetrahedron*, 2000, **56**, 8573–8577.

31 A. Yilmaz, S. Memon and M. Yilmaz, Synthesis and study of allosteric effects on extraction behavior of novel calixarene-based dichromate anion receptors, *Tetrahedron*, 2002, **58**, 7735–7740.

32 H. M. Chawla and T. Gupta, Novel bis-calix [4] arene based molecular probe for ferric iron through colorimetric, ratiometric, and fluorescence enhancement response, *Tetrahedron Lett.*, 2015, **56**, 793–796.

33 A. E.-G. E. Amr, A. M. Mohamed and A. A. Ibrahim, Synthesis of Some New Chiral Tricyclic and Macrocyclic Pyridine Derivatives as Antimicrobial Agents, *Z. Naturforsch., B*, 2003, **58**, 861–868.

34 S. K. Sharma and C. D. Gutsche, Upper Rim Substitution of Calix[4]arenes via Their Upper Rim A,C Dinitro Compounds1, *J. Org. Chem.*, 1999, **64**, 998–1003.

35 F. Sansone, L. Baldini, A. Casnati, M. Lazzarotto, F. Ugozzoli and R. Ungaro, Biomimetic macrocyclic receptors for carboxylate anion recognition based on *C*-linked peptidocalix[4]arenes, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4842–4847.

36 V. Šťastný, P. Lhoták, V. Michlová, I. Stibor and J. Sýkora, Novel biscalix[4]arene-based anion receptors, *Tetrahedron*, 2002, **58**, 7207–7211.

37 S. J. Loeb and B. R. Cameron, Calixarenes for Separations, *Am. Chem. Soc.*, 2000, **757**(ch. 21), 283–295.

38 A. E.-G. E.-S. Amr, M. Abo-Ghalia and M. M. Abdalah, Synthesis of Novel Macrocyclic Peptido-calix[4]arenes and Peptidopyridines as Precursors for Potential Molecular Metallacages, Chemosensors and Biologically Active Candidates, *Z. Naturforsch., B*, 2006, **61**, 1335–1345.

39 B.-H. Huisman, D. M. Rudkevich, A. Farrán, W. Verboom, F. C. J. M. van Veggel and D. N. Reinhoudt, Synthesis of (Hemi)Carceplex Adsorbates for Self-Assembly on Gold, *Eur. J. Org Chem.*, 2000, **2000**, 269–274.

40 A. M. van Wageningen, W. Verboom, X. Zhu, J. A. Ripmeester and D. N. Reinhoudt, Solid state NMR spectroscopy of calix [4] arene-based carceplexes, *Supramol. Chem.*, 1998, **9**, 31–36.

41 A. M. A. van Wageningen, J. P. M. van Duynhoven, W. Verboom and D. N. Reinhoudt, Synthesis and functionalization of calix[4]arene-based carceplexes, *J. Chem. Soc., Chem. Commun.*, 1995, 1941–1942.

42 P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven and D. N. Reinhoudt, A Novel Type of Stereoisomerism in Calix[4]arene-Based Carceplexes, *Angew. Chem., Int. Ed.*, 1994, **33**, 2345–2348.

43 A. M. van Wageningen, P. Timmerman, J. P. van Duynhoven, W. Verboom, F. C. van Veggel and D. N. Reinhoudt, Calix [4] arene-Based (Hemi) carcerands and Carceplexes: Synthesis, Functionalization, and Molecular Modeling Study, *Chem.–Eur. J.*, 1997, **3**, 639–654.

44 P. Timmerman, E. A. Brinks, W. Verboom and D. N. Reinhoudt, Synthetic receptors with preorganized cavities that complex prednisolone-21-acetate, *J. Chem. Soc., Chem. Commun.*, 1995, 417–418.

45 P. Timmerman, W. Verboom, F. C. van Veggel, W. P. van Hoorn and D. N. Reinhoudt, An organic molecule with a rigid cavity of nanosize dimensions, *Angew. Chem., Int. Ed.*, 1994, **33**, 1292–1295.

46 B. Tomapatanaget and T. Tuntulani, Lower rim tetra-substituted and upper rim ferrocene amide calix[4]arenes: synthesis, conformation and anion-binding properties, *Tetrahedron Lett.*, 2001, **42**, 8105–8109.

47 B. Tomapatanaget, T. Tuntulani and O. Chailapakul, Calix[4] arenes Containing Ferrocene Amide as Carboxylate Anion Receptors and Sensors, *Org. Lett.*, 2003, **5**, 1539–1542.

48 H. Iwamoto, Y. Yukimasa and Y. Fukazawa, Synthesis and binding behavior of a Zn(II)-porphyrin having calix[5]arene cap, *Tetrahedron Lett.*, 2002, **43**, 8191–8194.

49 H. Iwamoto, S. Nishi and T. Haino, Highly shape-selective guest encapsulation in the precisely defined cavity of a calix[4]arene-capped metalloporphyrin, *Chem. Commun.*, 2011, **47**, 12670–12672.

50 (*a*) T. Haino, H. Fukuoka, H. Iwamoto and Y. Fukazawa, Synthesis and Enantioselective Recognition of a Calix[5] arene-based Chiral Receptor, *Supramol. Chem.*, 2008, **20**, 51–57; (*b*) T. Haino, H. Fukuoka, M. Katayama and Y. Fukazawa, Enantioselective Recognition of Calix[5]arene-based Artificial Receptor Bearing Chiral Macrocycle for Chiral Ethyltrimethylammonium Salts, *Chem. Lett.*, 2007, **36**, 1054–1055.

51 C. Hocquelet, C. K. Jankowski and L. Mauclaire, New tubular products from calixarene–cyclodextrin coupling, *Tetrahedron*, 2007, **63**, 10834–10839.

52 B. H. Kim, E. J. Jeong, G. T. Hwang and N. Venkatesan, Multiple Cycloadditive Macrocyclization: An Efficient Method for Crown Ether-Type Cyclophanes, Bis-Calix[4] arenes and Silamacrocycles, *Synthesis*, 2001, 2191–2202.

53 G. T. Hwang and B. H. Kim, Cyclophane-type bis-calix[4] arenes: efficient synthesis via quadruple cycloadditive

macrocyclization and conformational study, *Tetrahedron Lett.*, 2000, **41**, 10055–10060.
54 S. Zahim, L. A. Wickramasinghe, G. Evano, I. Jabin, R. R. Schrock and P. Müller, Calix[6]azacryptand Ligand with a Sterically Protected Tren-Based Coordination Site for Metal Ions, *Org. Lett.*, 2016, **18**, 1570–1573.
55 L. A. Wickramasinghe, R. R. Schrock, C. Tsay and P. Müller, Molybdenum Complexes that Contain a Calix[6]azacryptand Ligand as Catalysts for Reduction of N2 to Ammonia, *Inorg. Chem.*, 2018, **57**, 15566–15574.
56 D. E. Phipps and P. D. Beer, A [2]catenane containing an upper-rim functionalized calix[4]arene for anion recognition, *Tetrahedron Lett.*, 2009, **50**, 3454–3457.
57 R. Miao, Q.-Y. Zheng, C.-F. Chen and Z.-T. Huang, A novel calix[4]arene fluorescent receptor for selective recognition of acetate anion, *Tetrahedron Lett.*, 2005, **46**, 2155–2158.
58 M. Segura, B. Bricoli, A. Casnati, E. M. Muñoz, F. Sansone, R. Ungaro and C. Vicent, A Prototype Calix[4]arene-Based Receptor for Carbohydrate Recognition Containing Peptide and Phosphate Binding Groups, *J. Org. Chem.*, 2003, **68**, 6296–6303.
59 J. H. Mai, J. M. Liu, S. Y. Li and H. F. Jiang, A fluorescent probe for fluoride ion based on 2-aminopyridyl-bridged calix[6]arene, *Chin. Chem. Lett.*, 2009, **20**, 1191–1194.
60 Y. K. Agrawal and K. R. Sharma, Speciation, liquid–liquid extraction, sequential separation, preconcentration, transport and ICP-AES determination of Cr(III), Mo(VI) and W(VI) with calix-crown hydroxamic acid in high purity grade materials and environmental samples, *Talanta*, 2005, **67**, 112–120.
61 M. O. Vysotsky, A. Bogdan, L. Wang and V. Böhmer, Template synthesis of multi-macrocycles by metathesis reaction, *Chem. Commun.*, 2004, 1268–1269.
62 O. Molokanova, A. Bogdan, M. O. Vysotsky, M. Bolte, T. Ikai, Y. Okamoto and V. Böhmer, Calix[4]arene-Based Bis[2] catenanes: Synthesis and Chiral Resolution, *Chem.–Eur. J.*, 2007, **13**, 6157–6170.
63 Y. Cao, L. Wang, M. Bolte, M. O. Vysotsky and V. Böhmer, Synthesis of huge macrocycles using two calix[4]arenes as templates, *Chem. Commun.*, 2005, 3132–3134.
64 L. Wang, M. O. Vysotsky, A. Bogdan, M. Bolte and V. Böhmer, Multiple Catenanes Derived from Calix[4]arenes, *Science*, 2004, **304**, 1312–1314.
65 (*a*) A. Bogdan, M. O. Vysotsky, T. Ikai, Y. Okamoto and V. Böhmer, Rational Synthesis of Multicyclic Bis[2] catenanes, *Chem.–Eur. J.*, 2004, **10**, 3324–3330; (*b*) M. O. Vysotsky, M. Bolte, I. Thondorf and V. Böhmer, New Molecular Topologies by Fourfold Metathesis Reactions within a Hydrogen-Bonded Calix[4]arene Dimer, *Chem.–Eur. J.*, 2003, **9**, 3375–3382.
66 (*a*) C. Gaeta, M. O. Vysotsky, A. Bogdan and V. Böhmer, Fourfold [2]Rotaxanes Based on Calix[4]arenes, *J. Am. Chem. Soc.*, 2005, **127**, 13136–13137; (*b*) O. Molokanova, M. O. Vysotsky, Y. Cao, I. Thondorf and V. Böhmer, Fourfold [2]Rotaxanes of Calix[4]arenes by Ring Closure, *Angew. Chem., Int. Ed.*, 2006, **45**, 8051–8055.
67 A. Bogdan, M. Bolte and V. Böhmer, Molecules with New Topologies Derived from Hydrogen-Bonded Dimers of Tetraurea Calix[4]arenes, *Chem.–Eur. J.*, 2008, **14**, 8514–8520.
68 Y. Rudzevich, Y. Cao, V. Rudzevich and V. Böhmer, Stepwise Synthesis and Selective Dimerisation of Bis- and Trisloop Tetra-urea Calix[4]arenes, *Chem.–Eur. J.*, 2008, **14**, 3346–3354.
69 Y. Rudzevich, V. Rudzevich, C. Moon, G. Brunklaus and V. Böhmer, Self-assembled dendrimers with uniform structure, *Org. Biomol. Chem.*, 2008, **6**, 2270–2275.
70 O. Molokanova, G. Podoprygorina, M. Bolte and V. Böhmer, Multiple catenanes based on tetraloop derivatives of calix[4] arenes, *Tetrahedron*, 2009, **65**, 7220–7233.
71 M. Chas and P. Ballester, A dissymmetric molecular capsule with polar interior and two mechanically locked hemispheres, *Chem. Sci.*, 2012, **3**, 186–191.
72 J. Holub, V. Eigner, L. Vrzal, H. Dvořáková and P. Lhoták, Calix [4] arenes with intramolecularly bridged meta positions prepared via Pd-catalysed double C–H activation, *Chem. Commun.*, 2013, **49**, 2798–2800.
73 F. Stejskal, P. Cuřínová and P. Lhoták, Unexpected formation of disulfide-based biscalix[4]arenes, *Tetrahedron*, 2016, **72**, 760–766.
74 X. Zhang, S. Tong, J. Zhu and M.-X. Wang, Inherently chiral calixarenes by a catalytic enantioselective desymmetrizing cross-dehydrogenative coupling, *Chem. Sci.*, 2023, **14**, 827–832.
75 P. Slavík, M. Dudič, K. Flídrová, J. Sýkora, I. Císařová, S. Böhm and P. Lhoták, Unprecedented Meta-Substitution of Calixarenes: Direct Way to Inherently Chiral Derivatives, *Org. Lett.*, 2012, **14**, 3628–3631.
76 K. Flídrová, S. Böhm, H. Dvořáková, V. Eigner and P. Lhoták, Dimercuration of Calix[4]arenes: Novel Substitution Pattern in Calixarene Chemistry, *Org. Lett.*, 2014, **16**, 138–141.
77 P. Slavík, K. Flídrová, H. Dvořáková, V. Eigner and P. Lhoták, Meta-arylation of calixarenes using organomercurial chemistry, *Org. Biomol. Chem.*, 2013, **11**, 5528–5534.
78 K. Flídrová, P. Slavik, V. Eigner, H. Dvořáková and P. Lhoták, meta-Bridged calix[4]arenes: a straightforward synthesis via organomercurial chemistry, *Chem. Commun.*, 2013, **49**, 6749–6751.
79 P. Slavík, H. Dvořáková, V. Eigner and P. Lhoták, Regioselective alkylation of a methylene group via meta-bridging of calix[4]arenes, *Chem. Commun.*, 2014, **50**, 10112–10114.
80 (*a*) P. Slavík, H. Dvořáková, M. Krupička and P. Lhoták, Unexpected cleavage of upper rim-bridged calix 4 arenes leading to linear oligophenolic derivatives, *Org. Biomol. Chem.*, 2018, **16**, 838–843; (*b*) P. Slavík and P. Lhoták, Unusual reactivity of upper-rim bridged calix[4]arenes - Friedel-Crafts alkylation via cleavage of the macrocyclic skeleton, *Tetrahedron Lett.*, 2018, **59**, 1757–1759; (*c*) P. Slavík, M. Krupička, V. Eigner, L. Vrzal, H. Dvořáková and P. Lhoták, Rearrangement of meta-Bridged Calix 4 arenes Promoted by Internal Strain, *J. Org. Chem.*, 2019, **84**, 4229–4235.

81 P. Slavík, M. Kohout, S. Böhm, V. Eigner and P. Lhoták, Synthesis of inherently chiral calixarenes via direct mercuration of the partial cone conformation, *Chem. Commun.*, 2016, **52**, 2366–2369.
82 P. Slavík, V. Eigner, S. Böhm and P. Lhoták, Mercuration of calix[4]arenes immobilized in the 1,2- and 1,3-alternate conformations, *Tetrahedron Lett.*, 2017, **58**, 1846–1850.
83 P. Slavík, V. Eigner and P. Lhoták, Shaping of calix[4]arenes via double bridging of the upper rim, *CrystEngComm*, 2016, **18**, 4964–4970.
84 P. Slavík, V. Eigner and P. Lhoták, Intramolecularly Bridged Calix[4]arenes with Pronounced Complexation Ability toward Neutral Compounds, *Org. Lett.*, 2015, **17**, 2788–2791.
85 P. Slavík, H. Dvořáková, V. Eigner and P. Lhoták, Meta-Bridged calix[4]arenes prepared by Friedel-Crafts alkylation, *New J. Chem.*, 2017, **41**, 14738–14745.
86 P. Slavík, V. Eigner and P. Lhoták, meta-Bridged calix[4]arenes with the methylene moiety possessing in/out stereochemistry of substituents, *New J. Chem.*, 2018, **42**, 16646–16652.
87 L. Vrzal, K. Flídrová, T. Tobrman, H. Dvořáková and P. Lhoták, Use of residual dipolar couplings in conformational analysis of meta-disubstituted calix[4]arenes, *Chem. Commun.*, 2014, **50**, 7590–7592.
88 M. Tlustý, P. Slavík, M. Kohout, V. Eigner and P. Lhoták, Inherently Chiral Upper-Rim-Bridged Calix[4]arenes Possessing a Seven Membered Ring, *Org. Lett.*, 2017, **19**, 2933–2936.
89 M. Tlustý, V. Eigner, M. Babor, M. Kohout and P. Lhoták, Synthesis of upper rim-double-bridged calix[4]arenes bearing seven membered rings and related compounds, *RSC Adv.*, 2019, **9**, 22017–22030.
90 M. Tlustý, D. Spálovská, M. Kohout, V. Eigner and P. Lhoták, Ketone transformation as a pathway to inherently chiral rigidified calix[4]arenes, *Chem. Commun.*, 2020, **56**, 12773–12776.
91 M. Tlustý, V. Eigner and P. Lhoták, Azide Decomposition as a Pathway to Intramolecularly Upper-Rim-Bridged Calix[4]arenes, *Synthesis*, 2022, **54**, 1301–1308.
92 M. Tlustý, V. Eigner, H. Dvořáková and P. Lhoták, The atropisomeric dynamic behaviour of symmetrical N-acylated amine-bridged calix[4]arenes, *New J. Chem.*, 2022, **46**, 11774–11781.