Applications of chiral C_3-symmetric molecules

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Throughout history symmetry and chirality have inspired artists and scientists alike. Given that rotational axes are the only elements of symmetry compatible with chirality, it is not surprising that C_2- and C_3-symmetrical molecules have attracted considerable attention. In recent years, the aesthetic appeal of C_2-symmetrical molecules has been translated into many widely-used applications some of which are of commercial importance by its exploitation in the area of asymmetric catalysis. In contrast, exploitation of the arguably greater aesthetic appeal of C_3-symmetric molecules is still in its infancy. This review, which surveys the applications of chiral C_3-symmetrical molecules in the areas of asymmetric catalysis, molecular recognition and nanoarchitecture, has been designed with a view to identifying some of the most promising areas of application of these very beautiful molecules.

Introduction

Symmetry, chirality and their combination are to be found in many creations of Nature, and in some of the greatest achievements of mankind. From a beautiful flower to Da Vinci's 'Vetruvian man', expression of these concepts provides continuing inspiration and example to artists and scientists alike. In chemistry, higher order symmetry has always attracted interest, and this has increased in recent years, stimulated for example, by the widespread use of C_2-symmetric chiral ligands in asymmetric synthesis and catalysis.

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C_3 Symmetry in particular, which is aesthetically pleasing in both a natural and synthetic context (Fig. 1(a) and (b)), has several potential uses in chemical endeavours. Indeed, in 1998 Moberg wrote an excellent review of the role of rotational symmetry in chemistry, with an emphasis on C_3 symmetry in asymmetric catalysis and chiral recognition.[1] In 1998, however, many of the molecules surveyed had yet to undergo assays as catalyst ligands or molecular hosts.

This present review draws on the literature from 1998 to date. We chose to focus on uses of C_3-symmetric molecules, rather than dwelling on their synthesis, although this still remains a challenge. We thus selected examples for inclusion based on their merits within the applications for which they were designed. By doing this, we anticipated that a picture of

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M. Paola Castaldi

M. Paola Castaldi obtained her Laurea degree in Pharmaceutical Chemistry from Università degli Studi di Padova (Italy) in 2002. During that period she did a final year Erasmus-exchange project at King's College London (Prof. M. North and Prof. G. Zagotto) working on the synthesis of monomers for the preparation of biocompatible polymers. Her PhD research (Prof. S. E. Gibson, 2002–2005) focused on the development of a novel approach to the introduction of multiple chiral centres around an (arene)tricarbonylchromium(0) complex in a single operation. This methodology has been applied to the synthesis of C_2- and C_3-symmetric ligands for asymmetric catalysis. In November 2005 she began postdoctoral studies at University of California, San Diego (Prof. Y. Tor and Prof. T. Hermann) working on RNA–small molecules interactions.

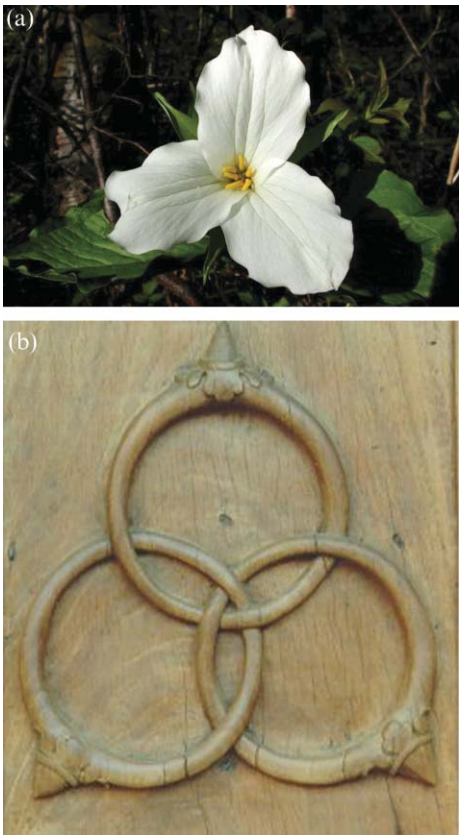


Fig. 1 (a) A Trillium flower. (b) The Borromean rings.

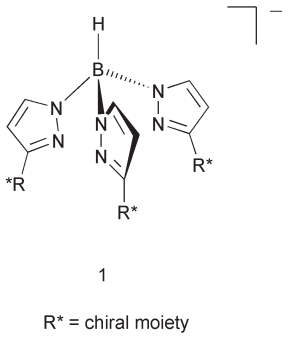
the current level of usefulness of C_3 symmetry combined with non-racemic chirality in chemistry would emerge. We have divided the review into three sections: asymmetric catalysis, molecular recognition—categories employed by Moberg; and nanoarchitecture, an area that has grown considerably in recent years.

Asymmetric catalysis

Incorporation of molecular symmetry into ligands and catalysts is one of several guiding principles behind their design, as the reduction of the number of possible intermediates or transition states is thought to simplify their mode of action and its interpretation. For example, it has been postulated that C_3-symmetric ligands that are chiral and tripodal should be highly effective in catalytic reactions involving octahedral metal complexes.[2]

From tris(pyrazolyl)hydroborate through tris(oxazoline) to tris(pyridine) ligands

A well-recognised synthetic strategy in inorganic and organometallic chemistry is to control the coordination number, geometry, physical properties and reactivity of metal complexes through the use of supporting ligands that contain sterically bulky substituents. Since their introduction in 1986,[3] tris(pyrazolyl)hydroborate (Tp) ligands bearing various sterically bulky pyrazolyl ring substituents, have been shown to be useful chelating ligands in organometallic and bioorganic



1

R* = chiral moiety

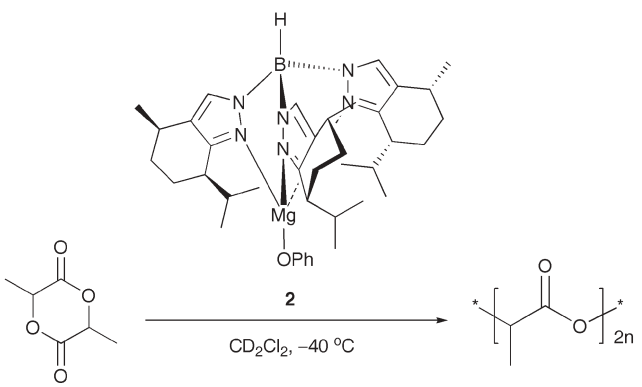
Fig. 2 Enantiomerically pure tris(pyrazolyl)hydroborate ligands.[3,4]

studies.[4] Efforts to construct optically active Tp ligands have focused on assembling C_3-symmetric molecules of generalized structure **1**, which features three identical, enantiomerically pure, substituted pyrazoles (Fig. 2).

The evolution of enantiomerically pure tris(pyrazolyl)hydroborate ligands and their application in the cyclopropanation of styrene,[5] and in a photolytic stereo- and regioselective C–H bond activation,[6] were reviewed in 1998.[1] More recently, magnesium derivatives of chiral C_3-symmetric tris(indazolyl)-borates derived from menthone, *e.g.* **2**,[7] have been investigated as catalysts for the polymerization of lactide (Scheme 1), an important process, given the growing use of biodegradable polymers in several areas, *e.g.* the field of biological tissue engineering.[8]

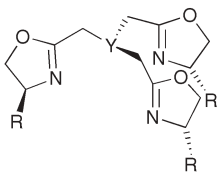
The chiral magnesium complex **2** showed significant selectivity in the polymerization of a 1:1 mixture of *rac*- and *meso*-lactide. In CD_2Cl_2 at −40 °C *meso*-lactide was polymerized exclusively to give polymers with a modest preference for syndiotactic junctions, *RSRSRS*, leaving behind unreacted *rac*-lactide.

There are a growing number of reports in the literature describing tris(oxazoline) ligands, the most notable examples being the $N(CH_2\text{-ox})_3$ and $CH(CH_2\text{-ox})_3$ (ox = 2-oxazolinyl) systems **3** and **4** (Fig. 3). The copper complexes of these have been employed in asymmetric allylic oxidations with good results (up to 88% ee for **3** and up to 81% ee for **4**).[9] The C_3-symmetric tripodal ligand **3** forms a dimeric Cu^I complex,[10]



mixture of rac and *meso*-lactide

Scheme 1 Diastereoselective ring opening polymerization of *meso*-lactide.[7]



3 Y = N
4 Y = CH

Fig. 3 C_3-Symmetric tris(oxazoline) ligands.[1,9]

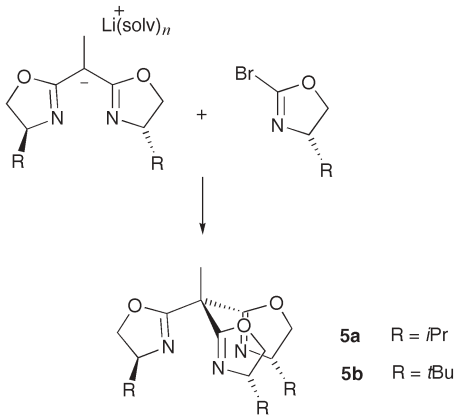
in which each metal ion is surrounded by two oxazolyl nitrogen atoms from one ligand and one from the second ligand. The way these conformationally very flexible tris(oxazolines) coordinate to the metal centre in active catalysts, however, remains an open question.

A successful synthetic strategy for the construction of conformationally more rigid ligands, more suitable for tripodal coordination at a single metal centre, has recently been established. Synthesis of structures of type **5** was achieved by coupling readily accessible bis(oxazoline) derivatives with preformed activated mono(oxazoline)rings (Scheme 2).[11]

Reaction of the isopropyl substituted **5a** with one molar equivalent of $[RhCl_3(H_2O)_3]$ cleanly gave a mononuclear tris(oxazoline)rhodium complex, the NMR spectroscopic data of which revealed a three-fold symmetric structure.[12] This new class of chiral tris(oxazoline) was first employed in the asymmetric cyclopropanation of styrene with *tert*-butyl and ethyl diazoacetate (Table 1).[12]

The preference for the *trans* diastereoisomer observed using both the isopropyl and the *tert*-butyl tris(oxazolinyl)ethanes **5a** and **5b**, was similar to results previously obtained with bis(oxazoline) derivatives (de = 64–94% *trans*, ee = 64–99% *trans*, ee = 45–97% *cis*).[13]

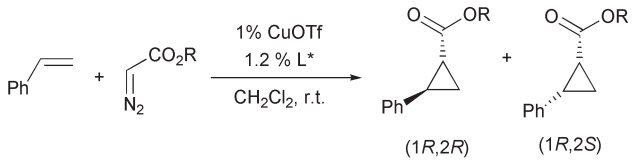
Guided by the use of tripodal N-donor ligands as models of the tris(histidine) binding sites found in many zinc-containing enzymes, members of this new class of chiral tris(oxazolines) were considered good candidates for mimics of zinc-dependent transesterases.[14] The C_3-symmetric dinuclear zinc complex **6** derived from **5a** and depicted in Fig. 4, showed modest but significant enantioselectivity in the kinetic resolution of



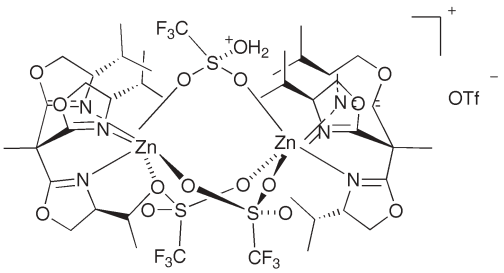
5a R = *i*Pr
5b R = *t*Bu

Scheme 2 Synthesis of the tripodal tris(oxazoline) derivatives **5a** and **5b**.[11]

Table 1 Copper(I)-catalysed asymmetric cyclopropanation of styrene[12]



Entry	L*	R	*cis*:*trans*	%ee *cis*	%ee *trans*
1	**5a**	*t*Bu	22:78	70	65
2	**5b**	*t*Bu	19:81	73	70
3	**5a**	Et	29:71	64	67
4	**5b**	Et	31:69	68	70



6

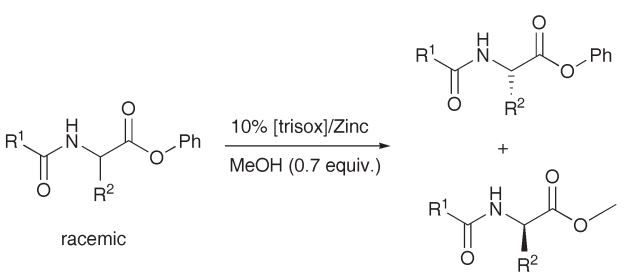
Fig. 4 A dinuclear zinc complex used as a biomimetic transesterification catalyst.[14]

various phenyl ester derivatives of N-protected amino-acids by transesterification with methanol (Table 2).

The importance of the tripodal-zinc environment for the observed stereoselectivity is revealed by the observation that a bidentate bis(oxazoline) ligand coordinated to a zinc salt failed to give any selectivity in the above reaction.

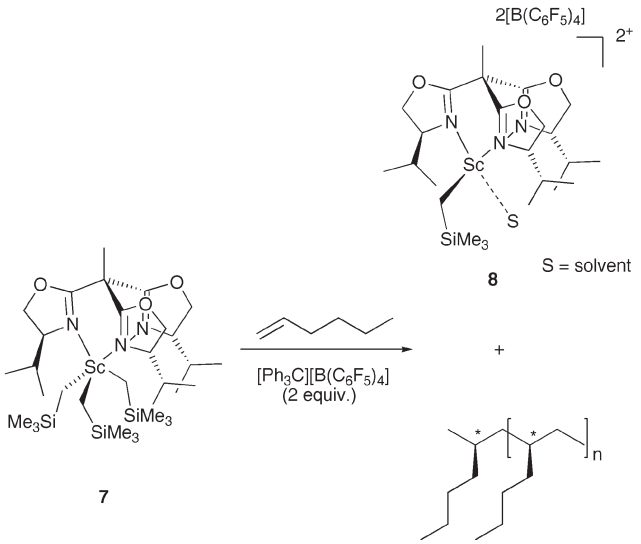
In 2005, during a study on olefin polymerization catalysis,[15] the possibility of controlling the tacticity and molecular weight distribution in the polymerization of 1-hexene using the trialkyl scandium pre-catalyst complex **7** was considered (Scheme 3).[16]

Table 2 Partial kinetic resolution of racemic amino acids esters by transesterification[14]



racemic

			Selectivity factor (*S*)		
Entry	R^1	R^2	$Zn(OTf)_2$	$Zn(OAc)_2$	$Zn(OCOCF_3)_2$
1	Ph	Ph	1.8	3.5	3.8
2	Ph	Me	1.3	2.7	3.0
3	Me	Me	2.0	4.5	5.1
4	Me	Bz	1.8	2.6	4.3



Scheme 3 Highly isotactic poly(1-hexene) produced by the active scandium complex **8**.[16]

Table 3 1-Hexene polymerization data for **8**[16]

Entry	T/°C	t/min	Yield/g	Activity/kg mol^{-1} h^{-1}	M_w
1	−30	3	1.01	2 030	750 000
2	−20	1.5	1.90	7 600	552 000
3	0	1	2.18	13 080	354 000
4	21	0.5	3.02	36 230	227 000

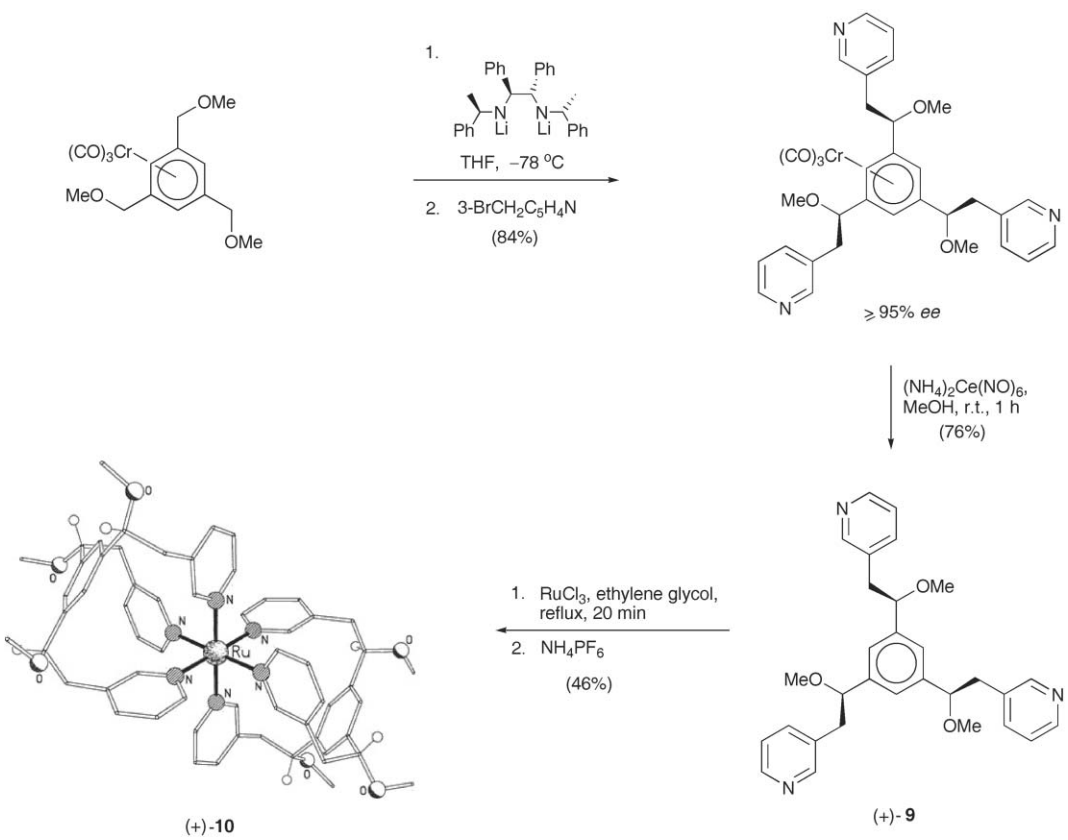
Polymerization studies were carried out at various temperatures and the activities and polymer characteristics recorded (Table 3).

At a polymerization temperature of −30 °C, the activity was a relatively low 2030 kg mol^{-1} h^{-1}, but the poly(1-hexene) produced was highly isotactic with a molecular-mass distribution of M_w = 750 000. Following the theory that dicationic species are the catalytically active units in certain rare-earth catalysed polymerizations,[15b] it was proposed that an in situ formed dicationic complex **8** is the active species in this polymerization of 1-hexene.

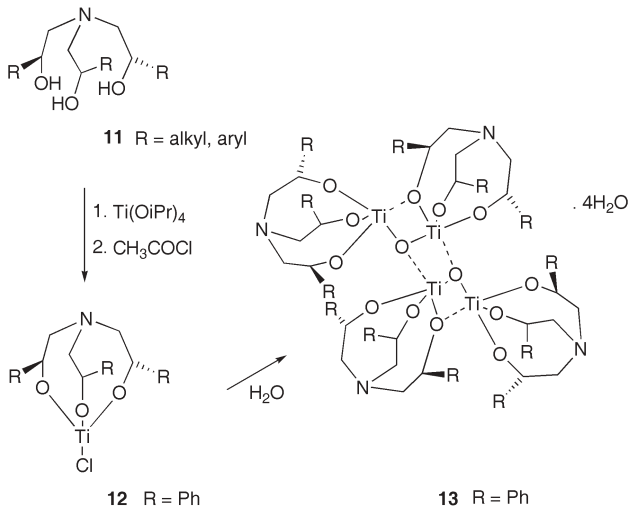
Recently a new approach to chiral C_3-symmetric molecules has delivered a range of potential ligands including the tris(pyridine) (+)-**9**, which has been shown to form the ruthenium complex (+)-**10**. (Scheme 4).[17] It is anticipated that derivatives of (+)-**9** will prove useful tools in the continuing search for more selective and more efficient asymmetric catalysts.

Enantiopure triols: C_3 symmetry and axial chirality

Since their first use in 1982 as chiral auxiliaries in the asymmetric reduction of ketones with metal hydrides,[18] a variety of C_3-symmetric enantiopure tris(alkanolamine) ligands **11** (Scheme 5) have been prepared[19] and used in asymmetric catalysis.[20] As reported[1] in 1998 zirconium complexes of these triols showed high selectivity in the desymmetrisation of *meso* epoxides (up to 93% ee),[20b–d] and titanium complexes catalysed an enantioselective sulfoxidation of aryl alkyl sulfides (up to



Scheme 4 Synthesis of tris(pyridine) ligand (+)-**9** and its ruthenium complex (+)-**10**.[17]



Scheme 5 Synthesis of the tetranuclear titanium precatalyst **11**.[21]

Table 4 Polymerization of ethylene with **12**/MAO and **13**/MAO[21]

Entry	Catalyst	T/°C	Yield/g	Activity/ kg mol^{-1} h^{-1}	M_η[a]/ kg mol^{-1}
1	**12**/MAO	30	2.5	250	625
2	**12**/MAO	0	3.7	375	420
3	**12**/MAO	10	3.0	300	550
4	**12**/MAO	50	3.0	300	380
5	**13**/MAO	30	0.7	70	330
6	**13**/MAO	0	0.8	80	205
7	**13**/MAO	10	0.7	74	250
8	**13**/MAO	50	0.8	80	370

[a] Determined from intrinsic viscosity at 135 °C.

84% ee).[20a,d] In 2004 the mono- and tetra-nuclear titanatranes, **12** and **13**, were introduced and shown to be active ethylene polymerization catalysts (Table 4).[21]

In all cases, the polymerization activity of compound **12** was four times greater than that observed for compound **13**, indicating that the activity per titanium atom was the same for both compounds, and that possibly a catalytically active monotitanate was formed from the tetranuclear system **13** upon activation with MAO.[21]

To develop tripodal triols further, in 2003 the potentially promising combination of C_3 symmetry and axial chirality was considered (Fig. 5).[22]

As attempts to introduce metals into the central cage of **14**, *e.g.* Ti(IV), proved to be difficult,[22] the design of the ligand was modified by introducing a central mesitylene-derived core to

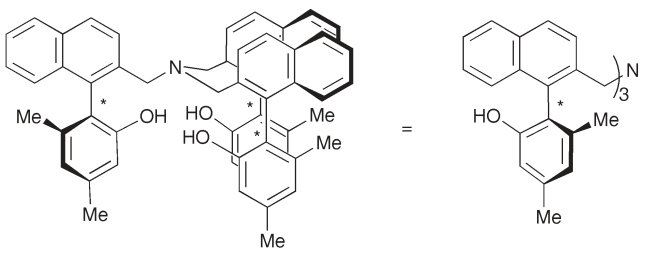
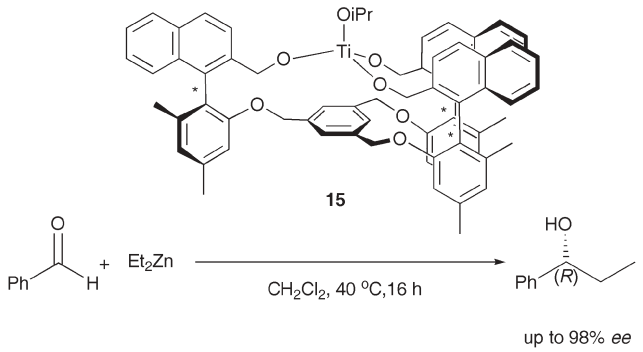
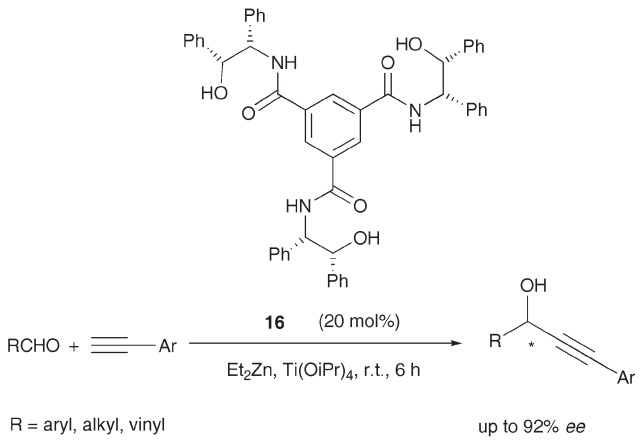


Fig. 5 The enantiopure C_3-symmetric axially chiral triol **14**.[22]



Scheme 6 Enantioselective addition of dialkylzinc to benzaldehyde catalysed by the C_3-symmetric titanium complex **15**.[23]



Scheme 7 Catalytic asymmetric alkynylation of aldehydes.[24]

obtain a more spacious cavity.[23] The rigid, C_3-symmetric titanium complex **15**, formed *in situ*, catalysed the ethylation of benzaldehyde with asymmetric inductions of up to 98% ee (Scheme 6).

In 2005 the application of the novel C_3-symmetric chiral triol **16** to the enantioselective alkynylation of aldehydes was reported (Scheme 7).[24]

A Ti(IV) complex of the C_3-symmetric tris(β-hydroxy amide) ligand **16** showed good enantioselectivity with aromatic aldehydes and α,β-unsaturated aldehydes (up to 92% ee).

From C_3-symmetric tripodal phosphanes to monodentate phosphanes

As reviewed in 1998,[1] chiral tripodal phosphanes **17** and **18** (Fig. 6) with C_3 symmetry were introduced in 1990, and the cationic rhodium complex of **17** displayed good catalytic activity in the enantioselective hydrogenation of dimethyl itaconate (50 °C, 20 h, 95% ee) and of methyl acetamidocinnammate (50 °C, 72 h, 89% ee).[2,25] However, the relative high temperature required for reasonable reduction rates suggested that dissociation of one arm of the chelating ligand was necessary for reaction with hydrogen.

In 1988, it was found that chiral monophosphanes **19** (Fig. 6), in which the three-fold rotational axis is a chirality axis, could not be resolved due to rapid racemisation.[26] In an attempt to address this issue, a more recent study focused on

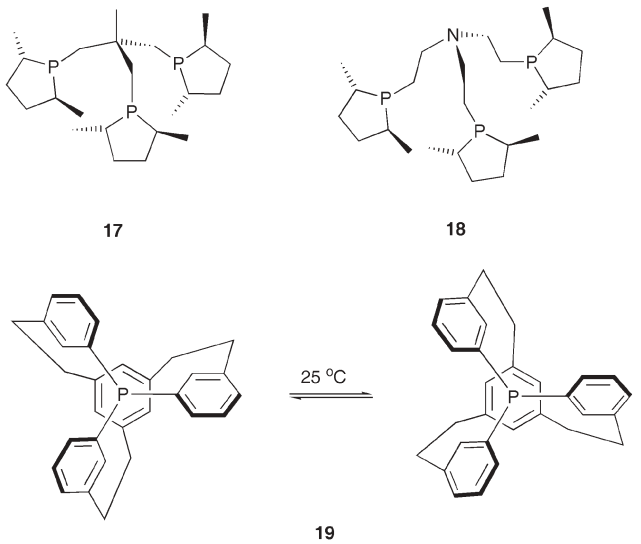


Fig. 6 C_3-Symmetric tripodal phosphanes **17** and **18**, and monophosphane **19**.[25,26]

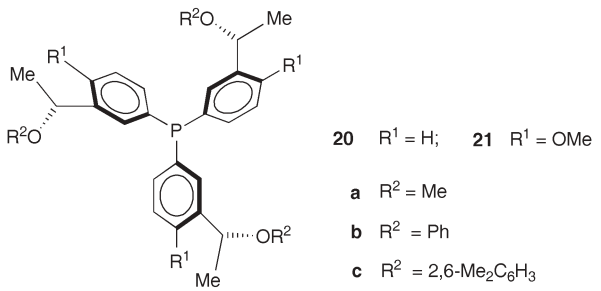


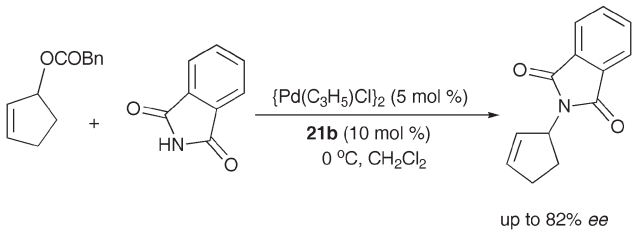
Fig. 7 Optically active C_3-symmetric triarylphosphanes.[27]

the synthesis and the use of C_3-symmetric monodentate phosphane ligands of types **20** and **21** (Fig. 7).[27]

The arrangement of the three aromatic groups around the central atom should lead to stable enantiomeric propeller–shaped conformations and it was proposed that this might provide chiral pockets that promote enantiodiscrimination.[27]

A study of their solid state structures revealed that rotation about the aryl–P bonds enables these ligands to populate conformations that are not perfectly C_3-symmetric. This type of ligand was tested in the palladium-mediated allylation reaction and enantioselectivities up to 82% ee were obtained for cyclic substrates using **21b** as ligand (Scheme 8).[27]

This did not match the best results previously reported by Trost for palladium-catalysed allylic alkylation of the same



Scheme 8 An asymmetric palladium catalysed allylation reaction (up to 82% ee).[27]

substrate using C_2-symmetric chiral amide ligands (up to 95% yield and 98% ee).[28]

Molecular recognition

Molecular recognition of biologically important entities by artificial receptors has been the subject of much research, the majority of which is directed towards either a better understanding of recognition phenomena in nature, or towards potential applications in separation science, catalysis, or biochemistry.[29] A three-fold rotational symmetry receptor is attractive because it simplifies the possible modes of coordination, and it requires an increased matching of the binding groups on the receptor and the target molecule that enhances the probability of discrimination.

Selective recognition of ammonium ions

In 1998, chiral C_3-symmetric receptors and their binding properties were surveyed.[1,30] Since then, considerable interest in developing receptors for NH_4^+,[31] has led to the rational design of receptors that are not only highly selective for binding NH_4^+ over K^+,[32] but also belong to a class of C_3-symmetric molecules that have enjoyed considerable success in several areas of chemical research. Receptors that are specific for NH_4^+ have potential applications as sensors in clinical analysis and environmental chemistry. The concentration of urea or creatinine in a biological sample can be determined indirectly by measuring the amount of NH_4^+ released upon enzyme-catalyzed hydrolysis. These receptors are also useful for determining the concentrations of NH_4^+ or ammonia in drinking water or in the air. One of the most effective NH_4^+ receptors is nonactin, **22**, a natural antibiotic that has been commercially employed as the recognition component in enzyme-based ion-selective electrodes (ISE).[31] A serious drawback of nonactin, however, is that it binds only about ten times more tightly to NH_4^+ than K^+ because the sizes of the two monocations are closely matched.

Exploiting the distinct symmetries of NH_4^+ and K^+ (K^+ has a closed electron shell and spherical symmetry, whilst NH_4^+ is tetrahedral), tripodal oxazoline receptors **23a–d** (Fig. 8), which have lone pairs of electrons that can readily adopt an optimal orientation for binding NH_4^+ by hydrogen bonding, were developed. An impressive selectivity for NH_4^+ over K^+ was observed with oxazoline **23b** (NH_4^+/K^+-selectivity $\sim$440 *cf.* NH_4^+/K^+-selectivity $\sim$10 for nonactin).

Following this study, receptors **23a–d** and the new derivatives **23e** and **23f** (Fig. 9)[33] were identified as efficient recognition systems for alkylammonium ions such as β-phenethylammonium ions and *n*-butylammonium, which are reasonable models for biologically important amines such as dopamine **24** and GABA **25** (γ-aminobutyric acid).[34]

It was observed that steric and electronic interactions involving the oxazoline substituents significantly affected the binding affinity. Of the oxazoline receptors tested, receptor **23e** exhibited the largest association constant for *n*-$BuNH_3^+$ (log K_{ass} = 6.65) but a relative low affinity for *t*-$BuNH_3^+$ (log K_{ass} = 3.80). Receptor **23a** showed the highest selectivity towards sterically more demanding alkylammonium ions such as *t*-$BuNH_3^+$ (log K_{ass} = 5.26). Some time later, it was

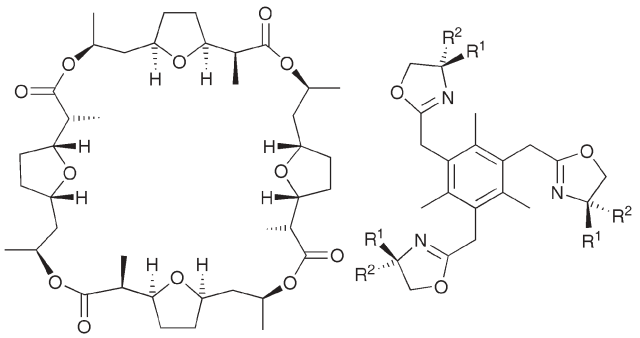


Fig. 8 The natural antibiotic nonactin **22** and the artificial tris(oxazoline) receptors **23** for selective recognition of NH_4^+ over K^+.[32]

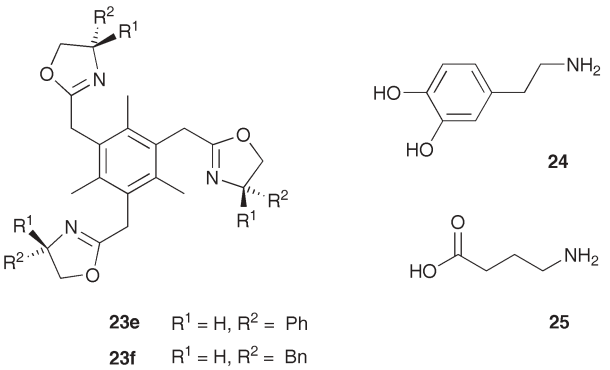


Fig. 9 Artificial receptors for alkylammonium ions.[33,34]

discovered that receptor **23e**, with its C_3-symmetric "screw-sense" chiral environment, displayed a moderate level of discrimination (71:29) between the enantiomers of α-phenylethylammonium ions (Table 5, entry 1).[35]

In 2003, the study of the binding properties of the tripodal oxazoline receptor **23e** was extended to primary amines with chiral centres at the β-position.[36] One difficulty in the recognition of β-chiral amines *via* their ammonium ions is that the β-chiral centre is relatively remote from the binding site. To overcome this problem, bifurcated H-bonds were used to block the free rotation of β-substituents (Fig. 10).

Guests that have a β-OH functionality, which could act as a hydrogen bond acceptor, were examined initially, and it was found that the β-OH group does indeed seem to play a role in chiral discrimination, presumably by forming a bifurcated H-bond. (Table 6, entries 1–3 *cf.* entry 4). When the β-OH

Table 5 Enantioselective binding of tris(oxazoline) **23e** toward racemic ammonium salts[35]

Entry	Racemic guest ($RNH_3^+Cl^-$)	Enantioselectivity
1	α-Phenylethylamine	71 (*R*):29 (*S*)
2	α-(1-Naphthyl)ethylamine	70:30
3	Tryptophan methyl ester	67 (*S*):33 (*R*)
4	Alanine methyl ester	53 (*S*):47 (*R*)
5	Phenylalanine methyl ester	55 (*S*):45 (*R*)

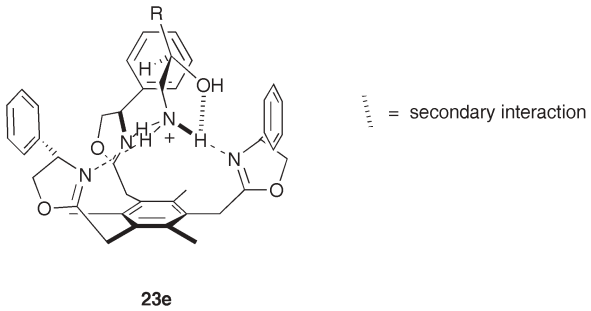
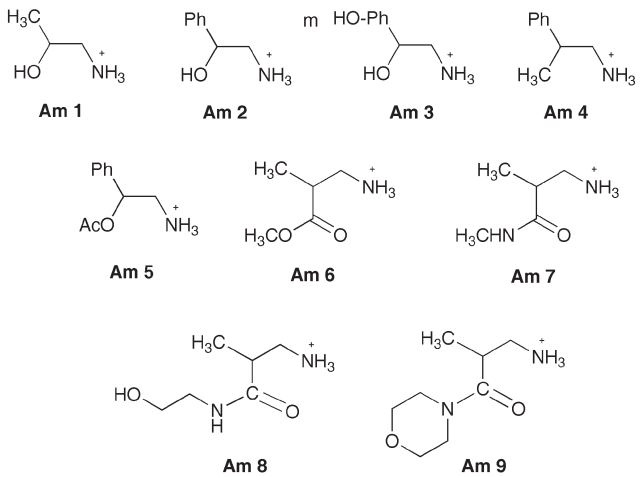


Fig. 10 Diastereomeric inclusion complexes between receptor **23e** and β-chiral primary ammonium ions.[36]

Table 6 Selective binding of **23e** towards racemic ammonium salts of β-chiral amines **Am1–Am9**[36]



Entry	Racemic guest	Enantioselectivity
1	**Am1**	63:37
2	**Am2**	75:25
3	**Am3**	72:28
4	**Am4**	50:50
5	**Am5**	58:42
6	**Am6**	58:42
7	**Am7**	71:29
8	**Am8**	61:39
9	**Am9**	83:17

group was changed to β-acetoxy or β-carbomethoxy (Table 6, entries 5 and 6), lower selectivity was observed. In the cases of carboxamide derivatives (Table 6, entries 7–9), the levels of enantiodiscrimination observed, seem to indicate that the carboxamide functionality also participates in intramolecular bifurcated H-bonding.

In the course of the above studies on the molecular recognition of amines through their ammonium salts using oxazoline based receptors **23a–f**, it was discovered that these receptor systems, which contain a benzene fluorophore, acted as a fluorescence sensor for ammonium and organoammonium ions.[37] The fluorescence intensity observed when receptor **23b** was titrated with varying concentrations of NH_4^+, increased gradually and reached a plateau when an equimolar amount of NH_4^+ was added. This saturation behaviour indicated the formation of a strong 1:1 host–guest complex, which was not

detected with metal cations such as K^+, Na^+ and Mg^{2+} under the same experimental conditions.

Molecular recognition of carbohydrates

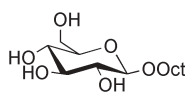
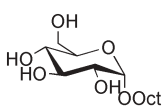
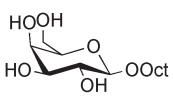
Understanding carbohydrate recognition is one of the key goals of chemical biology.[38] Oligosaccharides are known to mediate cell-cell recognition processes, including the infection of cells by bacteria and viruses, and fulfil various functions in the immune response. Recognition of carbohydrates is also important for their metabolism and for the transport of these highly polar molecules across cell membranes. Systematic studies with synthetic receptors should lead to a better understanding of carbohydrate recognition in biological processes.[39] In 2001, receptor **23e** (Fig. 9) was tested as a C_3-symmetric host for sugars, on the basis that the three oxazoline nitrogens may act as H-bonding acceptors, and the central phenyl group may act as a π-donor for CH–π interactions (Table 7).[40]

Anomer-selective molecular recognition between α and β *n*-octyl-D-glucopyranosides (Table 7, entries 1 and 2), and diastereoisomer-selective discrimination between the β anomer of *n*-octyl-D-glucopyranoside and the β anomer of *n*-octyl-D-galactopyranoside were ascribed to steric interactions and the phenyl substituents on the oxazoline rings. Since hosts (*S*)-**23e** and (*R*)-**23e** gave essentially the same binding constants for each guest (Table 7), it was concluded that the chirality of the host had no effect on the binding.

At the same time, a study on monosaccharide binding to cyclic hexapeptides **26a–c**, each composed of alternating (*S*)-proline and 5-substituted-3-aminobenzoic acid subunits was reported (Fig. 11).[41]

Upfield shifts were observed in the ^{1}H NMR spectra of equimolar mixtures of D-glycoside derivatives and receptors

Table 7 Binding constants between hosts (*S*)-**23e**, (*R*)-**23e** and guests in $CDCl_3$ at 295 K[40]

Entry	Guest	K_{ass}/M^{-1} (*S*)-**23e**	K_{ass}/M^{-1} (*R*)-**23e**
1	 β-*D*-glucoside	1120	1190
2	 α-*D*-glucoside	270	310
3	 β-*D*-galactoside	250	250

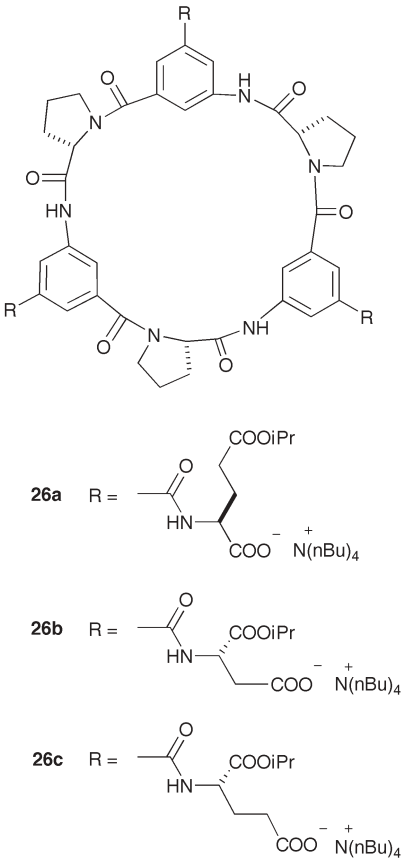


Fig. 11 Cyclopeptides **26a–c** present a cyclic array of carboxylate groups around their cavity.[41]

26a–c compared with the spectra of the individual components. As shown in Table 8, the complexes formed between peptides **26a–c** and all the glycosides tested had binding constants of the same order of magnitude. The selectivity of the receptors with respect to a specific epimer or anomer was only moderate. In general, peptide **26b** formed slightly more stable complexes than the other two receptors, indicating that the orientation of the carboxylate groups in the aspartic acid residues of **26b** seemed to be better suited for monosaccharide binding.

As receptor (*S*,*S*,*S*)-**27** (Fig. 12) had proven successful in the enantioselective recognition of *N*-Cbz-Glu (*N*-carbobenzyloxy-protected glutamic acid), with differences in stability of the diastereomeric complexes of up to 4.6 kJ mol^{-1},[42] the same substrate was tested for inclusion complexation of

Table 8 D-Glycoside association constants of complexes of peptides **26a–c** in 4% CD_3OD–$CDCl_3$ at 298 K[41]

Entry		K_{ass}/M^{-1} **26a**	**26b**	**26c**
1	α-Methylglucopyranoside	420	660	550
2	β-Methylglucopyranoside	550	810	650
3	β-Octylglucopyranoside		560	
4	α-Methylmannopyranoside	450	700	440
5	α-Methylgalactopyranoside	300	790	390
6	β-Methylgalactopyranoside	400	540	430
7	α-Methylribopyranoside	160	290	190

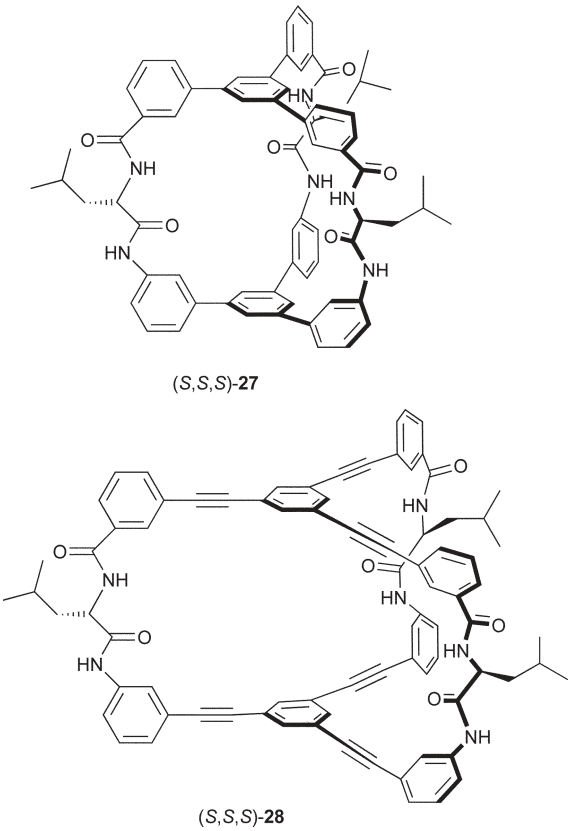


Fig. 12 Extension of the 'floor' and 'ceiling' in (*S*,*S*,*S*)-**27** by acetylene insertion gives a larger cavity in (*S*,*S*,*S*)-**28**.[42,43]

monosaccharides. It transpired that (*S*,*S*,*S*)-**27** was unable to accommodate carbohydrates in its cavity, and so the platforms which make up its 'floor' and 'ceiling' were extended by the introduction of acetylene spacers between the phenyl rings, to give the C_3-symmetric receptor (*S*,*S*,*S*)-**28** (Fig. 12).[43]

In contrast to computational predictions and ^{1}H NMR evidence that (*S*,*S*,*S*)-**28** contained a non-collapsed, open-cavity binding site, the affinities of the receptor towards the monosaccharides tested (Fig. 13) were only modest, with all measured association constants (K_{ass}) below 300 M^{-1}.

Glycoconjugates carrying human oligosaccharide antigens have been synthesised.[44] Orderly interactions between cells or between cells and substrates are essential for the formation of tissues and organs in multicellular systems, and defects in this process could provide a common basis for malformations and oncogenic transformations.[45] In 1991 it was reported that the Lewis^x antigen (the trisaccharide **29** shown in Fig. 14, [Galβ 1→4(Fucα 1→3)GlcNAc]) bound to cell membrane lipids undergoes homophilic association in the presence of calcium

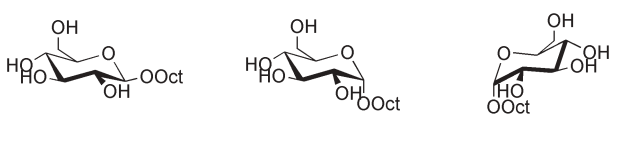


Fig. 13 Monosaccharides investigated as guests in (*S*,*S*,*S*)-**28**.[43]

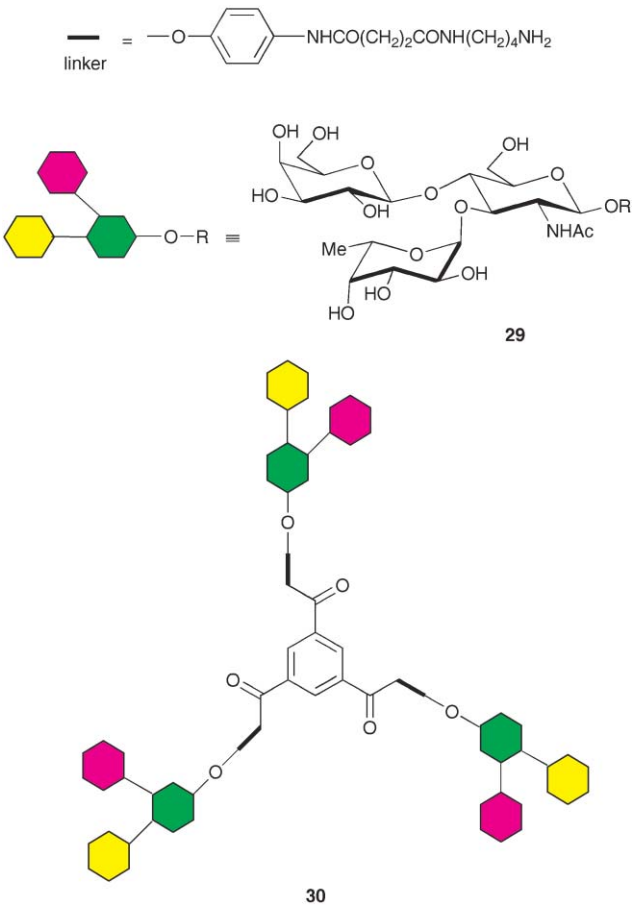


Fig. 14 The Lewis^x trisaccharide **29** and its C_3-symmetric conjugate **30**.[45,46]

ions.[45a] In 2003 a C_3-symmetric carrier of three Lewis^x antigen, **30** (Fig. 14) was designed in the anticipation that a structure of this type would (a) induce enhanced self-association due to multivalent effects, (b) facilitate analysis relative to nonsymmetric models, and (c) show higher water solubility than other glycolipid models because of the three hydrophilic Lewis^x units around the hydrophobic core.[46]

The ^{1}H NMR broadening observed upon treatment of an aqueous solution of **30** with $CaCl_2$ was considered consistent with Ca^{2+}-dependent Lewis^x–Lewis^x associations.[45a]

In 2005 a C_3-symmetric synthetic receptor with high affinity and selectivity in human and equine serum for the clinical anticoagulant heparin was reported (Fig. 15).[47] Heparin concentration and activity is monitored during surgery, and in post-operative therapy, to prevent complications such as haemorrhaging. Heparin is a heterogeneous mixture of diverse chain lengths consisting of repeating copolymers of 1→4-linked iduronic acid and glucosamine residues [Fig. 15(b)]. Because heparin does not consist of a single entity, its concentration must be defined by considering various subunits so that a binding constant can be measured. Receptor **31**, shown in Fig. 15, was designed with a large cavity in order to allow the arms, containing the boronic acid and ammonium groups, to encompass a large surface of oligosaccharide; the affinity is also raised by cooperatively increasing the number of interactions.

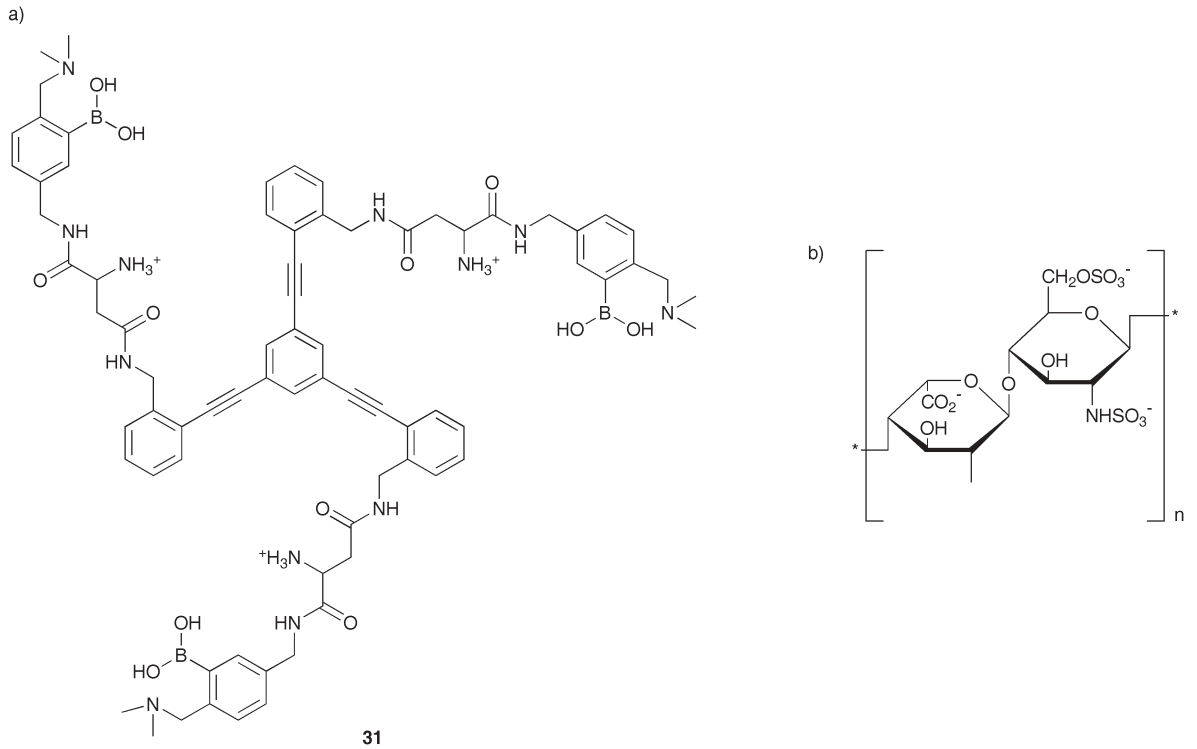


Fig. 15 (a) Heparin receptor **31**; (b) major unit of heparin.[47]

A fluorescent scaffold was incorporated into the design of the receptor in order to provide an indicator assay. The fluorescence emission was subsequently used to generate calibration curves for heparin in serum at clinically relevant dosing levels. These calibration curves allow the heparin concentration in an unknown sample to be determined by comparative analysis of the fluorescence emission.

Cyclic peptides as selective chloride ion receptors

Cyclization of linear peptides or covalent bridging of their constituent amino acids at appropriate places are widely used methods to constrain their conformational degrees of freedom, preorganize their ligand binding elements, and induce desirable structural biases essential for their biological activities, *e.g.* ion transport across membranes,[48] anion binding by directed hydrogen bonding interactions,[49] or host–guest interaction.[50]

In 1996 it was demonstrated that α-aminoxy acids can induce an eight-membered-ring intramolecular hydrogen bond (the N–O turn) when inserted between adjacent residues in peptides, a result of the repulsion of the lone-pairs of electrons of the nitrogen and oxygen atoms of the aminoxy group (Fig. 16).[51]

A few years later, it was predicted that cyclic hexapeptide **32** (Fig. 17) should fold into consecutive N–O turns with strong hydrogen bonds and adopt a C_3-symmetric and bracelet-like conformation.[52] Given its small pore size (d = 3.22 Å), hexapeptide **32** was expected to bind small ions. Its carbonyl groups may coordinate with cations, whereas the amide NH's may form intermolecular hydrogen bonds with anions. Thus, both cations and anions were screened for possible complexation. Interestingly, hexapeptide **32** was found to bind halide ions but not alkali metal ions. The affinity for halide ions followed the order $Cl^- \gg F^- \gg Br^-$, and the authors suggested that the selectivity was mainly governed by size complementarity rather than hydrogen-bonding interactions.

Recently, the novel cyclic hexapeptide **33** (Fig. 17), which consists of alternating D-α-amino and D-α-aminoxy acids, was found to display enhanced binding towards anions, whilst maintaining good selectivity towards the chloride ion. (K_{ass} = 15 000 M^{-1} for hexapeptide **33**, K_{ass} = 11880 M^{-1} for hexapeptide **32**).[53] The backbone of **33**, is thought to be more flexible than that of cyclic peptide **32**, which is made up solely of (*R*,*S*)-α-aminoxy acid residues, and thus adopts consecutive N–O turns.

In 2004 novel optically active cyclooligomers **34a–c** (Fig. 18), were synthesised and tested for their anion binding properties, and as antimicrobial agents against some Gram-positive and Gram-negative bacteria.[54]

Examination of receptor **34c** revealed the highest association constant for tetra-*n*-butylammonium chloride (TBACl) (Table 9, entry 2), a relatively high affinity for tetra-*n*-butylammonium acetate (TBAA) (Table 9, entry 1), and a

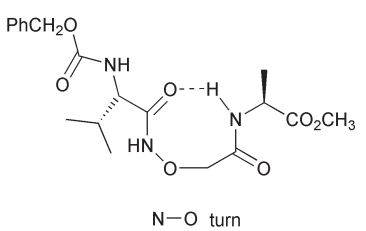
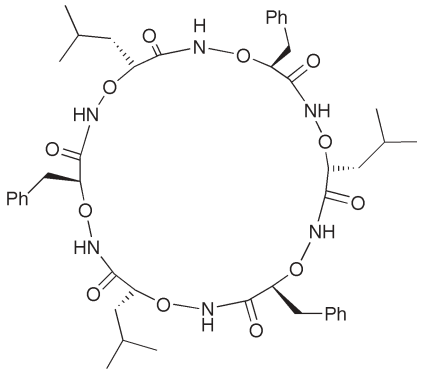
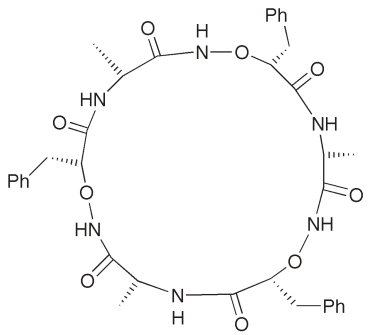


Fig. 16 Insertion of an α-aminoxy acid between adjacent amino acids leads to a strong eight-membered-ring hydrogen bond (N–O turn).[51]



32

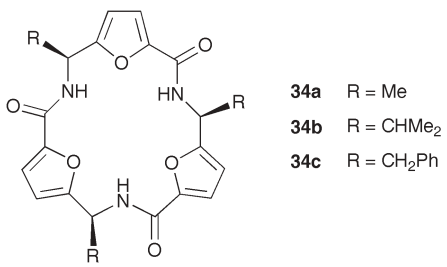


33

Fig. 17 The halide ions receptor **32** and the selective chloride ion receptor **33**.[52,53]

weak binding with the corresponding iodide (TBAI), probably due to its size (Table 9, entry 3). In the polar solvent DMSO-d_6, a moderate association constant was measured for TBA[Ac-(D-Ala)$_2$], (Table 9, entry 4), in spite of the competition from solvent molecules also for the H-bonding sites.

Similar studies with receptor **34b** and various anions did not reveal any binding, suggesting that its binding site was inaccessible due to the presence of bulky *iso*-propyl groups. The strong binding of **34c** with acetate and chloride (Table 9, entries 1 and 2) encouraged the authors to test these cyclic peptides for their antimicrobial activities. Compounds **34b** and **34c** showed excellent activity against *Escherichia coli* and displayed comparable activities against Gram-positive bacteria like *Bacillus cereus*. Cyclopeptide **34a** showed very mild activity against fungi like *Candida albicans*, in contrast to **34b** and **34c**, which did not display any antifungal activity.



34a R = Me
34b R = $CHMe_2$
34c R = CH_2Ph

Fig. 18 Peptidomimetic cyclic trimers **34a–c**.[54]

Table 9 Association constants (K_{ass}/M^{-1}) of **34c** with different TBA salts[54]

Entry	Salt	log K_{ass}/M^{-1}
1	TBAA[a]	5.50
2	TBACl[a]	8.46
3	TBAl[a]	0.47
4	TBA[Ac$^-$(D-Ala)$_2$][b]	1.78

[a] CD_3CN. [b] DMSO-d_6.

Nanoarchitecture

The development of strategies for synthesizing nanomolecules, both supramolecular and macromolecular, is one of the key challenges in chemistry at present. C_3-Symmetrical molecules readily adopt interesting conformations resembling for example helices or propellers, and they thus represent attractive architectural components in this area.

Supramolecular constructs

Self-assembly has created new possibilities in both biology and materials science because it facilitates the rapid formation of nanosized, complex architectures, that adopt stable and compact conformations despite their non-covalent, reversible nature.[55] Amplification of chirality is a well-known phenomenon in classical covalent polymers.[56] Pioneering studies by Green and co-workers, using poly(alkyl isocyanates),[57] distinguished two effects that influence the amplification of chirality and referred to them as the ''sergeants-and-soldiers'' principle and the ''majority-rules'' effect.[58] The sergeants-and-soldiers principle describes the control of the movements of large numbers of cooperative achiral units (the soldiers) by a few chiral units (the sergeants), whereas in the majority-rules effect, a slight excess of one enantiomer leads to a strong bias towards the helical sense preferred by the enantiomer that is present in excess.

In 1997, stereochemical features of associated disk-shaped molecules in a dilute alkane solution (10^{-4}–10^{-6} mol L^{-1}) were studied.[59] Extended-core disk-shaped molecules have attracted interest because they display liquid-crystalline properties over a broad temperature range, due to the stability of the molecular stacks being maintained by many secondary interactions.[60]

Attempts to apply the sergeant-and-soldiers principle to mixtures of **35a** and **35b** in hexane were described. On introducing on average one molecule of chiral **35a** per eighty molecules of achiral **35b**, the chiral component (the sergeant) dictated the helical sense of the total stack (of soldiers). To explain the cooperative response of compound **35b**, it was proposed that C_3-symmetrical molecules of type **35** adopt a propeller-like conformation in which the bipyridine wedges are tilted with respect to the central trimesic core.[61] In hexane, molecules **35** aggregate in columnar stacks, and the packing between sequential molecules will be optimal when all bipyridine wedges are tilted in the same direction. This results in a preferred stable chiral conformation of each disk-shaped molecule (Fig. 19).

In 2002 a library of twelve C_3-symmetrical disks (Fig. 20), containing central amides (**35a**, **36b–f**) or ureas (**37a–f**), was

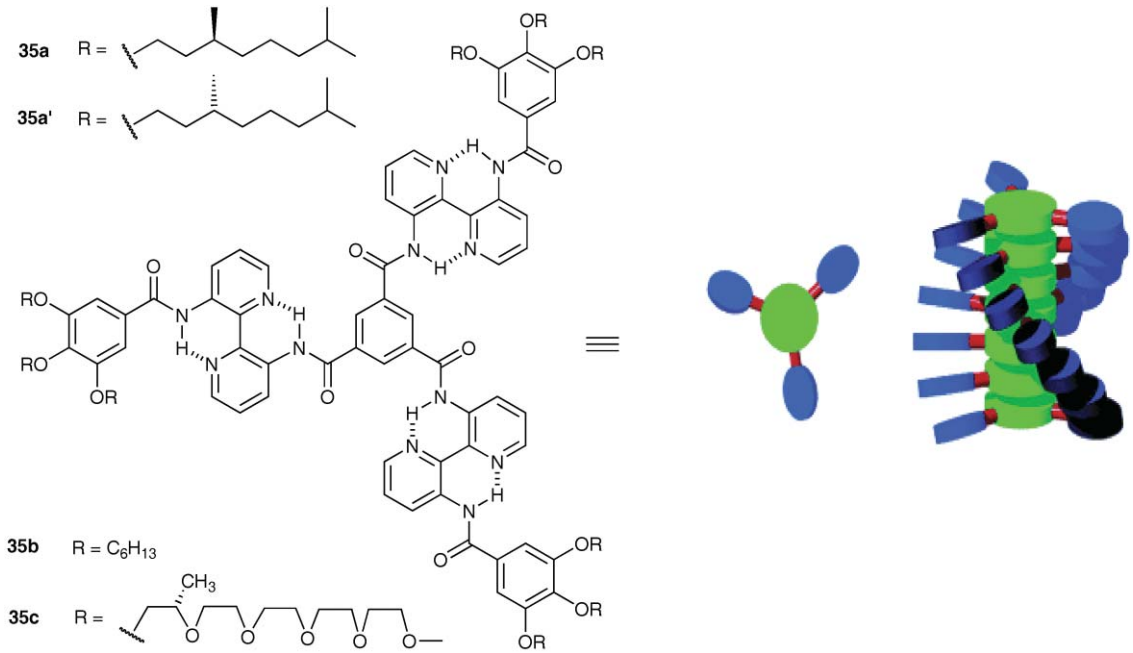


Fig. 19 Self-assembled helical aggregates of C_3-symmetrical disk-shaped molecules.[59]

created in order to study the exact nature and the relative importance of secondary interactions in supramolecular aggregation phenomena, the ultimate aim being the design of new organogelators and helical fibres.[62] In an organogel, the liquid is prevented from flowing by continuous, three dimensional, entangled networks of fibres of low molecular weight organogelators,[63] held together solely by non-covalent forces, including hydrogen bonding and π–π stacking. To clarify the features governing self-assembly in apolar media, several π–π interacting groups and hydrogen bonding units were combined to afford a series of C_3-symmetrical disks (Fig. 20). The π–π interactions were increased by replacing 'small' alkyl tails (**36e**, **36f**, **37e**, **37f**) by 'medium' gallic groups (**36c**, **36d**, **37c**, **37d**) or 'large' bipyridinyl groups (**35a**, **36b**, **37a**, **37b**). The intermolecular hydrogen bonding amide moieties in **35a** and **36b–f** were replaced by urea ones in **37a–f**. Because a urea has two hydrogens to form hydrogen bonds, whereas an amide has only one, the urea unit was considered stronger and more rigid.

The presence of elongated, columnar stacks may lead to the formation of macroscopic organogels. In this study, gels were formed on dissolving the compounds in an apolar solvent, heating and then cooling. If the reaction vessel could be inverted without product movement, the substance was judged a gel. Minimal gel concentrations were determined by this method (the lowest value measured was 1.2 mg mL^{-1} for **37f**) and it was possible to see micrometre long strands consisting of thousands of molecules (2 μm for **37a**), thus revealing the substantial cumulative effect of the hydrogen bonding interactions. Furthermore, both 'small' and 'large' amide disks made from a mixture of **36e** and **36f** or a mixture of **35a** and **36b**, showed a strong amplification of chirality, with one chiral molecule of **36e** or **35a** capable of organizing as many as 200 and 80 achiral molecules of **36f** or **36b**, respectively, in either a right- or a left-handed helical stack. In mixtures of the 'large' ureas **37a** and **37b** no "sergeants-and-soldiers" effect was observed. Upon mixing solutions of the achiral 'small' urea disk **37f** and the chiral 'small' urea disk **37e**, an initial aggregate was formed just above room temperature (30–40 °C), but it proved to be unstable.

In 2005 it was demonstrated that aggregates of C_3-discotic molecules **35a** and **35b** (Fig. 19), previously shown to be governed by the sergeant-and-soldiers principle,[59] also displayed a majority-rules effect.[58,64] A consequence of the propeller-shape of these molecules is that stacking inevitably leads to a helical superstructure and, if homochiral peripheral information is present, a preferred helical sense will result. If contradictory chiral information is present at the periphery in small amounts, as is the case in the majority-rules experiments, this minor enantiomer is unlikely to strongly affect the helicity of the aggregate and it will act in accordance with the helical sense preferred by the majority.

In 2004 the self-assembly characteristics of a new class of hexasubstituted aromatics that form columnar superstructures were reviewed.[65a] These structures consist of a central benzene ring that supports three amides in a 1,3,5-relationship with substituents other than hydrogen between them (Fig. 21, **38a–c** and **39a–c**).

The principle behind the design of the first members of this new class of molecules (**38a–c**) was to probe whether substituents in the 2,4,6-positions would force the 1,3,5-triamides into conformations favorable for intermolecular hydrogen bonding. Indeed, energy minimized dimeric models showed that to relieve steric congestion, the amides twist out of the aromatic plane, thus allowing three intermolecular hydrogen bonds to occur, and hence modulating the distance between adjacent benzene rings. Self-assembly through a combination of hydrogen bonds and π–π interactions provided

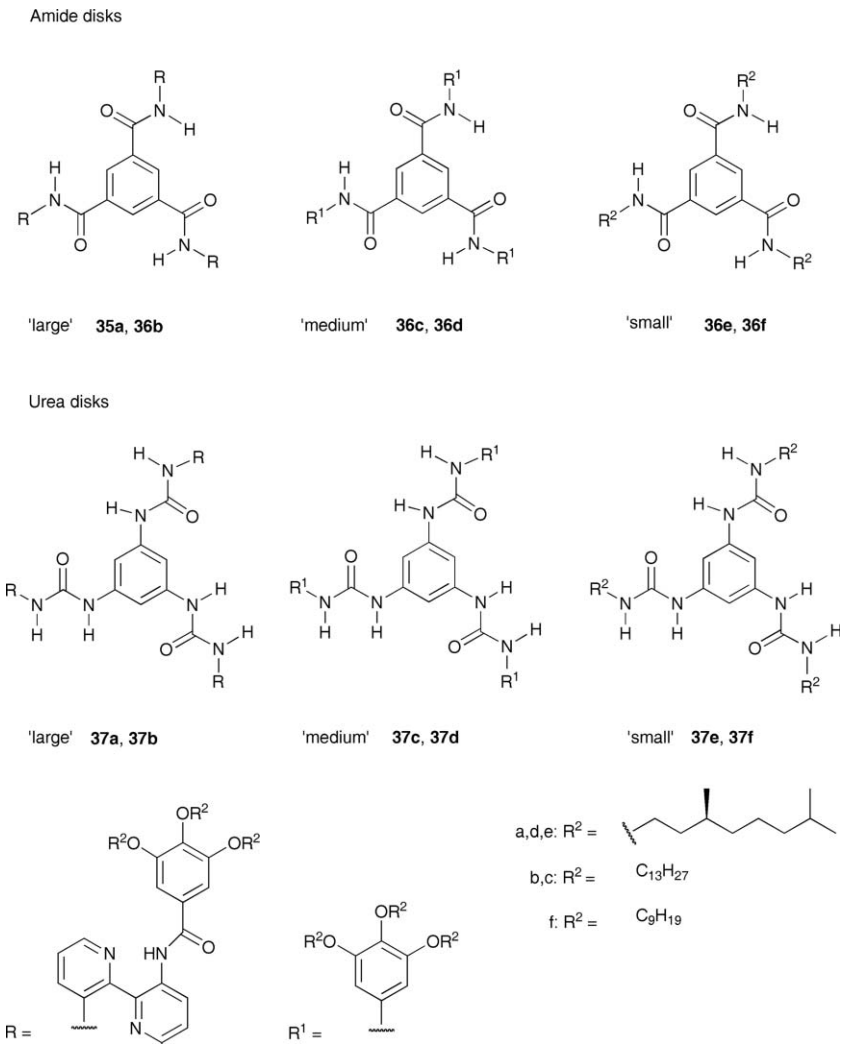


Fig. 20 A library of C_3-symmetrical disks containing central amides (**35a**, **36b–f**) or ureas (**37a–f**).[62]

arrays of stacked columns, which are prototypes of molecular-scale wires that have an insulating hydrocarbon sheath surrounding a conductive aromatic core. For the first series of molecules, **38a–c**, the assembly process was found to be dominated by the size and polarity of the amide side chains.

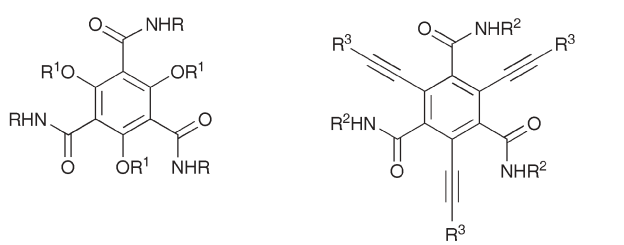


Fig. 21 Crowded arenes **38** and **39** that self-assemble into columns.[65]

For example when the amide substituents are relatively small, such as the phenylethyl substituents of **38a**, the material assembles into extremely regular cylinders that are hexagonally packed into millimetre scale domains. When the phenylethyl side chain is exchanged for CH_2COO*t*Bu (**38b**, Fig. 21), however, the material is no longer able to stack into perfect cylinders, giving rise to a distorted hexagonal lattice. Although the series **39a–c** has been less well studied, it appears that the substituents on the side chain of **39** have less influence on the mesomorphism and each of the derivatives shown in Fig. 21, **39a–c**, displays a hexagonal arrangement of cylinders. A second interesting feature of the molecules shown in Fig. 21 is that each of the subunits has a permanent dipole moment, whose direction is perpendicular to the ring plane. Therefore, as the molecules stack, the dipole could sum to yield columns that have a macroscopic dipole moment. It has also been shown that chiral centres incorporated into the amide side chains (Fig. 21, **38c** and **39c**) control the hierarchy of ordering in the stack. First the chiral centres in the side chains organize the columns into helices, then these chiral columns further stack in concentrated solutions to create superhelical arrangements.

Macromolecular constructs

Research in dendrimers is an expanding area at the interface between conventional organic chemistry and polymer science.[66] Chiral dendrimers offer the possibility of investigating the impact of chirality on macromolecular systems and providing valuable data on the relationship between chirality at molecular and macroscopic levels.[67] In addition, special attention has been focused on the development of novel and efficient catalytically active hyperbranched macromolecules.[66d,68] Dendritic catalysts are often proposed to fill the gap between homogeneous and heterogeneous catalysts. They combine excellent solubility in common organic solvents (an advantage of homogeneous catalysts) with easy removal from the reaction media (an advantage of heterogeneous catalysts) by membrane and ultrafiltration techniques.[68a] Few chiral dendrimers with overall C_3 symmetry were reviewed in 1998,[1,69] as it was unclear whether or not the overall C_3 symmetry of the macromolecules was of any importance in the microenvironments experienced by a guest molecule or a substrate bound to a catalytically active site.

In 2004 chiral polyaromatic amide dendrimers bearing a C_3-symmetric core derived from (*S*)-serine and (*R*)-serine (**40b**, **41c** and **41b**, **41c**, respectively, Fig. 22) and their chiral properties were investigated.[70]

A decrease in the specific rotation was observed on passing from the core systems **40a** and **41a** to the first (**40b**, **41b**) and second (**40c**, **41c**) generations of the corresponding dendrimers (Table 10). Considering that the solution concentration used in the calculation of the specific rotation $[\alpha]_D^{20}$ is expressed in g per 100 mL, these results can be explained by the decreasing number of stereogenic centres present in the progression from solutions of the core molecules **40a** and **41a** to solutions of the same concentration of corresponding first and second generation dendrimers. Therefore, the determination of molar rotation values $[\Phi]_D^{20}$ was calculated as this parameter is normalized for the number of moles of the compound in solution. As shown in Table 10, a decrease in the molar rotation values was observed on passing from **40a** and **41a** to the first generation dendrimers **40b** and **41b**. However, when the molar rotations of the second generation dendrimers **40c** and **41c** were analysed, these values not only increased with respect to the core systems **40a** and **41a**, but they almost doubled with respect to the values obtained for the smaller dendritic systems. These results were interpreted as an indication of the presence of chiral substructures within the dendritic macromolecule induced by the stereogenic centres at the core.

Table 10 Specific rotation and molar rotation values of the chiral core molecules (**40a**, **41a**) and of the corresponding first (**40b**, **41b**) and second generation dendrimers (**40c**, **41c**)[70a]

Entry	Compound	*c* in $CHCl_3$	$[\alpha]_D^{20}$	$[\Phi]_D^{20}$
1	**40a**	1.03	−44.6	−2322.9
2	**41a**	1.05	+45.7	+2343.6
3	**40b**	1.05	−11.9	−2040.1
4	**41b**	1.01	+11.7	+2082.9
5	**40c**	1.05	−10.8	−3826.4
6	**41c**	1.02	+10.4	+3811.8

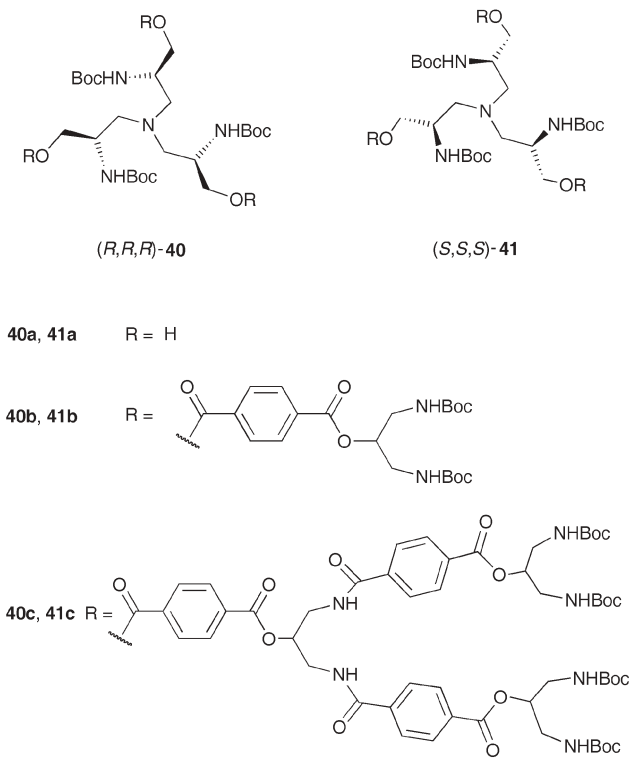
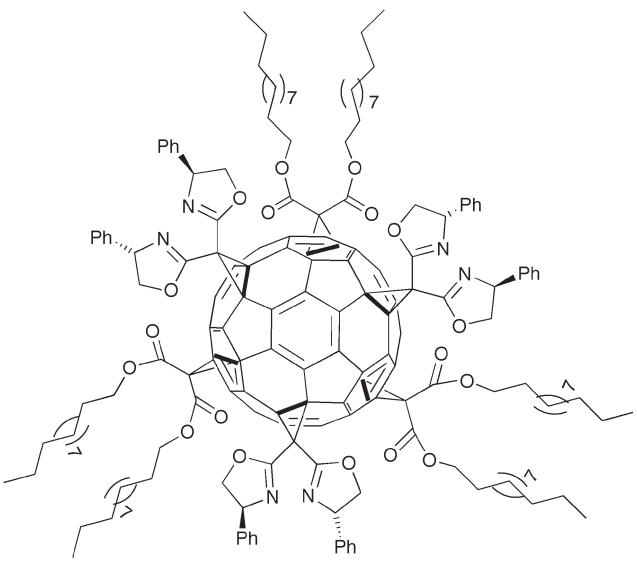


Fig. 22 C_3-symmetric core unit derived from (*S*)-serine [(*R*,*R*,*R*)-**40a**)] and from (*R*)-serine [(*S*,*S*,*S*)-**41a**)]. First generation **40b**, **41b**, and second generation **40c**, **41c** dendrimers.[70]

Buckminsterfullerene, C_{60}, has been used as a spherical building block for the construction of globular dendrimers[71] and lipofullerenes[72] (Fig. 23 and 24). Enantiomerically pure C_3-symmetrical lipofullerenes **42** were reported in 2000 as potential intercalation components of lipid membranes.[73]

The related C_3-symmetric dendritic hexakis-adduct **43** and some analogues have been tested as chiral catalysts



42

Fig. 23 C_3-symmetric fullerene **42**.[73]

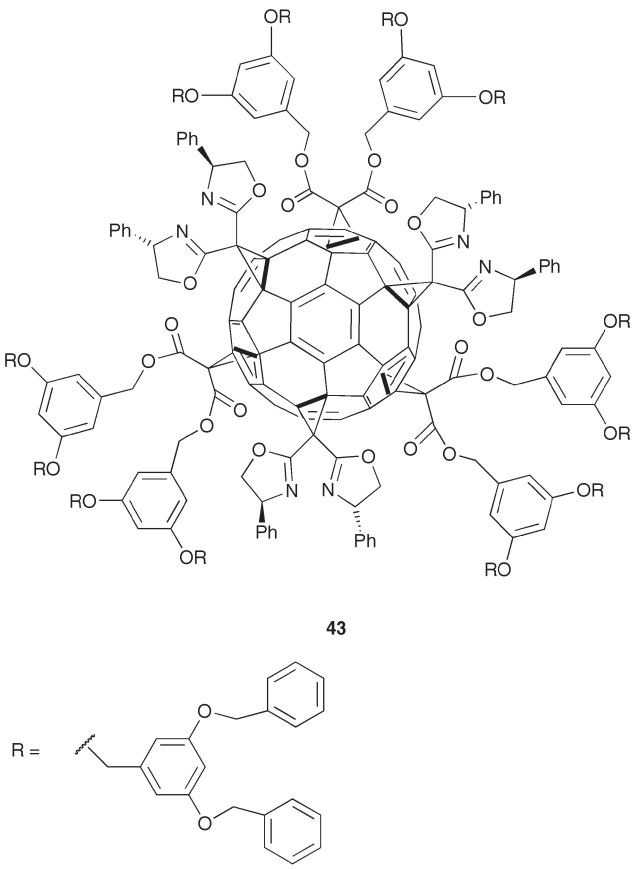
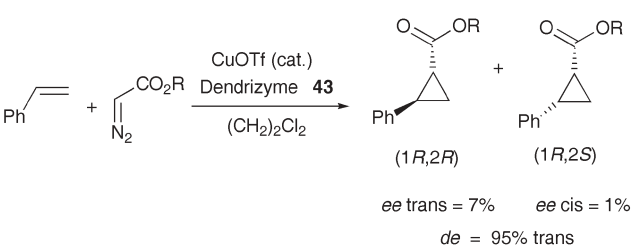


Fig. 24 C_3-symmetric fullerene dendrimer **43**.[73]

(dendrizymes) in the cyclopropanation of styrene with ethyl diazoacetate (Scheme 9).[73,74]

Although very low enantioselectivities were observed, a pronounced diastereoselectivity in favour of the *trans* products (de = 95%) was reported.

In 1999 an interesting investigation of the chiroptical properties of optically active C_3-symmetric poly(methyl methacrylates) (PMMAs) **44** (Fig. 25) was undertaken.[75] By the appropriate choice of a chiral initiator [(+)- or (−)-2,3-dimethoxy-1,4-bis(dimethylamino)butane **45**, (+)- or (−)-DDB], PMMAs **44** with either positive or negative rotation could be obtained.[76] Enhancement (by a factor of 5) of optical rotation values was observed upon addition of achiral PMMAs to the optically active polymer **44**. In the C_3-symmetrical star-shaped polymer **44** all three chains adopt the same helicity sense because they all have the same absolute configuration.



Scheme 9 Cyclopropanation of styrene using the C_3-symmetric C_{60} dendrimer **43**.[73]

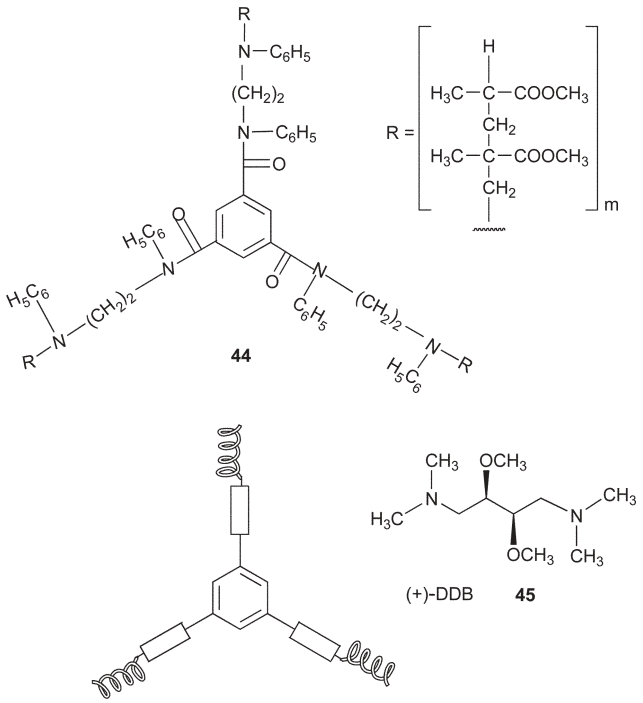


Fig. 25 The C_3-symmetrical star-shaped polymer **44**, and chiral catalyst (+)-**45**.[75,76]

Conclusions

In the area of catalysis, it is apparent that C_3-symmetrical ligands have been assayed in several areas of molecular catalysis since 1998, including cyclopropanation, allylic oxidation, alkynylation of aldehydes and allylic alkylation. The reactions included here were selected on the basis of their relative high selectivities, and the merely modest to good enantioselectivities encountered (typically 70–90%) suggest that C_3 symmetry has yet to deliver a so-called 'privileged' ligand class. In view of the vast number of C_2-symmetric ligands and the range of substrates surveyed in the identification of maybe a dozen 'privileged' ligand types, this situation is almost certainly due to lack of research effort to date, and should be viewed as a continuing challenge. The recent use of C_3-symmetric ligands in lactide, ethene, and 1-hexene polymerization studies is an important development that has provided very promising results, and the concept of using them to mimic symmetry elements found in some biocatalysts is both elegant and exciting. The seemingly exotic combination of C_3 symmetry and axial chirality in ligand **14** and catalyst **15**, which gives enantioselectivities of up to 98% for the ethylation of benzaldehyde, perhaps provides a glimpse of the future.

In the period reviewed, excellent results in the field of molecular recognition have been achieved with the C_3-symmetric tripodal oxazoline receptors **23**. The spectacular selective recognition of ammonium over potassium ions has been followed with promising results obtained using alkylammonium ions regarded as models for dopamine and γ-aminobutyric acid, and ammonium ions derived from amines with chiral β centres. In view of the importance of carbohydrates in biological recognition processes, carbohydrate recognition has understandably received considerable attention and generated

some extremely encouraging results, particularly in the area of heparin analysis. Of note for the future is the concept of using C_3-symmetric carriers to mimic cell membranes. A C_3-symmetric carrier of three carbohydrates such as **30** is trivalent and thus more likely to self-associate than a conventional monovalent structure. Moreover, effects arising from symmetrical carriers of this nature should be easier to analyse, and in this particular case, the presence of three hydrophilic groups around the hydrophobic core gives good water solubility relative to other glycolipid models.

The construction of nanomolecules has claimed the attention of many chemists in recent years. C_3-Symmetrical molecules are attractive insomuch as they readily form inter alia helical and propellerlike conformations, and nanostructures based on C_3 symmetry and chirality have been used in organogels, fibres, components of lipid membranes, and dendrimers to date. Although the combination of C_3 symmetry and chirality has generated some stunning structures, the potential of these systems is yet to be fully determined, and there is a need for more structure-reactivity studies. Thus although the first catalytic assay of the C_3-symmetric fullerene dendrimer **43** gave very poor enantioselectivity, it is envisaged that a greater understanding of the factors that control reactions on C_{60} cores and other nanostructures, a task that may be rendered easier by the use of C_3 symmetry, will underpin their evolution towards highly selective catalyst supports in the years ahead.

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