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Mannich and *O*-Alkylation Reactions of Tetraalkoxyresorcin[4]arenes – The Use of Some Products in Ligand-Assisted Reactions

Benjamin R. Buckley,[a] Jonathan Y. Boxhall,[a] Philip C. Bulman Page,[a] Yohan Chan,[a] Mark R. J. Elsegood,[a] Harry Heaney,*[a] Kathryn E. Holmes,[a] Matthew J. McIldowie,[b] Vickie McKee,[a] Matthew J. McGrath,[a] Mauro Mocerino,[b] Andrew M. Poulton,[a] Edward P. Sampler,[a] Brian W. Skelton,[c] and Allan H. White[c]

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The measurement of the pK_a of racemic tetramethoxyresorcin[4]arenes explains the failure to obtain good yields in attempted Mannich reactions of these substrates under classical reaction conditions. The failure is related to the lack of adequate concentrations of the iminium ions that results from the reduced acid strength of tetraalkoxyresorcin[4]arenes compared with that of the parent octahydroxyresorcin[4]arenes. However, the preparation of a series of Mannich bases derived from racemic tetraalkoxyresorcin[4]arenes was accomplished under microwave-assisted aprotic reaction conditions and the use of preformed iminium ion intermediates. When the reactions were carried out with the use of chiral bis(aminol) ethers, mixtures of diastereomers were obtained that could be separated by flash chromatography. The absolute configurations of the enantiomerically pure tetrabenzoxazine derivatives were established in some cases by X-ray crystallographic analysis and by a comparison of the nuclear magnetic resonance spectroscopic data. The alkylation of racemic tetramethoxyresorcin[4]arenes was achieved with the use of an excess of 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide in acetonitrile containing potassium carbonate. Enantioselective ligand-assisted reactions of aromatic aldehydes are also reported with the use of dialkylzinc reagents both in the absence and in the presence of terminal alkynes.

Introduction

Calixarenes provide a diverse range of molecular assemblies that have been used for a variety of purposes, and their chemistry is widely studied and continues to generate considerable interest.[1] The availability of cyclic tetramers that can be prepared in high yields by the acid-catalyzed interaction of aldehydes with resorcinol has made the study of resorcin[4]arenes **1** particularly attractive.[2] Many reactions of resorcinarenes have been carried out with mild electrophiles.[3] Mannich reactions are such reactions and have been studied widely; they include the use of secondary amines,[4] including aza-crown secondary amines,[4e]which have been used under mild classical conditions with aqueous formaldehyde at an early stage[4a–4d] and can lead to tetra(dialkylaminomethyl) derivatives.[4k–4o] Oxazolidines derived from secondary β-amino alcohols[4f] and aminal bis(dimethylamino)methane[4g] have been used as the equivalents of secondary amines and formaldehyde in Mannich reactions. In some cases, it was recognized that the resorcinarenes were strong enough acids as to not require the addition of a protic acid. Mannich reactions that can lead to partial aminoalkylation of resorcin[4]arenes have also been reported with the use of diisopropylamine as the secondary amine.[5] Mannich reactions involving primary amines and formaldehyde have also been widely used and lead to tetrabenzoxazine derivatives.[4a,6] Dissymmetry, generated by the unsymmetrical substitution of calixarenes, is related to the nonplanar structures of the parent compounds;[7a] it was also recognized that a number of chiral calixarene conformers are thermally racemized by processes involving "through-the-annulus rotation".[7b] The alkyl group that is present in resorcinarenes, for example compound **2**, precludes "through-the-annulus rotation". The first example of the optical resolution of a chiral calixarene used chiral liquid chromatography.[7c] Considerable effort has been devoted to the synthesis of inherently chiral calixarenes, some of which are C_4 symmetric axially chiral calixarenes. However, the majority of published examples describe products that have been obtained as racemates and

[a] Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK
E-mail: h.heaney@lboro.ac.uk
[b] Department of Applied Chemistry, Curtin University of Technology,
GPO Box U 1987, Perth WA 6845, Australia
[c] Department of Chemistry, University of Western Australia, Crawley WA 6009, Australia
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have defied resolution except by using chiral HPLC techniques.[8] This has inevitably only allowed for a very small amount of optically pure material to be available for use in other studies.[9] An exception to this problem was provided by studies carried out by us,[9a] and others,[9b,9c] with the use of optically pure (α-methylbenzyl)amines and formaldehyde. This reaction resulted in the highly diastereoselective formation of tetrabenzoxazines derived from a number of octahydroxyresorcin[4]arenes, for example **2a**. Methylation of the residual phenolic hydroxy groups was carried out by deprotonation with *n*-butyllithium in tetrahydrofuran at –78 °C followed by the reaction with methyl triflate in order to preclude diastereomerization and the loss of axial chirality after ring opening of the 1,3-oxazine ring and removal of the chiral auxiliary.[10]

Results and Discussion

In order to avoid confusion in publications in this area we believe that it will be valuable to define the direction in which the groups are found around the periphery of the upper polar rim of resorcinarenes by reference to a modification of the Cahn–Ingold–Prelog rules; their seminal paper discussed, inter alia, axial chirality and mentioned the use of the *M* and *P* notation.[11a] Prelog and his coworkers also discussed the problem of specification of the axial chirality of C_2 and C_{2v} symmetric molecules, specifically with respect to axially chiral and pseudochiral biphenyl derivatives.[11b] They also showed that a new kind of stereoisomerism, cycloenantiomerism and cyclodiastereomerism can be considered when the two directions in a cyclic structure can be distinguished from each other, and they used the (*R*)- and (*S*)-designations in this connection.[11c] They prepared and considered cyclohexaalanyls and cyclodiglycyltetraalanyl in order to exemplify this concept.[11d] The nomenclature and vocabulary of organic stereochemistry was recently considered in more detail and a preference for the use of the (*P*)/(*M*) convention[12a,12b] was strongly recommended[12c] rather than the (*aR*)/(*aS*) descriptors that are regarded as obsolete. We therefore propose to use in this and subsequent papers the (*P*)/(*M*) notation to define the axis of chirality of C_n symmetric resorcin[*n*]arenes that is present in inherently chiral resorcin[*n*]arene derivatives. Thus, a clockwise priority of the sequence of groups that are attached to the phenolic groups, viewed from a position *above* the polar rim in the benzenoid rings, is defined to have *P* axial chirality as in compound (*P*,*R*,*S*)-**2a**, shown in Figure 1. The designations are defined in the following sequence: axial chirality (*P*), chiral auxiliary (*R*) and the interring stereogenic centre (*S*). In a number of other papers in this area, C_4 symmetric compounds are frequently shown in an abbrevi-

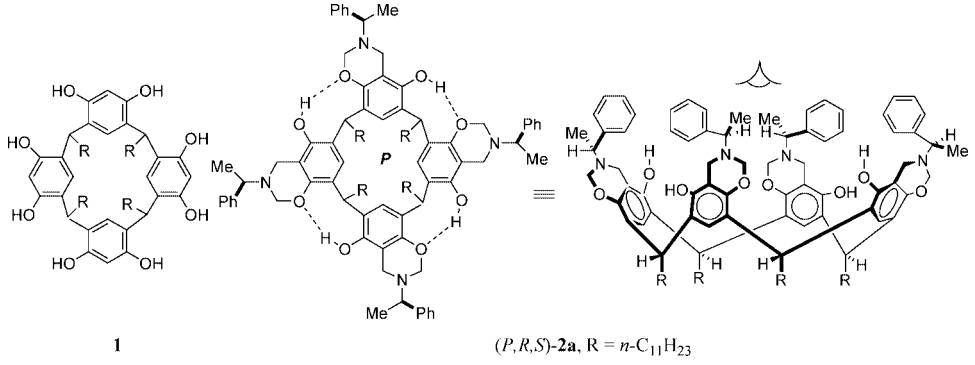
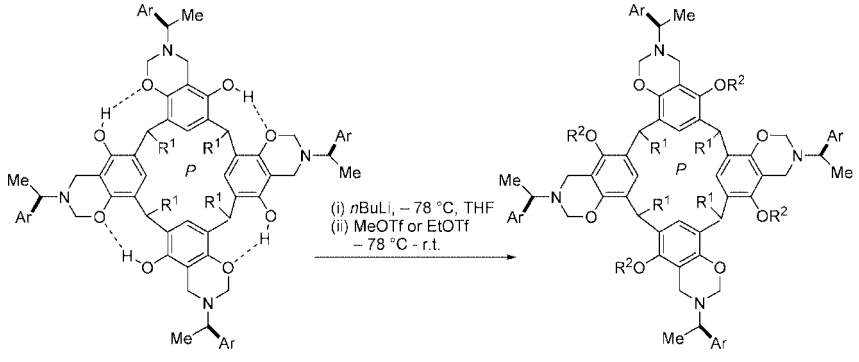
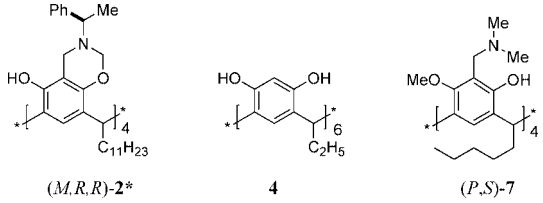


Figure 1. Representation of resorcin[4]arenes, including axial stereochemistry.



Scheme 1. Alkylation of diastereomerically pure tetrabenzoxazines.

ated form [e.g. (*M*,*R*,*R*)-**2***], which is a diastereomer of **2a**, shown in Figure 2, where the benzenoid ring is viewed from *within* the cavity: this places the hydrogen atom at the methine interring position away from the observer for pseudoaxial R groups. In practice, it is found that substituents at the interring stereogenic centre are pendant and take a pseudoaxial orientation. It is not always the case that the polar rim is depicted above the benzenoid rings and sometimes, in abbreviated structures, the rings are viewed from outside the cavity of the resorcin[*n*]arene. In our opinion, these alternative representations may have led to confusion in some cases.

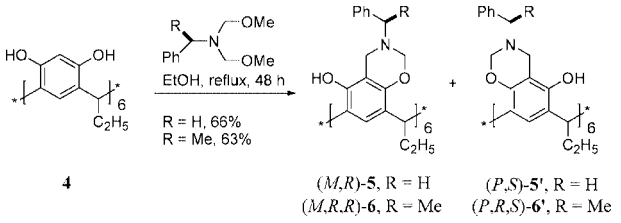


(*M*,*R*,*R*)-**2*** **4** (*P*,*S*)-**7**

Figure 2. Abbreviated representation of resorcin[4]- and resorcin[6]arenes.

Like other workers who used *p*-substituted (α-methylbenzyl)amines,[9e] we found that resorcinarene **1** (R = $C_{11}H_{23}$) also gave a single diastereomer in good yield in the Mannich reaction of formaldehyde and (*R*)-(+)-4-methoxy-(α-methylbenzyl)amine. However, we were disappointed to find that the preparation of enantiomerically pure derivatives in high yields by the alkylation of the residual phenolic hydroxy groups in the diastereomerically pure tetrabenzoxazine derivatives, for example **2a** and **2b** (Scheme 1), has been limited to methylation and ethylation. Some authors have assumed that enantiomerically pure resorcinarene derivatives are only accessible on a 100 mg scale. It is worth noting that enantiomerically pure resorcinarene derivatives such as **3a**, **3b** and **3d** can be prepared on a multigram scale. For example, with the use of a high-speed stirrer, we were able to deprotonate and then methylate resorcinarene **2b** (18 g) and obtain derivative **3b** in 94% yield. We have also investigated the Mannich reactions of resorcin[6]arene **4** with *N*,*N*-bis(methoxymethyl)-*N*-benzylamine and *N*,*N*-bis(methoxymethyl)-*N*-(α-methylbenzyl)amine but found that, as expected, the former reaction gave a racemic mixture (**5** and **5′**), whereas in the latter reaction, a 1:1 mixture of diastereomers **6** and **6′** was produced, as shown in Scheme 2. We found that the reactions of bis(aminol) ethers provided significantly higher yields of products than the reactions carried out with the corresponding amine together with paraformaldehyde and a catalytic amount of sodium hydroxide.

In addition, we have been unable to methylate the four residual hydroxy groups in the racemic tetrabenzoxazine that is obtained when methylamine is used as the primary amine; presumably, this is a result of the ease with which the benzoxazine nitrogen atoms can undergo quaternization. Axially chiral nonracemic compound **7** was available from our earlier study,[10] and large quantities of racemic resorcinarene derivatives, such as **7**, were required for other

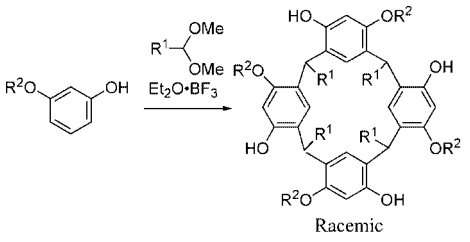


4 (*M*,*R*)-**5**, R = H (*M*,*R*,*R*)-**6**, R = Me (*P*,*S*)-**5'**, R = H (*P*,*R*,*S*)-**6'**, R = Me

Scheme 2. Mannich reactions of a resorcin[6]arene with the use of bis(aminol) ethers.

studies. The report of the formation of racemic tetramethoxyresorcin[4]arenes by the boron trifluoride catalyzed reaction of octanal or dodecanal with resorcinol monomethyl ether[13] provided, in principle, an alternative and shorter route to our previously reported chiral resorcin[4]arene derivatives and the racemate of **7**, as well as access via the additional diastereomers to a pair of enantiomers from a single initial reaction. Reactions of iminium salts with arenes that possess enhanced nucleophilicity such as phenols are well-known.[14] It appeared possible that the racemate of **7** could also be prepared by a Mannich reaction with the use of dimethylamine and formaldehyde. The possibility that a range of other tetraalkoxyresorcin[4]arene derivatives could be accessed also provided an opportunity to prepare other axially chiral resorcin[4]arene derivatives on a multigram scale, for example from 3-benzyloxyphenol,[15] 3-isopropyloxyphenol[16] and 3-*cyclo*-pentyloxyphenol.[17] We have recently shown[17] that a wide range of 3-alkoxyphenol derivatives (**8**) are readily available from 3-iodophenol and the appropriate alcohols with copper(I) iodide-9,10-phenanthroline as a catalyst,[18] or from resorcinol monobenzoate and the appropriate alcohols in Mitsunobu reactions[19] followed by base-catalyzed alcoholysis. Racemic tetraalkoxyresorcin[4]arenes **9a**–**9e** were prepared, in good to excellent yields, with the use of a previously reported protocol,[13] or a modification, as shown in Scheme 3, by the reaction of boron trifluoride (200 mol-%) with 1,1-dimethoxyalkanes or aldehydes and 3-alkoxyphenol derivatives **8a**–**8d**.[20]

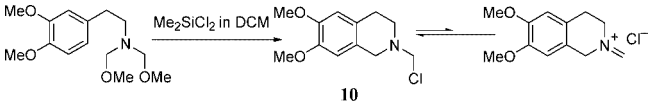
The large number of Mannich reactions that have been reported for octahydroxyresorcin[4]arenes that afford products in high yields under mild reactions from the reaction of aqueous formaldehyde with a variety of secondary amines[4] and primary amines[6] encouraged us to investigate similar reactions with tetraalkoxyresorcin[4]arenes. However, we have been unable to obtain products of Mannich reactions with the use of aqueous formaldehyde and primary or secondary amines under a variety of reaction conditions, including the addition of toluene to ethanolic solutions of the potential coreactants. There is some evidence that a variety of intermediates are involved in Mannich reactions, which are dependent on the specific reaction conditions used,[21] but apparent failure of the reaction may also result from very low equilibrium concentrations of the reactive intermediates.[22] For example, furan is reported to not take part in Mannich reactions under classical reaction conditions.[23] However, both thiophene,[24] a weakly nucleo-



8a, R^2 = Me — **9a**, R^1 = *n*-C_5H_{11}, R^2 = Me
8a, R^2 = Me — **9b**, R^1 = *n*Pr, R^2 = Me
8a, R^2 = Me — **9c**, R^1 = *n*-C_7H_{15}, R^2 = Me
8a, R^2 = Me — **9d**, R^1 = *n*-$C_{11}H_{23}$, R^2 = Me
8a, R^2 = Me — **9e**, R^1 = $PhCH_2CH_2$, R^2 = Me
8a, R^2 = Me — **9f**, R^1 = *i*Bu, R^2 = Me
8b, R^2 = *i*Pr — **9g**, R^1 = *n*-C_5H_{11}, R^2 = *i*Pr
8b, R^2 = *i*Pr — **9h**, R^1 = *i*Bu, R^2 = *i*Pr
8c, R^2 = *n*Bu — **9i**, R^1 = *n*-C_5H_{11}, R^2 = *n*Bu
8d, R^2 = *c*-C_5H_9 — **9j**, R^1 = *n*-C_5H_{11}, R^2 = *c*-C_5H_9

Scheme 3. Formation of racemic tetraalkoxyresorcinarenes.

philic aromatic compound, and furan[25] do give Mannich bases in good yields when the reaction is carried out with preformed iminium salts. NMR experiments show that the position of the equilibrium between an iminium chloride and the chloromethylamine depends on the solvent system used and the precise structure of the Mannich reagent.[26] The ^{13}C NMR spectrum of a solution of *N*,*N*-dimethyl(methylene)iminium chloride in a mixture of sulfur dioxide and deuteriodichloromethane shows resonances at δ = 38.7, 49.4, 79.0 and 168.1 ppm; the resonances at 79.0 and 168.1 ppm are due to the chloromethyl and iminium carbon atoms, respectively. Treatment of the bis(aminol) ether derived from 3,4-dimethoxy-2-phenylethylamine and methanol with trichloromethylsilane gave a stable pale-yellow crystalline solid in a quantitative yield (Scheme 4). The ^{13}C NMR spectra of that solid, determined in deuteriochloroform or deuterioacetonitrile, even in the presence of sufur dioxide, does not show the presence of an iminium carbon atom; a resonance at δ = 78.4 ppm is observed and indicates that the equilibrium lies well in favour of chloromethylamine **10**.[26]



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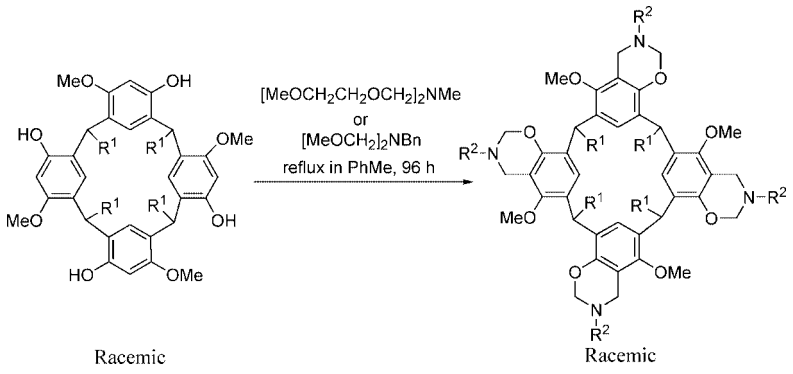
Scheme 4. Formation of 2-chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.

The fact that some reactions of resorcinarenes have been shown to be sufficiently acidic to undergo Mannich reactions without the addition of electrophilic initiators suggested that an investigation of the relative acidities of tetraalkoxyresorcinarenes would be valuable. Titrimetric methods have been used to determine the pK_a values of calixarenes.[27] The pK_a value of the first four phenolic hydroxy groups that are deprotonated in the case of the acetaldehyde derived resorcinarene (**1**, R = Me) gave a value that is two pK_a units more acidic than resorcinol.[27] Gas-phase calculation of the pK_a values for a number of phenols gave a value for 3-methoxyphenol of 9.5.[28] We therefore decided to determine the pK_a value for tetramethoxyresorcinarene **9a**, derived from 3-methoxyphenol and hexanal. We looked for a NMR spectroscopic technique that would not depend on the measurement of the NMR integrals. Such a method has been used to determine the solvolysis rate of trifluoroacetate by 2,2,2-trifluoroethanol buffered by 2,6-lutidine.[29] The methyl singlet in the ^1H NMR spectrum of 2,6-lutidine resonates at δ = 2.504 ppm and was found to shift downfield over the course of the reaction in a first-order fashion. Because modern NMR spectrometers can be used to determine frequency shifts to less than 0.1 Hz, this change in chemical shift could therefore be used to determine the extent of deprotonation of a tetramethoxyresorcinarene: the observed chemical shift is the weighted average of the shifts of protonated and unprotonated 2,6-lutidine. Our experiments were carried out in hexadeuterioacetone. In order to assess the value of this method for the determination of the relative pK_a values, we carried out NMR experiments with resorcinol and 3-methoxyphenol and obtained average pK_a values for the protonated and unprotonated species, over three determinations, of 9.47 and 9.71, respectively. The pK_a of resorcinol in water is reported to be 9.81.[30] The value that we obtained for tetramethoxyresorcinarene **9a** was 10.05; this value is two pK_a units less acidic than a related octahydroxyresorcinarene. It is clear that in order to obtain good reactivity in Mannich reactions, more forcing reaction conditions are required in order to displace the equilibrium that exists between the iminium ion and its precursor to favour the formation of the iminium ion.

We have previously reported the use of a number of bis(aminol) ethers,[26,31] including *N*,*N*-bis(methoxymethyl)-*N*-[(*R*)-(+)-(α-methylbenzyl)]amine and its enantiomer, as bis(iminium ion) precursors, particularly in connection with the preparation of tetrabenzoxazine derivatives of octahydroxyresorcin[4]arenes.[6m,10] We carried out a number of trial experiments with a variety of solvents with 0.1 mmol of tetramethoxyresorcin[4]arene **9a** and a tenfold-excess of *N*,*N*-bis(methoxymethyl)-*N*-benzylamine in which the solutions were heated under reflux. The use of toluene as the solvent resulted in the formation of racemic tetrabenzoxazine **11a** in 74% yield when the reaction was heated under reflux for 15 h. On a larger scale (ca. 1 mmol), the reaction mixture had to be heated under reflux in toluene for about 96 h to achieve a comparable yield. In order to be able to achieve a high enough boiling point for the reaction, we prepared a bis(aminol) ether from methylamine and 2-methoxyethanol as the alcohol component. A 12 mmol-scale reaction was complete after 96 h when tetramethoxyresorcin[4]arene **9a** reacted with *N*,*N*-bis(2-methoxyethoxymethyl)-*N*-methylamine to afford product **11b** in 73% yield. A similar reaction with tetramethoxyresorcin[4]arene **9e** gave anticipated product **11c** in 71% yield. The reactions are shown in Scheme 5. The use of the higher temperature evidently and successfully was able to shift the equilibrium that exists between the precursors used and the related iminium ions to favour the latter.



9a, $R^1 = n\text{-}C_5H_{11}$,
9e, $R^1 = PhCH_2CH_2$,

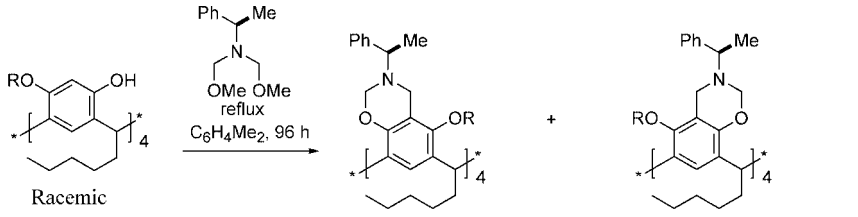
11a, $R^1 = n\text{-}C_5H_{11}$, R^2 = Bn, 74%
11b, $R^1 = n\text{-}C_5H_{11}$, R^2 = Me, 73%
11c, $R^1 = PhCH_2CH_2$, R^2 = Me, 71%

Scheme 5. Formation of racemic tetrabenzoxazines from tetraalkoxyresorcinarenes.

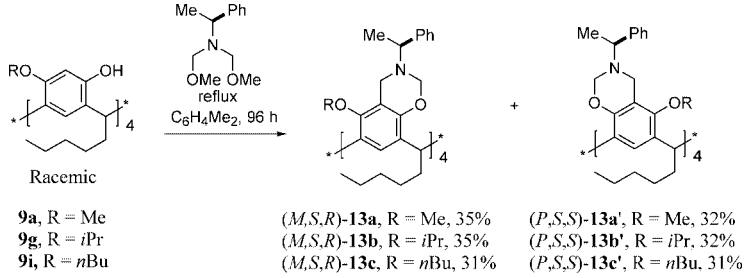
We next turned our attention to reactions designed to produce diastereomers by the use of chiral bis(methoxymethyl)amino ethers derived from (*R*)-(+)- and (*S*)-(–)-(α-methylbenzyl)amine.[6m,10] We found that reactions of racemic tetraalkoxyresorcinarenes **9a**, **9g**, **9i** and **9j** with the chiral bis(aminol) ethers also proceeded slowly, and that when the reacting components were heated under reflux in a mixture of xylenes as the solvent, the reactions were normally complete after about 96 h. In this way we prepared 1:1 mixtures of the diastereomers. The diastereomers were separated by flash chromatography on silica gel, and the yields of the isolated products are shown in Schemes 6 and 7. The most obvious evidence that distinguishes the two diastereomers from one another in the ^{1}H NMR spectra of the crude reaction mixtures is the two AB systems for the O–CH_2–N residues at δ = 4.58 ppm (J = 10.0 Hz) and δ = 4.63 ppm (J = 10.0 Hz), and at δ = 4.55 ppm (J = 10.0 Hz) and δ = 4.98 ppm (J = 10.0 Hz). The first diastereomer to be eluted upon column chromatography from the reaction mixture of resorcinarene **9a** and (*R*)-(+)-(α-methylbenzyl)-amine was found to be known compound **12a**.[10] In each case the first eluted diastereomer crystallized and was found to be the (*P*,*R*,*S*)-diastereomer; that is **12a**, **12b** and **12c**: the other diastereomers failed to produce crystals that were suitable for X-ray crystallography but analysis of the spectroscopic data showed that they were (*M*,*R*,*R*)- compounds **12a′**, **12b′** and **12c′** (Scheme 6). Similarly, in the case of the products of the reactions of *N*,*N*-bis(methoxymethyl)-*N*-[(*S*)-(–)-(α-methylbenzyl)]amine, the first compound that was eluted was shown, by comparison of the ^{1}H NMR spectra, to be the (*M*,*S*,*R*)-diastereomer (Scheme 7). The ^{1}H NMR spectra of compounds **15a** and **15a′** illustrate this feature and are shown below. The structures of compounds **12c** and **13b** were also confirmed by X-ray crystallographic analysis, shown in Figures 3 and 4.

We carried out additional reactions in order to assess the possibility that the long reaction times that were observed in the reactions of bis(aminol) ethers were related to the position of the equilibrium between the iminium species and its counterion and the iminium ion precursor. It was also a possibility that the polarity of the solvent system that was used might be important. We found that compound **7** was formed in 93% yield when a solution of tetramethoxyresorcinarene **9a** and bis(dimethylamino)methane was heated under reflux in 1,2-dichloroethane for 15 h, whereas the two components failed to react at room temperature. This result may be compared to a similar reaction in which a solution of bis(dimethylamino)methane and octahydroxyresorcinarene **1** (R = n-C_5H_{11}) was stirred in 1,2-dichloroethane at room temperature for 15 h, which gave the known Mannich base in 92% yield. The addition of protic acids, for example anhydrous hydrogen chloride, to the reaction mixtures was found to hinder the reactions, and this led us to conclude that the reactions should be more successful if they were carried out with an iminium ion source in the presence of a base. Such a protocol has been used previously.[32] A solution of bis(dimethylamino)methane together with a 30-fold excess of anhydrous potassium carbonate was stirred in dichloromethane, and this was followed by the addition of acetyl chloride; tetramethoxyresorcinarene **9a** was then added after 30 min, and the mixture was stirred at room temperature for 120 h to afford very pure crystalline racemic product **7** in 98% yield (Scheme 8) that was suitable for X-ray structural analysis (Figure 5).

We next prepared an iminium salt from *N*,*N*-bis-(methoxymethyl)-*N*-benzylamine by stirring a solution in dry light petroleum with acetyl chloride at room temperature for 24 h after which time the mixture was cooled to –20 °C to afford a colourless crystalline solid from which the solvent was removed. It is interesting to note that the addition of acetyl chloride to the solution of *N*,*N*-bis-(methoxymethyl)-*N*-benzylamine in light petroleum resulted in the rapid formation of a colourless precipitate at room temperature which dissolved after a short time. We assume that this initial precipitate was the related *N*-acetylammonium salt, which isomerized to form the *O*-acetyloxonium salt; the required iminium ion precursor. The addition of a solution of resorcinarene **9a** in 1,2-dichloro-



Scheme 6. Formation of diastereomeric tetrabenzoxazines from tetraalkoxyresorcinarenes and *N*,*N*-bis(methoxymethyl)-*N*-[(*R*)-(+)-(α-methylbenzyl)]amine.



Scheme 7. Formation of diastereomeric tetrabenzoxazines from tetraalkoxyresorcinarenes and *N*,*N*-bis(methoxymethyl)-*N*-[(*S*)-(–)-(α-methylbenzyl)]amine.

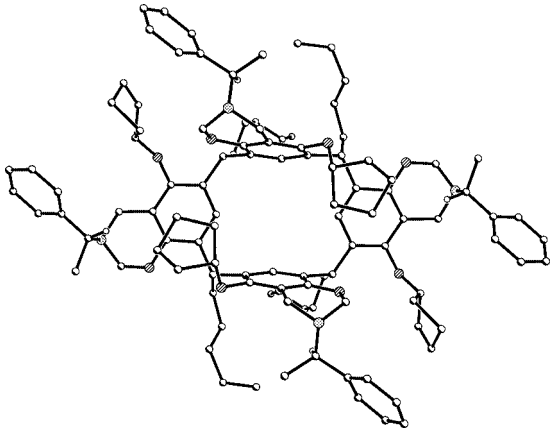


Figure 3. X-ray structure of tetrabenzoxazine (*P*,*R*,*S*)-**12c**; the majority of the hydrogen atoms are omitted for clarity.

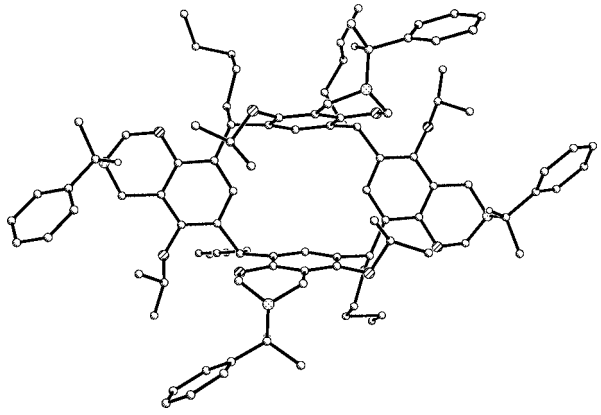
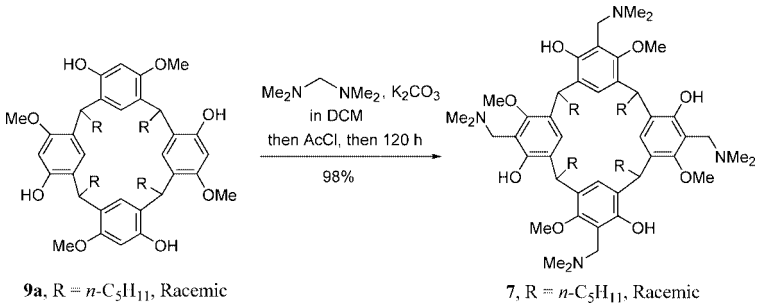


Figure 4. X-ray structure of tetrabenzoxazine (*M*,*S*,*R*)-**13b**; the majority of the hydrogen atoms are omitted for clarity.

ethane to the cold solid followed by heating the mixture under reflux for 15 h afforded tetrabenzoxazine **11a** in 80% yield.

The primary mechanism that is involved in the now well-established microwave-assisted technology is dielectric loss rather than the simple effect of heat.[33] Despite our success in carrying out Mannich reactions of tetraalkoxyresorcin-[4]arenes at high temperatures, the length of time required to obtain high yields of products prompted us to investigate the use of microwave-assisted reactions. There are a number of potential advantages that accrue in addition to shortened reaction times; they include improved yields and cleaner products. A number of reviews confirm the potential benefit of syntheses that are carried out with the use of microwave assistance,[34] which includes the use of environmentally benign solvent-free reactions.[34b] A number of Mannich reactions have been carried out with microwave assistance.[35] However, as far as we are aware, there is only one example of a microwave-assisted Mannich reaction that involves the use of phenols.[36] We were pleased to find that experiments carried out with a CEM Discover-focused microwave apparatus established that reactions could be carried out with much reduced reaction times, and that improved yields and cleaner products could be obtained. For example, the reaction of tetramethoxyresorcinarene **9a** in bis(dimethylamino)-methane (10 equiv.) afforded, after 10 min and a power of up to 300W followed by cooling of the reaction mixture to 110 °C, a quantitative yield of compound **7**. Experiments



9a, R = *n*-C_5H_{11}, Racemic — **7**, R = *n*-C_5H_{11}, Racemic

Scheme 8. Formation of a Mannich base with the use of a preformed iminium ion source.

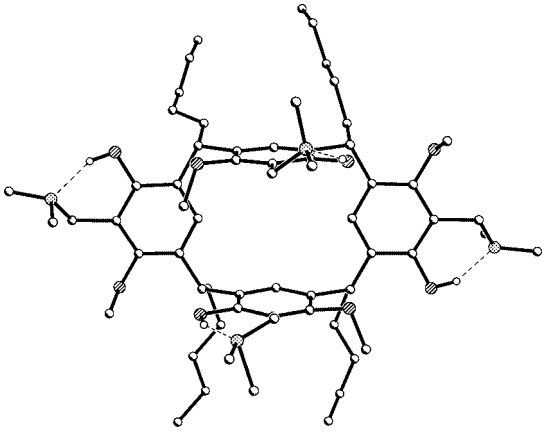
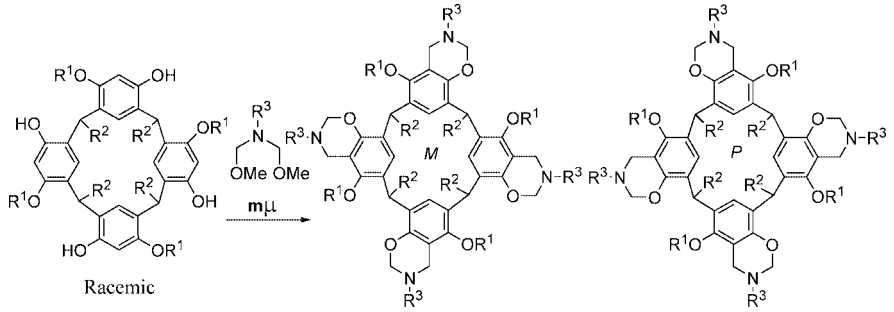


Figure 5. X-ray structure of Mannich base **7**; the majority of the hydrogen atoms are omitted for clarity.

with bis(aminol) ethers are shown in Scheme 9 and Table 1. In the case of the reactions of *N*,*N*-bis(methoxymethyl)-*N*-[(*S*)-(–)-(α-methylbenzyl)]amine, the first diastereomer that is eluted upon column chromatography was shown to correspond to diastereomer **A** by comparison of the spectroscopic data with those obtained previously; that is, the product was found to have the absolute configuration (*M*,*S*,*R*). The ^{1}H NMR spectra of compounds **15a** and **15a′**, shown in Figures 6 and 7, illustrate this feature. It is of interest to note that a sequence of 2 × 10 min or 3 × 10 min, with the reaction allowed to cool to room temperature between irradiations, afforded better yields of products than those observed for the reactions carried out for 20 or 30 min, respectively. We have also been able to carry out reactions on a one-gram scale with these conditions.

We also investigated the feasibility of (*R*)-(+)-(α-methylbenzyl)amine as the chiral auxiliary in the formation of diastereomeric amides from racemic tetramethoxyresorcinarenes. The alkylation of calixarenes and resorcinarenes with ethyl-, or methylbromoacetate is documented to provide the corresponding ether–ester derivatives in high yield.[37] The direct conversion of esters into amides by aminolysis is also well-established,[38] and this method has been recently applied to a calixarene tetraester.[39] In the case of the calixarene, the authors indicate that the aminolysis reaction worked well for *n*-alkylamines but did not work with benzylamine or aniline. However, given that their procedure was carried out in a dilute ethanolic solution of amine heated under reflux, we felt that more vigorous conditions should be investigated. Thus, tetraester **18** was heated at 100 °C with neat (*R*)-(+)-(α-methylbenzyl)amine for several hours but gave a complex mixture. It has also been suggested that the use of a strong base, for example sodium hydride, in DMF promotes aminolysis reactions.[40] In our hands, this protocol also produced a complex mixture of

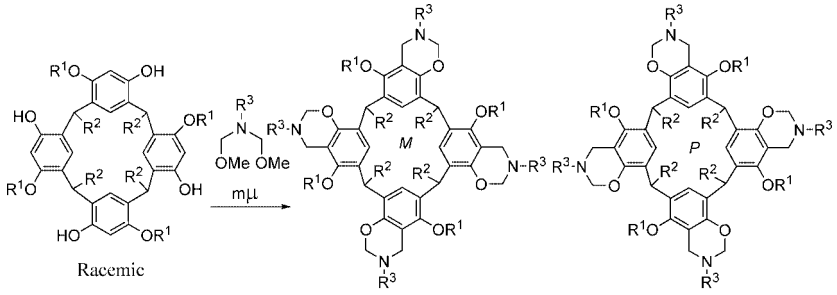


Racemic

R^1 = Me, R^2 = *n*-C_5H_{11}	R^3 = Bn	Racemic **11**	
R^1 = Me, R^2 = *n*-C_5H_{11}	R^3 = (*S*)-α-MeBn **13a**		**13a'**
R^1 = Me, R^2 = *n*-$C_{11}H_{23}$	R^3 = (*S*)-α-MeBn **14a**		**14a'**
R^1 = Me, R^2 = *i*Bu	R^3 = (*S*)-α-MeBn **15a**		**15a'**
R^1 = *i*Pr, R^2 = *n*-C_5H_{11}	R^3 = (*S*)-α-MeBn **13b**		**13b'**
R^1 = *i*Pr, R^2 = *i*Bu	R^3 = (*S*)-α-MeBn **16a**		**16a'**
R^1 = *c*-C_5H_9, R^2 = *n*-C_5H_{11}	R^3 = (*S*)-α-MeBn **17a**		**17a'**

Scheme 9. Microwave-assisted Mannich reactions to produce tetrabenzoxazines.

Table 1. Reactions of bis(aminol) ethers with tetraalkoxyresorcinarenes with the use of focused microwave irradiation.



R^1	R^2	R^3	Power [W]	Temp. [°C]	Time [min.]	Product **A**[a] Yield [%]	Product **B**[a] Yield [%]
Me	*n*-C_5H_{11}	Bn	<300	150	10	(**11a**) 82	(racemic)
Me	*n*-C_5H_{11}	α-Me-Bn	<300	150	10	(**13a**′) 38	(**13a**′) 36
Me	*n*-$C_{11}H_{23}$	α-Me-Bn	<300	150	2×10	(**14a**) 33	(**14a**′) 31
Me	*i*Bu	α-Me-Bn	<300	150	2×10	(**15a**) 43	(**15a**′) 43
*i*Pr	*n*-C_5H_{11}	α-Me-Bn	<300	140	3×10	(**13b**) 39	(**13b**′) 39
c-C_5H_9	*n*-C_5H_{11}	α-Me-Bn	<300	140	3×10	(**17a**) 37	(**17a**′) 35
*i*Pr	*i*Bu	α-Me-Bn	<300	140	3×10	(**16a**) 37	(**16a**′) 37

[a] The compound number, given in brackets before the yield, refers to compounds shown in Scheme 9.

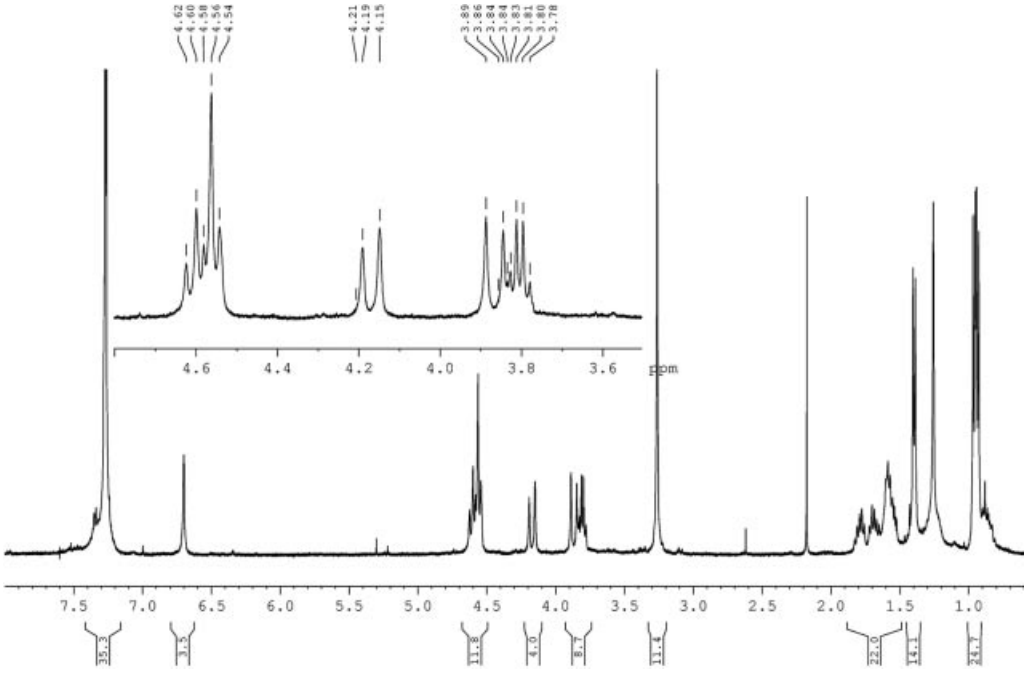


Figure 6. ^{1}H NMR spectrum of compound **15a**.

compounds that was not separated. The use of an acid chloride derived from the carboxylic acid related to ester **18** was also investigated, but an attempted reaction with (*R*)-(+)-(α-methylbenzyl)amine again gave a complex mixture of products. The report of the formation of 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide from 2-bromoacetyl bromide suggested the use of that reagent.[40] When resorcinarenes **9b**, **9c** and **9d** were heated under reflux in acetonitrile with anhydrous potassium carbonate and an excess of 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide for 15 h, the expected diastereomeric tetraamides, shown in Scheme 10, were isolated by flash chromatography after workup in 47–60% combined yields. It is interesting to note that when dry acetone was substituted for acetonitrile in the above reactions, none of the expected amides was formed. The absolute stereochemistry of compound (*M*,*R*,*R*)-**20a** was established by single-crystal X-ray structure determination, shown in Figure 8.[41] After this part of the study had been completed, the successful aminolysis of a compound related to **18** was reported in which the reaction of an ester was heated with (*S*)-(–)-(α-methylbenzyl)amine at 160 °C.[37b,42]

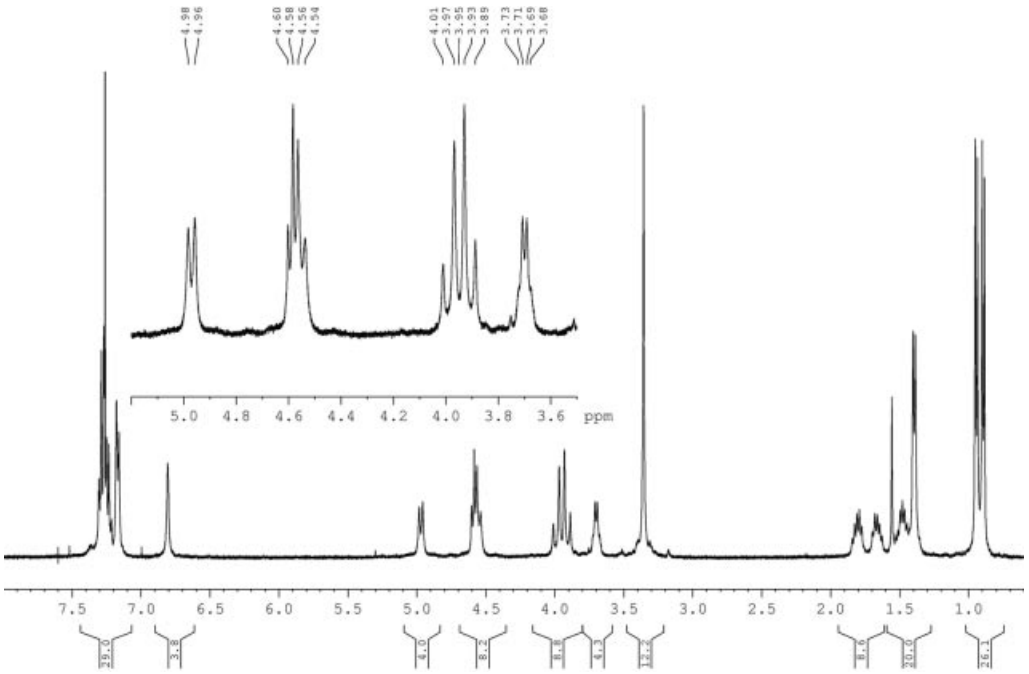
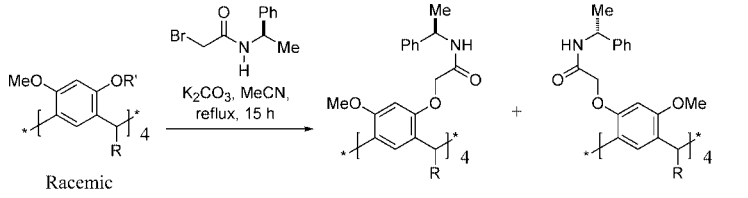


Figure 7. ^{1}H NMR spectrum of compound **15a′**.



18, R = *n*-C_7H_{15}, R' = CH_2CO_2Et
9b, R = *n*Pr, R' = H
9c, R = *n*-C_7H_{15}, R' = H
9d, R = *n*-$C_{11}H_{23}$, R' = H

(*M*,*R*,*R*)-**20a**, R = *n*Pr (*P*,*R*,*S*)-**20a'**, R = *n*Pr
(*M*,*R*,*R*)-**20b**, R = *n*-C_7H_{15} (*P*,*R*,*S*)-**20b'**, R = *n*-C_7H_{15}
(*M*,*R*,*R*)-**20c**, R = *n*-$C_{11}H_{23}$ (*P*,*R*,*S*)-**20c'**, R = *n*-$C_{11}H_{23}$

Scheme 10. Formation of diastereomeric amides from tetramethoxyresorcinarenes and 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide.

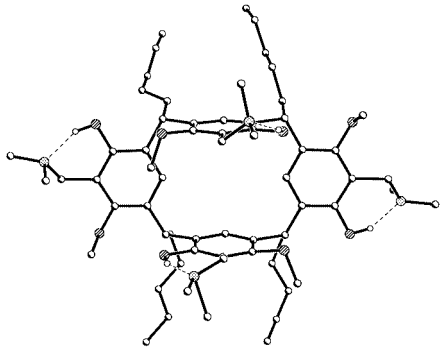
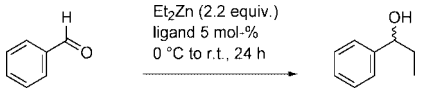


Figure 8. X-ray structure of amide **20a**; the majority of the hydrogen atoms are omitted for clarity.

Having prepared a range of chiral resorcin[4]arene derivatives that contain nitrogen and oxygen, we wanted to investigate their potential use in ligand-assisted reactions. Our interest in the ligand-assisted addition of dialkylzinc reagents to benzaldehyde with the use of resorcin[4]arene derivatives was indicated in an earlier communication.[43] The use of the β-amino alcohol prolinol as a chiral ligand in reactions of Grignard and organolithium reagents with benzaldehyde and 2,2-dimethylpropanal was reported at an early stage,[44] and a significant amount of work has been published on the addition of dialkylzinc reagents to aromatic aldehydes, and in particular, with the use of β-amino alcohol-based ligands.[45,46] The related enantioselective synthesis of diarylmethanols and diarylmethylamines has been reviewed recently.[47] Ligand-assisted alkynylation reactions of aldehydes with alkynylzinc reagents have also been reported recently;[48] they have been shown to provide an interesting and valuable route to chiral propargylic alcohols.[49] We were interested in exploring the possible use of our chiral resorcin[4]arene derivatives in this latter type of reaction.

In our preliminary investigation of the addition reactions of diethylzinc, we chose to use a number of substituted resorcinarene derivatives that we had previously reported.[10] The compounds that were chosen contained hydroxy and

benzylamino groups in order to establish the possible influence of the axial chirality, as well as chiral groups attached to the nitrogen atom, on the enantioselectivity of the addition to benzaldehyde, shown in Scheme 11.



Scheme 11. The ligand-assisted addition of diethylzinc to benzaldehyde.

The majority of the reactions were carried out by the addition of a solution of the dialkylzinc reagent in hexanes to a solution of the potential ligand in toluene. The mixture was then cooled to –78 °C before the aromatic aldehyde was added. The reaction mixtures were warmed to room temperature, and after 12 h, the mixture was worked up and analyzed by either chiral gas chromatography or chiral HPLC followed by isolation of the product and determination of its optical rotation. The use of tetramethoxyresorcinarene **21**, which lacked axial chirality, afforded 1-phenylpropanol in 84% yield in the reaction with diethylzinc. However, the product was racemic. The ^{1}H NMR spectrum of ligand **21**, taken at ambient temperature, consisted of a number of broad signals that indicated the presence of a number of conformers that interconvert slowly on the NMR time scale. As expected, when the ^{1}H NMR spectrum of the ligand was determined at higher temperatures the signals sharpened. A number of possible interactions between the amino and the hydroxy groups are possible, which suggests that the result obtained is not unexpected. Tetra-*N*,*N*-dimethylbenzylamine derivative **22**, where the only chiral element is the axis of chirality, provided an interesting result: 1-phenylpropanol was produced in 71% yield with an *ee* of 42%, in favour of the (*R*)-(+)-enantiomer. In the case of the reactions in which we used diastereomers **23** and **24**, the *ee*'s that resulted were only from the influence of the chiral auxiliaries. 1-Phenylpropanol was obtained in 80% yield with an *ee* of 56% in favour of the (*S*)-(–)-enantiomer in the reaction of diethylzinc with benzaldehyde in the presence of ligand **23** (5 mol-%). In a similar reaction, ligand **24** (5 mol-%) afforded 1-phenylpropanol in 75% yield with an *ee* of 55% in favour of the (*R*)-(+)-enantiomer (Figure 9).

Because the overall yields and the induced enantioselectivities were lower than those already established in the literature when ligands **21**–**24** were used, we turned our attention to the use of some of our tetrabenzoxazine derivatives. The potential ligands investigated were compounds (*M*,*S*,*R*)-**13a**, (*P*,*R*,*S*)-**12b** and its enantiomer (*M*,*S*,*R*)-**13b**, (*M*,*R*,*R*)-**12b′**, (*P*,*R*,*S*)-**12c** and (*M*,*R*,*R*)-**12c′**. The first results that were obtained showed that we were able to reduce the amount of ligand to 1 mol-% in the addition of diethylzinc to benzaldehyde without any change in the conversion or the enantioselectivity of the reaction under the standardized reaction conditions. We were pleased to find that although ligand (*M*,*S*,*R*)-**13a** produced a 95% conversion yield with an *ee* of 39% in favour of (*R*)-(+)-1-phenyl propanol, ligand **12b** was much superior and gave a 95% conversion with an *ee* of 83% in favour of (*S*)-(–)-1-phenyl propanol. Ligand **12c** gave only a 65% conversion and an *ee* of 58% in favour of (*S*)-(–)-1-phenyl propanol. Ligands **12b′** and **12c′** evidently had their axial chirality and the chirality of their amino residues mismatched: ligand **12b′** gave a 95% conversion but an *ee* of only 5%, whereas ligand **12c′** gave a 63% conversion and a 5% *ee* (Figure 10).

The above results reveal a number of interesting features. The enantioselectivity of the reaction was affected by several parameters. The steric effect of the ether moiety had a pronounced influence on the *ee*, and the isopropyl group was found to induce the highest amount of selectivity and the methyl group generated the lowest selectivity. The relative configurations of the ligands was also shown to be important; only the matched systems [(*P*,*R*,*S*-) and (*M*,*S*,*R*-)] showed selectivity. The influence of the calix is also important; a reaction with simple chiral benzoxazine derivative (*R*)-**25** resulted in reduced activity (57% yield) and an *ee* of only 18%. In an NMR experiment in which a solution of

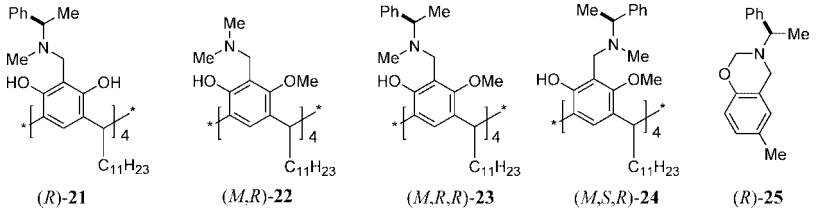


Figure 9. Structures of potential ligands.

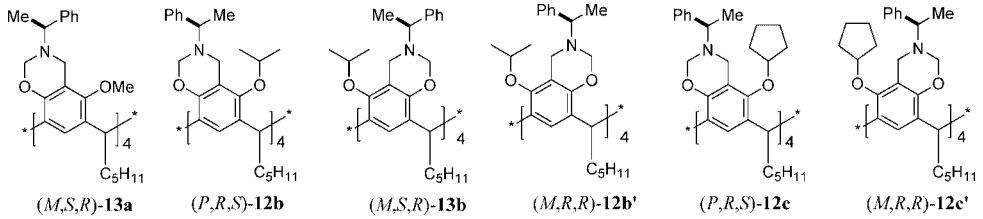
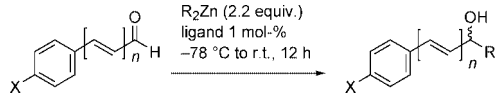


Figure 10. Structures of potential ligands.

diethylzinc was added to a solution of resorcinarene derivative (*P*,*R*,*S*)-**12b**, no change was observed in the resonances of the benzoxazine moieties. Ligand (*P*,*R*,*S*)-**12b** was recovered unchanged after the NMR experiment. The use of chiral titanium-based catalysts in the enantioselective addition reactions of dialkylzinc reagents to aldehydes has proven to be an effective adjunct to catalyst systems that are based on chiral amino alcohols, diols and sulfonamides that are derived from chiral primary diamines.[50] However, the absence of hydroxy groups or secondary amino groups in our ligands, for example (*P*,*R*,*S*)-**12b**, rendered the addition of titanium tetraisopropoxide to our catalyst systems redundant: the titanium tetraisopropoxide functioned as a catalyst in its own right, and when 2 mol-% of the catalyst was added to the system the *ee* decreased to 31%.

We next investigated reactions of aromatic aldehydes with different organozinc reagents in the presence of ligand (*P*,*R*,*S*)-**12b** and its enantiomer (*M*,*S*,*R*)-**13b**. We found that the reactions of dimethylzinc or diisopropylzinc with benzaldehyde gave, by comparison with the results obtained with diethylzinc, both reduced conversions and enantioselectivities in the presence of ligand (*P*,*R*,*S*)-**12b**. Once again, ligand **12c** gave poorer results. Reactions of 4-chloro- or 4-methoxybenzaldehyde with diethylzinc again provided the best conversions and enantioselectivities in the presence of ligand (*P*,*R*,*S*)-**12b**, or its enantiomer (*M*,*S*,*R*)-**13b**. In the reaction of diethylzinc with 4-methoxybenzaldehyde in which toluene was omitted from the reaction mixture, the conversion increased significantly and the *ee* increased slightly. This latter result suggests that toluene successfully competes with the aromatic aldehyde for the cavity of the ligand in some cases. Finally, we have carried out preliminary experiments in which a mixture of dimethylzinc and phenylacetylene are added to a solution of ligand **13b** and upon their reaction with benzaldehyde afforded 1,3-diphenylprop-2-yn-1-ol in an isolated yield of 59% and an *ee* of 64%. These results are collected in Table 2.

Table 2. Reactions of aromatic aldehydes with dialkylzinc reagents in the presence of chiral ligands.



Ligand	Aldehyde	Dialkylzinc	Conversion [%]	*ee*	Product configuration
12b	X = chloro (*n* = 0)	diethylzinc	68	73	(–)
12c	X = chloro (*n* = 0)	diethylzinc	19	61	(–)
13b	X = methoxy (*n* = 0)	diethylzinc	48	63	(+)
13b[a]	X = methoxy (*n* = 0)	diethylzinc	95	68	(+)
13b	X = H (*n* = 1)	diethylzinc	95	41	(+)[b]
12b	X = H (*n* = 0)	dimethylzinc	29	70	(–)
12b	X = H (*n* = 0)	diisopropylzinc	66	26	(–)
12c	X = H (*n* = 0)	diisopropylzinc	74	27	(–)
13b	X = H (*n* = 0)	methyl(phenylethynyl)zinc	59[c]	64	(+)[b]
2a	X = H (*n* = 0)	methyl(phenylethynyl)zinc	73[c]	25	(+)[b]

[a] Reaction was carried out without added toluene. [b] Rotation values for the pure enantiomers are very small; therefore, the probable configurations were deduced from the HPLC traces. [c] Isolated yields.

Although the mechanism of the ligand-assisted reactions reported here is unclear, there are certain features that distinguish these reactions from those reported by other workers. Most importantly, the ligand can be recovered after its interaction with a dialkylzinc reagent. In addition, the size of the alkyl group that is attached to the oxygen atom is important. Finally, the calix is crucially important as evidenced by the low enantioselectivity that was obtained when simple benzoxazine derivative (*R*)-**25** was used. These factors implicate the interaction of the aromatic aldehyde with the chiral bowl of the ligand, and the delivery of the alkyl group from the organozinc reagent from a complex that involves the nitrogen and oxygen atoms in the ligand.

Conclusions

In this paper we define unambiguously the axes of chirality in resorcin[*n*]arenes. The experimental work reported in this paper has shown that Mannich reactions of tetraalkoxyresorcin[4]arenes, which are two pK_a units less acidic than the related resorcin[4]arenes, can be carried out using a number of different protocols. Microwave-assisted reactions allow for the preparation of benzoxazine derivatives on a multigram scale in high yields and after short reaction times. We also established that alkylation reactions can be carried out efficiently with a chiral nonracemic α-bromoacetamide derivative. Chiral nonracemic tetrabenzoxazine derivatives were also shown to take part in ligand-assisted reactions of aromatic aldehydes with organozinc reagents.

Experimental Section

General Experimental Detail: All infrared spectra were obtained with a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer or a Bruker Vector 22 FTIR spectrometer, thin film spectra were acquired with sodium chloride plates. All ^{1}H- and ^{13}C NMR spectra were measured at 250.13 and 62.86 MHz, respectively, with a Bruker AC 250 MHz spectrometer, at 400.13 and 100.62 MHz, respectively, with a Bruker DPX 400/Avance 400 MHz spectrometer, at 200 MHz and 50.3 MHz, respectively, with a Varian Gemini 2000 spectrometer or at 500 and 125.8 MHz, respectively, with a Bruker ARX-500 and referenced to internal TMS (tetramethylsilane). Mass spectra were recorded with a Jeol-SX102 instrument with the electron-impact (EI) or fast atom bombardment (FAB) modes by the EPSRC national mass spectrometry service at the University of Wales, Swansea with the electrospray (ES) technique. GC–MS analysis was performed with a Fisons GC 8000 series (AS 800) instrument, equipped with a 15 m × 0.25 mm DB-5 column and an electron-impact low-resolution mass spectrometer. Melting points were recorded with an Electrothermal-IA 9100 melting point instrument and are uncorrected. Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, or on a Optical Perkin–Elmer 141 polarimeter that were operated at λ =

589 nm, which corresponds to the sodium D line, at the temperatures indicated. Microanalyses were performed with a Perkin–Elmer Elemental Analyser 2400 CHN or at the Central Science Laboratory, University of Tasmania. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored by thin layer chromatography (TLC) on aluminium-backed plates coated with Merck Kieselgel 60 F254 silica gel. TLC plates were visualized by UV radiation at a wavelength of 254 nm or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Reactions that required anhydrous conditions were carried out in flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Reaction solvents were used as obtained commercially, unless otherwise stated. Light petroleum (b.p. 40–60 °C) was distilled from calcium chloride prior to use. Ethyl acetate was distilled from calcium sulfate or -chloride. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran was distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical. Microwave reactions were carried out in a CEM Discover focused microwave set at a maximum of 300 W.

Tetrabenzoxazine (*P*,*R*,*S*)-2c: Tetraundecylresorcin[4]arene **1**[51] (6.10 g, 5.5 mmol) was dissolved in anhydrous ethanol (350 mL) under a nitrogen atmosphere and *N*,*N*-bis(methoxymethyl)-*N*-(*R*)-(+)-α-methyl-(4-methoxybenzyl)amine (5.00 g, 33.0 mmol) was added in one portion. Formaldehyde (37% solution in water, 5 mL, 62.0 mmol) was added in one portion, and the mixture was heated under reflux overnight. After this time, the reaction was cooled to room temperature, and the precipitate was filtered and washed with large amounts of ethanol (95%) to afford (*P*,*R*,*S*)-**2c** as a pale pink solid (7.2 g, 73%). M.p. 80 °C (dec.). $[\alpha]_D^{25}$ = +110 (*c* = 0.75, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3356, 3053, 2967, 2845, 2305, 1611, 1512, 1469, 1263, 1035, 896, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.88 (t, *J* = 7.2 Hz, 12 H), 1.27–1.37 (m, 72 H), 2.15 (m, 4 H), 2.23 (m, 4 H), 3.66 (s, 12 H), 3.72 (d, *J* = 17.2 Hz, 4 H), 3.77 (q, *J* = 6.4 Hz, 4 H), 3.94 (d, *J* = 17.6 Hz, 4 H), 4.21 (t, *J* = 7.6 Hz, 4 H), 4.86 (d, *J* = 10.0 Hz, 4 H), 5.08 (d, *J* = 10.0 Hz, 4 H), 6.74–6.76 (m, 8 H), 7.15 (s, 4 H), 7.19–7.21 (m, 8 H), 7.66 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.4, 22.7, 28.2, 29.5, 29.8, 29.8, 29.9, 32.0, 32.7, 33.7, 44.6, 55.1, 57.0, 80.7, 108.9, 113.7, 121.0, 123.5, 124.4, 128.2, 136.7, 148.7, 149.6, 158.6 ppm, two obscured CH_2 signals remain. $C_{116}H_{164}N_4O_{12}$ (1806.56): calcd. C 77.12, H 9.15, N 3.10; found C 77.02, H 9.08, N 3.00.

Tetrabenzoxazine (*P*,*R*,*S*)-3b: Tetrabenzoxazine (*P*,*R*,*S*)-**2b** (18.0 g, 12.1 mmol) was dissolved in dry THF (500 mL) under an atmosphere of nitrogen and cooled to –78 °C. The solution was vigorously stirred with an overhead stirrer, and *n*-butyllithium (2.5 M solution in hexanes, 24.2 mL, 60.5 mmol) was added dropwise, and the reaction was stirred for 30 min. Methyl trifluoromethanesulfonate (10.0 g, 60.5 mmol) was added dropwise, and the reaction was stirred for 40 min. After this time, the reaction was quenched with methanol (20 mL). The mixture was then warmed to room temperature and concentrated. The residue produced was partitioned between CH_2Cl_2 (200 mL) and water (200 mL). The organic layer was washed with water (2 × 250 mL), dried and solvents were removed under reduced pressure. The residue was purified on silica gel (5% methanol/CH_2Cl_2) to afford (*P*,*R*,*S*)-**3b** as a pale yellow foam (17.6 g, 94%). $[\alpha]_D^{25}$ = +135.0 (*c* = 0.46, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3054, 2986, 1421, 1265, 896, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.4 Hz, 12 H), 2.11–2.31 (m, 8 H), 2.69 (t, *J* = 7.6 Hz, 8 H), 3.21 (s, 12 H), 3.81 (q, *J* = 6.4 Hz, 4 H), 3.87 (d, *J* = 16.8 Hz, 4 H), 4.19 (d, *J* = 16.8 Hz, 4 H), 4.53 (t, *J* = 7.6 Hz, 4 H), 4.57 (d, *J* = 10 Hz, 4 H), 4.64 (d, *J* = 10 Hz, 4 H), 6.84 (s, 4 H), 7.12–7.22 (m, 40 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 34.6, 35.3, 37.6, 44.5, 57.1, 59.9, 79.6, 112.4, 124.4, 125.5, 127.3, 127.5, 128.2, 128.4, 128.5, 128.5, 142.7, 144.0, 150.3, 153.8 ppm, obscured aromatic signal remains. LRMS (FAB): *m*/*z* = 1541 $[M - 1]^+$. $C_{104}H_{108}N_4O_8$ (1541.99): calcd. C 80.80, H 7.30, N 3.62; found C 80.86, H 6.90, N 3.56.

Tetrabenzoxazine (*P*,*R*,*S*)-3d: Tetrabenzoxazine (*P*,*R*,*S*)-**2c** (7.00 g, 3.9 mmol) was dissolved in dry THF (300 mL) under an atmosphere of nitrogen and cooled to –78 °C. The solution was vigorously stirred with an overhead stirrer, and *n*-butyllithium (2.5 M solution in hexanes, 7.8 mL, 19.4 mmol) was added dropwise, and the reaction was stirred for 30 min. Methyl trifluoromethanesulfonate (2.20 g, 19.4 mmol) was added dropwise, and the reaction was stirred for 45 min. After this time, the reaction was quenched with methanol (10 mL). The mixture was then warmed to room temperature and concentrated. The residue produced was separated between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with water (2 × 150 mL), saturated brine solution (100 mL), dried and the solvents were removed under reduced pressure. The residue was purified on silica gel (45% ethyl acetate/light petroleum) to afford (*P*,*R*,*S*)-**3d** as a pale yellow oil (5.60 g, 78%). $[\alpha]_D^{25}$ = +116.0 (*c* = 0.80, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3052, 2925, 2852, 2304, 1610, 1512, 1465, 1265, 1174, 1035, 943, 835, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 8.0 Hz, 12 H), 1.25–1.34 (m, 72 H), 1.36 (d, *J* = 6.4 Hz, 12 H), 1.80 (m, 4 H), 1.89 (m, 4 H), 3.27 (s, 12 H), 3.76 (q, *J* = 6.4 Hz, 4 H), 3.79 (s, 12 H), 3.85 (d, *J* = 16.8 Hz, 4 H), 4.14 (d, *J* = 16.8 Hz, 4 H), 4.42 (t, *J* = 7.6 Hz, 4 H), 4.57 (d, *J* = 10.0 Hz, 4 H), 4.60 (d, *J* = 10.0 Hz, 4 H), 6.71 (s, 4 H), 6.81–6.83 (m, 8 H), 7.18–7.20 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.3, 22.7, 28.3, 29.4, 29.8, 29.8, 30.0, 30.1, 32.0, 35.4, 35.8, 44.5, 55.2, 56.5, 60.1, 79.5, 112.2, 113.7, 124.5, 127.8, 128.6, 128.8, 136.0, 150.1, 153.5, 158.8 ppm, obscured CH_2 signal remains. LRMS (FAB): *m*/*z* = 1862 $[M + H]^+$

Tetramethoxy-tetrakis(dimethylamino)-resorcinarene (7): K_2CO_3 (2.50 g, 18.0 mmol) and dry CH_2Cl_2 (50 mL) were mixed together under an atmosphere of nitrogen. *N*,*N*,*N*,*N*-Tetramethylmethylenediamine (0.85 mL, 6.0 mmol) was added in one portion. Acetyl chloride (0.45 mL, 6.0 mmol) was added dropwise, and the reaction was stirred for 30 min. Tetramethoxyresorcinarene **9a** (0.50 g, 0.6 mmol), dissolved in dry CH_2Cl_2 (10 mL), was added dropwise, and the reaction was stirred for 5 d at room temperature. After this time, the reaction was filtered to remove any solid material. The filtrate was then washed with water (2 × 100 mL), dried and the solvents were removed under reduced pressure. The residue was taken up in diethyl ether (50 mL) and allowed to slowly evaporate to furnish **7** as colourless crystals (0.63 g, 98%). IR (CH_2Cl_2): $\tilde{\nu}$ = 3424, 2954, 1641, 1602, 1462 1265, 1089, 896, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (br. t, *J* = 6.4 Hz, 12 H), 1.24–1.35 (m, 24 H), 1.78 (m, 4 H), 1.90 (m, 4 H), 2.23 (s, 24 H), 3.44 (s, 12 H), 3.55 (d, *J* = 14.0 Hz, 4 H), 3.67 (d, *J* = 14.4 Hz, 4 H), 4.48 (t, *J* = 7.6 Hz, 4 H), 6.72 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.8, 28.2, 32.3, 35.9, 36.0, 44.3, 56.2, 61.1, 113.7, 125.6, 127.5, 128.0, 154.1, 154.3 ppm. $C_{64}H_{100}O_8N_4$(1053.50): calcd. C 72.97, H 9.57, N 5.32; found C 72.68, H 9.60, N 5.14. HRMS (FAB): calcd. for $C_{64}H_{100}O_8N_4$ $[M]^+$ 1052.7541; found 1052.7572.

Representative Procedure for the Reaction of Bis(aminol) Ethers with Tetraalkoxy-resorcinarenes under Standard Conditions Heated under Reflux

Tetrabenzoxazine (11a): Tetramethoxyresorcinarene **9a** (1.00 g, 1.2 mmol) was dissolved in toluene (90 mL). *N*,*N*-bis(methoxymethyl)-*N*-benzylamine (1.18 g, 6.1 mmol) in toluene (10 mL) was added in one portion, and the reaction mixture was heated under reflux for 2 d. After this time, the reaction was cooled to room

temperature, and the solvent was removed under reduced pressure. The residue was suspended in hexane and left overnight in the refrigerator. The solid produced was filtered and washed with cold hexane to furnish **11a** as a pale brown powder (1.2 g, 74%). M.p. 152–153 °C (dec.). IR (CH_2Cl_2): $\tilde{\nu}$ = 2930, 2856, 2304, 1589, 1475, 1264, 1082, 947, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (br. t, 12 H), 1.31–1.40 (m, 24 H), 1.79–1.84 (m, 4 H), 1.92–1.97 (m, 4 H), 3.40 (s, 12 H), 3.62 (d, J = 12.8 Hz, 4 H), 3.74 (d, J = 12.4 Hz, 4 H), 3.93 (d, J = 16.8 Hz, 4 H), 4.04 (d, J = 16.4 Hz, 4 H), 4.46 (t, J = 7.2 Hz, 4 H), 4.56 (d, J = 9.6 Hz, 4 H), 4.69 (d, J = 9.6 Hz, 4 H), 6.76 (s, 4 H), 7.22–7.34 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.7, 27.9, 32.2, 35.6, 35.7, 47.3, 55.3, 60.0, 80.2, 112.1, 124.5, 127.3, 128.0, 128.3, 128.8, 129.4, 138.0, 150.0, 153.8 ppm. LRMS (FAB): m/z = 1348 $[M - 1]^+$. $C_{88}H_{108}N_4O_8$ (1349.82): calcd. C 78.30, H 8.06, N 4.15; found C 78.13, H 7.95, N 4.06.

Tetrabenzoxazine (11b): Tetramethoxyresorcinarene **9a** (10.0 g, 12.0 mmol) was dissolved in toluene (450 mL), and *N*-methyl-*N*,*N*-bis([(methoxy)ethyl]oxymethyl)amine (12.6 g, 61.0 mmol) in toluene (50 mL) was added in one portion. The reaction mixture was heated under reflux for 4 d. After this time, the reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was suspended in hexane and left overnight in the refrigerator. The solid produced was filtered and washed with cold hexane to furnish **11b** as a yellow powder (9.3 g, 73%). M.p. 179–181 °C (dec.). IR (CH_2Cl_2): $\tilde{\nu}$ = 2931, 2304, 1589, 1473, 1265, 1088, 895, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (br. t, 12 H), 1.29 (m, 24 H), 1.75–1.87 (m, 8 H), 2.46 (s, 12 H), 3.42 (s, 12 H), 3.83 (d, J = 16.0 Hz, 4 H), 3.93 (d, J = 16.0 Hz, 4 H), 4.44 (t, J = 8.0 Hz, 4 H), 4.50 (d, J = 8.0 Hz, 4 H), 4.67 (d, J = 8.0 Hz, 4 H), 6.67 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.7, 27.8, 32.1, 35.4, 35.6, 39.6, 48.8, 60.1, 83.0, 112.0, 124.6, 127.8, 129.0, 149.2, 153.7 ppm. LRMS (FAB): m/z = 1045 $[M + H]^+$. $C_{64}H_{92}N_4O_8$ (1045.44): calcd. C 73.53, H 8.87, N 5.36; found C 73.71, H 8.85, N 5.25.

Tetrabenzoxazine (11c): Tetramethoxyresorcinarene **9e** (1.00 g, 1.0 mmol) was dissolved in toluene (40 mL) and *N*-methyl-*N*,*N*-bis([(methoxy)ethyl]oxymethyl)amine (1.30 g, 6.2 mmol) in toluene (5 mL) was added in one portion. The reaction mixture was heated under reflux for 3 d. After this time, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified on silica gel (30% ethyl acetate/light petroleum) to furnish **11c** as an off-white powder (0.84 g, 71%). M.p.178–182 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12–2.20 (m, 8 H), 2.47 (s, 12 H), 2.64 (t, J = 8.0 Hz, 8 H), 3.37 (s, 12 H), 3.86 (d, J = 16.0 Hz, 4 H), 3.94 (d, J = 16.0 Hz, 4 H), 4.53–4.57 (m, 8 H), 4.68 (d, J = 8.0 Hz, 4 H), 6.79 (s, 4 H), 7.07–7.17 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.4, 35.1, 37.6, 39.6, 48.6, 60.0, 83.1, 112.2, 124.4, 125.5, 127.4, 128.2, 128.4, 128.8, 142.6, 149.4, 153.9 ppm. LRMS (FAB): m/z = 1181 $[M]^+$.

Tetrabenzoxazines (*P*,*R*,*S*)-12b/(*M*,*R*,*R*)-12b′: Prepared according to the representative procedure from tetrapentyl-tetraisopropyloxyresorcinarene **9g** (2.00 g, 2.1 mmol). The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (1:9) to afford (*P*,*R*,*S*)-**12b**/(*M*,*R*,*R*)-**12b′**. *First eluting diastereomer (P,R,S)-**12b***: Colourless foam (0.88 g, 27%). $[\alpha]_D^{25}$ = +131.4 (c = 1.4, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2969, 2926, 2858, 1467, 1110, 940, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C,): δ = 0.77 (d, J = 4.0 Hz, 12 H), 0.85 (t, J = 6.2 Hz, 12 H), 0.98–1.10 (m, 12 H), 1.15–1.34 (m, 24 H), 1.39 (d, J = 6.4 Hz, 12 H), 1.69–1.77 (m, 4 H), 1.93–2.03 (m, 4 H), 3.83 (q, J = 6.4 Hz, 4 H), 3.86 (d, J = 16.8 Hz, 4 H), 4.14 (d, J = 16.8 Hz, 4 H), 4.12 (m, 4 H), 4.31 (t, J = 7.2 Hz, 4 H), 4.53 (d, J = 9.8 Hz, 4 H), 4.59 (d, J = 9.8 Hz, 4 H), 6.82 (s, 4 H), 7.22–7.34 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.6, 21.9, 22.6, 22.7, 28.1, 32.1, 36.0, 36.7, 45.5, 57.0, 73.7, 79.5, 113.0, 125.3, 127.2, 127.5, 128.4, 129.1, 144.2, 149.8, 151.84 ppm. HRMS (FAB): calcd. for $C_{100}H_{132}O_8N_4$ $[M]^+$ 1517.0045; found 1517.0057. *Second eluting diastereomer (M,R,R)-**12b′**:* Colourless foam (0.91 g, 28%). $[\alpha]_D^{25}$ –9.1 (c = 1.5, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2968, 2926, 2857, 1461, 1110, 942, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.82–0.94 (m, 24 H), 1.03 (d, J = 5.2 Hz, 12 H), 1.18–1.32 (m, 24 H), 1.41 (d, J = 6.4 Hz, 12 H), 1.67–1.76 (m, 4 H), 1.92–2.04 (m, 4 H), 3.72–3.92 (m, 12 H), 4.10 (m, 4 H), 4.34 (t, J = 7.2 Hz, 4H), 4.52 (d, J = 10.0 Hz, 4 H), 4.93 (d, J = 10.0 Hz, 4 H), 6.86 (s, 4 H), 7.18–7.34 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.2, 22.3, 22.6, 22.7, 27.9, 32.1, 36.3, 36.5, 46.7, 57.9, 74.0, 78.8, 113.3, 125.7, 127.0, 127.4, 128.3, 144.5, 150.2, 152.1 ppm. HRMS: calcd. for $C_{100}H_{132}O_8N_4$ $[M + H]^+$ 1518.0144; found 1518.0123.

Tetrabenzoxazines (*P*,*R*,*S*)-12c/(*M*,*R*,*R*)-12c′: Prepared according to the representative procedure from tetrapentyl-tetracyclopentyloxyresorcinarene **9e** (0.34 g, 0.33 mmol). The residue was placed on a column of silica gel and eluted with ethyl acetate/ hexane (1:9) to afford (*P*,*R*,*S*)-**12c**/(*M*,*R*,*R*)-**12c′**. *First eluting diastereomer (P,R,S)-**12c**:* Colourless foam (0.13 g, 25%). $[\alpha]_D^{25}$ = +129.8 (c = 1.6, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2953, 2867, 1583, 1464, 1321, 1228, 1170, 1117, 939 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.87 (t, J = 5.8 Hz, 12 H), 1.12–1.33 (m, 40 H), 1.39 (d, J = 6.0 Hz, 12 H), 1.44–1.59 (m, 16 H), 1.62–1.81 (m, 4 H), 1.93–2.08 (m, 4 H), 3.84 (q, J = 6.5 Hz, 4 H), 3.87 (d, J = 17.0 Hz, 4 H), 4.18 (d, J = 17.0 Hz, 4 H), 4.29 (m, 4 H), 4.44 (t, J = 7.2 Hz, 4 H), 4.66 (m, 8 H), 6.87 (m, 4 H), 7.19–7.36 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.6, 22.7, 23.6, 23.7, 28.1, 32.1, 32.6, 32.8, 36.1, 36.7, 45.4, 57.2, 79.6, 84.5, 112.5, 125.4, 125.5, 127.2, 127.5, 128.4, 144.3, 150.0, 152.4 ppm. LRMS (ESI): m/z = 1622 $[M + H]^+$ (the isotopic distribution of the observed data matched the theoretical $[M + H]^+$ isotopic distribution). *Second eluting diastereomer (M,R,R)-**12c′**:* Colourless foam (0.12 g, 24%). $[\alpha]_D^{25}$ –5.0 (c = 1.6, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2952, 2867, 1583, 1490, 1457, 1320, 1228, 1169, 941 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.90 (t, J = 6.4 Hz, 12 H), 1.18–1.40 (m, 40 H), 1.45 (d, J = 6.0 Hz, 12 H), 1.50–1.66 (m, 16 H), 1.68–1.81 (m, 4 H), 1.94–2.06 (m, 4 H), 3.79 (q, J = 6.4 Hz, 4 H), 3.86 (d, J = 16.8 Hz, 4 H), 3.92 (d, J = 16.8 Hz, 4 H), 4.29 (m, 4 H), 4.44 (t, J = 7.2 Hz, 4 H), 4.57 (d, J = 9.4 Hz, 4 H), 4.95 (d, J = 16.8 Hz, 4 H), 6.88 (m, 4 H), 7.15–7.46 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.2, 22.7, 23.4, 23.6, 28.0, 32.1, 32.8, 36.2, 36.6, 46.8, 57.8, 78.8, 84.6, 112.8, 127.0, 127.4, 128.3, 144.4, 150.2, 152.8 ppm. LRMS (ESI): m/z = 1622 $[M + H]^+$ (the isotopic distribution of the observed data matched the theoretical $[M + H]^+$ isotopic distribution].

Tetrabenzoxazines (*M*,*S*,*R*)-13a/(*P*,*S*,*S*)-13a′: Prepared according to the representative procedure from tetrapentyl-tetramethoxyresorcinarene **9a** (5.0 g, 6.1 mmol). The residue was placed on a column of silica gel and eluted with ethyl acetate/ hexane (1:5) to afford (*M*,*S*,*R*)-**13a**/(*P*,*S*,*S*)-**13a′**. *First eluting diastereomer (M,S,R)-**13a**:* Pale yellow foam (3.00 g, 35%). $[\alpha]_D^{25}$ –107.0 (c = 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (br. t, J = 6.8 Hz, 12 H), 1.33 (m, 24 H), 1.38 (d, J = 6.8 Hz, 12 H), 1.79–1.82 (m, 4 H), 1.89–1.91 (m, 4 H), 3.25 (s, 12 H), 3.80 (q, J = 6.4 Hz, 4 H), 3.84 (d, J = 16.8 Hz, 4 H), 4.15 (d, J = 17.2 Hz, 4 H), 4.24 (t, J = 7.6 Hz, 4 H), 4.58 (d, J = 10.0 Hz, 4 H), 4.63 (d, J = 10.4 Hz, 4 H), 6.73 (s, 4 H), 7.26 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.3, 22.7, 27.9, 32.2, 35.4, 35.7, 44.6, 57.2, 60.0, 79.5, 112.2, 124.5, 127.3, 127.5, 127.8, 128.4, 128.8, 144.1, 150.1, 153.5 ppm. LRMS

(FAB): *m*/*z* = 1405 [M]$^+$. *Second eluting diastereomer (P,S,S)-**13a**′:* Pale yellow foam (2.70 g, 32%). $[\alpha]_D^{25}$ = +7.0 (*c* = 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (br. t, 12 H), 1.30 (m, 24 H), 1.38 (d, *J* = 6.4 Hz, 12 H), 1.75–1.80 (m, 4 H), 1.90–1.95 (m, 4 H), 3.33 (s, 12 H), 3.70 (q, *J* = 6.4 Hz, 4 H), 3.88 (d, *J* = 16.8 Hz, 4 H), 3.97 (d, *J* = 17.2 Hz, 4 H), 4.44 (t, *J* = 7.6 Hz, 4 H), 4.55 (d, *J* = 10.0 Hz, 4 H), 4.98 (d, *J* = 10.0 Hz, 4 H), 6.80 (s, 4 H), 7.18–7.30 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.4, 22.7, 27.8, 32.2, 35.4, 36.1, 45.3, 57.4, 60.2, 79.2, 112.2, 124.5, 127.1, 127.4, 127.9, 128.4, 128.5, 144.4, 150.3, 154.0 ppm. LRMS (FAB): *m*/*z* = 1405 [M]$^+$.

Tetrabenzoxazines (*M*,*S*,*R*)-13b/(*P*,*S*,*S*)-13b′: Prepared according to the representative procedure from tetrapentyl-tetraisopropyloxyresorcinarene **9c** (2.0 g, 2.1 mmol). The residue was placed on a column of silica gel and eluted with ethyl acetate/hexane (1:4) to afford (*M*,*S*,*R*)-**13b**/(*P*,*S*,*S*)-**13b**′. *First eluting diastereomer (M,S,R)-**13b**:* Yellow foam (1.20 g, 35%). $[\alpha]_D^{25}$ –116.0 (*c* = 0.32, $CHCl_3$). IR (CH_2Cl_2): ṽ = 3054, 2986, 2305, 1421, 1265, 896, 749, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.77 (d, *J* = 4.0 Hz, 12 H), 0.85 (t, *J* = 6.2 Hz, 12 H), 0.98–1.10 (m, 12 H), 1.15–1.34 (m, 24 H), 1.39 (d, *J* = 6.4 Hz, 12 H), 1.69–1.77 (m, 4 H), 1.93–2.03 (m, 4 H), 3.83 (q, *J* = 6.4 Hz, 4 H), 3.86 (d, *J* = 16.8 Hz, 4 H), 4.14 (d, *J* = 16.8 Hz, 4 H), 4.12 (m, 4 H), 4.31 (t, *J* = 7.2 Hz, 4 H), 4.53 (d, *J* = 9.8 Hz, 4 H), 4.59 (d, *J* = 9.8 Hz, 4 H), 6.82 (s, 4 H), 7.22–7.34 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.6, 21.9, 22.6, 22.7, 28.1, 32.1, 36.0, 36.7, 45.5, 57.0, 73.7, 79.5, 113.0, 125.3, 127.2, 127.5, 128.4, 129.1, 144.2, 149.8, 151.84 ppm. LRMS (FAB): *m*/*z* = 1518 [M]$^+$. *Second eluting diastereomer (P,S,S)-**13b**′:* Yellow foam (1.10 g, 32%).$[\alpha]_D^{25}$ = +3.0 (*c* = 0.36, $CHCl_3$). IR (CH_2Cl_2): ṽ = 2968, 2926, 2857, 1461, 1110, 942, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.82–0.94 (m, 24 H), 1.03 (d, *J* = 5.2 Hz, 12 H), 1.18–1.32 (m, 24 H), 1.41 (d, *J* = 6.4 Hz, 12 H), 1.67–1.76 (m, 4 H), 1.92–2.04 (m, 4 H), 3.72–3.92 (m, 12 H), 4.10 (m, 4 H), 4.34, (t, *J* = 7.2 Hz, 4 H), 4.52 (d, *J* = 10.0 Hz, 4 H), 4.93 (d, *J* = 10.0 Hz, 4 H), 6.86 (s, 4 H), 7.18–7.34 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.2, 22.3, 22.6, 22.7, 27.9, 32.1, 36.3, 36.5, 46.7, 57.9, 74.0, 78.8, 113.3, 125.7, 127.0, 127.4, 128.3, 144.5, 150.2, 152.1 ppm. LRMS (FAB): *m*/*z* = 1518 [M]$^+$.

Tetrabenzoxazines (*M*,*S*,*R*)-13c/(*P*,*S*,*S*)-13c′: Prepared according to the representative procedure from tetrapentyl-tetra-*n*-butyloxyresorcinarene **9i** (1.00 g, 1.0 mmol). The residue was placed on a column of silica gel and eluted with ethyl acetate/light petroleum (1:7) to afford (*M*,*S*,*R*)-**13c**/(*P*,*S*,*S*)-**13c**′. *First eluting diastereomer (M,S,R)-**13c**:* Pale yellow foam (0.50 g, 31%). $[\alpha]_D^{25}$ –105.0 (*c* = 0.23, $CHCl_3$). IR (CH_2Cl_2): ṽ = 3053, 2958, 2305, 1466, 1421, 1265, 896, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.93 (t, *J* = 7.2 Hz, 12 H), 0.97 (t, *J* = 6.4 Hz, 12 H), 1.41 (m, 32 H), 1.46 (d, *J* = 6.8 Hz, 12 H), 1.56–1.65 (m, 8 H), 1.86–1.92 (m, 4 H), 1.97–2.02 (m, 4 H), 3.50–3.41 (m, 4 H), 3.47–3.52 (m, 4 H), 3.89–3.95 (m, 8 H), 4.26 (d, *J* = 16.8 Hz, 4 H), 4.54 (t, *J* = 7.2 Hz, 4 H), 4.69 (d, *J* = 10.0 Hz, 4 H), 4.73 (d, *J* = 10.0 Hz, 4 H), 6.85 (s, 4 H), 7.31–7.39 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 14.3, 14.4, 19.6, 21.6, 23.0, 28.2, 32.5, 32.9, 36.2, 36.3, 45.2, 57.9, 72.7, 80.1, 112.9, 125.3, 127.5, 127.9, 127.9, 128.7, 129.0, 144.8, 150.5, 153.3 ppm. HRMS (FAB): calcd. for $C_{104}H_{140}N_4O_8$ [M]$^+$ 1573.0671; found 1573.0708. $C_{104}H_{140}N_4O_8$ (1574.25): calcd. C 79.35, H 8.96, N 3.56; found C 79.27, H 9.03, N 3.62. *Second eluting diastereomer (P,S,S)-**13c**′:* Pale yellow foam (0.50 g, 31%). $[\alpha]_D^{25}$ = +21.0 (*c* = 0.51, $CHCl_3$). IR (CH_2Cl_2): ṽ = 3053, 2959, 2305, 1590, 1465, 1421, 1265, 896, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.77 (t, *J* = 7.2 Hz, 12 H), 0.86 (br. t, 12 H), 1.15–1.24 (m, 8 H), 1.30 (m, 24 H), 1.39 (d, *J* = 6.4 Hz, 12 H), 1.41–1.48 (m, 8 H), 1.74–1.79 (m, 4 H), 1.88–1.93 (m, 4 H), 3.32–3.43 (m, 8 H), 3.70 (q, *J* = 6.8 Hz, 4 H), 3.88 (2× br. d, 8 H), 4.43 (t, *J* = 7.2 Hz, 4 H), 4.53 (d, *J* = 10.0 Hz, 4 H), 4.90 (d, *J* = 10.0 Hz, 4 H), 6.77 (s, 4 H), 7.12–7.27 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 14.2, 14.4, 19.5, 21.4, 23.0, 28.1, 32.5, 32.7, 36.1, 36.4, 46.1, 58.1, 72.6, 79.6, 113.0, 125.1, 127.3, 127.9, 128.1, 128.6, 128.9, 144.8, 150.6, 153.6 ppm. LRMS (FAB): *m*/*z* = 1573 [M]$^+$. $C_{104}H_{140}N_4O_8$ (1574.25): calcd. C 79.35, H 8.96, N 3.56; found C 79.45, H 9.02, N 3.53.

Representative Procedure for the Reaction of Bis(aminol) Ethers with Tetraalkoxyresorcinarenes Under Microwave-Assisted Conditions

Tetrabenzoxazine 11a: Tetramethoxyresorcinarene **9a** (0.50 g, 0.6 mmol) was suspended in *N*,*N*-bis(methoxymethyl)-*N*-benzylamine (0.93 g, 4.8 mmol) in a CEM microwave tube. The suspension was heated under microwave irradiation at 150 °C for 10 min (without cooling). The obtained orange oil was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to afford **11a** (0.66 g, 82%).

Tetrabenzoxazines (*M*,*S*,*R*)-13a and (*P*,*S*,*S*)-13a′: Prepared according to the representative procedure from tetrapentyl-tetramethoxyresorcinarene **9a** (0.46 g, 0.6 mmol) and *N*,*N*-bis(methoxymethyl)-*N*-[(*S*)-(–)-(α-methylbenzyl)]amine (0.83 g, 4.5 mmol). The suspension was heated under microwave irradiation at 150 °C for 10 min (without cooling). The obtained orange oil was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to afford (*M*,*S*,*R*)-**13a** (0.29 g, 38%) and (*P*,*S*,*S*)-**13a**′ (0.27 g, 36%) as pale yellow foams.

Tetrabenzoxazines (*M*,*S*,*R*)-13b: and (*P*,*S*,*S*)-13b′: Prepared according to the representative procedure from tetrapentyl-tetraisopropyloxyresorcinarene **9c** (0.10 g, 0.1 mmol). The suspension was heated under microwave irradiation at 140 °C for 3 × 10 min. The obtained orange oil was placed on a column of silica gel and eluted with hexane/ethyl acetate (6:1) to afford (*M*,*S*,*R*)-**13b** (0.063 g, 39%) and (*P*,*S*,*S*)-**13b**′ (0.064 g, 39%) as pale yellow foams.

Tetrabenzoxazines (*M*,*S*,*R*)-14a and **(*P*,*S*,*S*)-14a′:** Prepared according to the representative procedure from tetraundecyl-tetramethoxyresorcinarene **9d** (0.50 g, 0.43 mmol). The suspension was heated under microwave irradiation at 150 °C for 2 × 10 min. The obtained orange oil was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to afford (*M*,*S*,*R*)-**14a** and (*P*,*S*,*S*)-**14a**′. *First eluting diastereomer (M,S,R)-**14a**:* Pale yellow oil (0.25 g, 33%). $[\alpha]_D^{25}$ –95.2 (*c* = 0.84, $CHCl_3$). IR ($CHCl_3$): ṽ = 3060, 2922, 2852, 2359, 1589, 1467, 1321, 1229, 1098, 944, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 6.4 Hz, 12 H), 1.17–1.27 (m, 72 H), 1.31 (d, *J* = 6.4 Hz, 12 H), 1.55–1.82 (m, 8 H), 3.18 (s, 12 H), 3.72 (q, *J* = 6.4 Hz, 4 H), 3.76 (d, *J* = 16.8 Hz, 4 H), 4.08 (d, *J* = 16.8 Hz, 4 H), 4.34 (t, *J* = 7.6 Hz, 4 H), 4.53 (d, *J* = 10.0 Hz, 4 H), 4.63 (d, *J* = 10.0 Hz, 4 H), 6.65 (s, 4 H), 7.08–7.29 (m, 20 H) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 14.1, 20.1, 21.3, 22.7, 28.3, 29.4, 29.8, 29.8, 30.0, 30.1, 32.0, 35.4, 35.8, 57.3, 60.1, 70.0, 112.2, 124.6, 127.3, 127.5, 127.8, 128.4, 128.8, 144.1, 144.4, 150.1, 153.6 ppm. HRMS (FAB): calcd. for $C_{116}H_{164}O_8N_4$ [M + H]$^+$ 1742.2627; found 1742.2627. *Second eluting diastereomer (P,S,S)-**14a**′:* Pale yellow oil (0.24 g, 31%). $[\alpha]_D^{25}$ –15.4 (*c* = 0.63, $CHCl_3$). IR ($CHCl_3$): ṽ = 3059, 2922, 2851, 2346, 1589, 1467, 1322, 1230, 1095, 946, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 12 H), 1.24–1.30 (m, 72 H), 1.38 (d, *J* = 6.4 Hz, 12 H), 1.76–1.94 (m, 8 H), 3.33 (s, 12 H), 3.69 (q, *J* = 6.4 Hz, 4 H), 3.88 (d, *J* = 16.8 Hz, 4 H), 3.96 (d, *J* = 16.8 Hz, 4 H), 4.43 (t, *J* = 7.2 Hz, 4 H), 4.55 (d, *J* = 10.0 Hz, 4 H), 4.99 (d, *J* = 10.0 Hz, 4 H), 6.80 (s, 4 H), 7.16–7.34 (m, 20 H) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 14.1, 21.4, 22.7, 28.2, 29.4, 29.75, 29.83, 29.9, 30.1, 32.0, 35.4, 36.1, 45.4, 57.4, 60.2, 79.2, 112.3, 124.5, 127.2, 127.4,

127.8, 128.4, 144.4, 150.3, 154.0 ppm. HRMS (FAB): calcd. for $C_{116}H_{164}O_8N_4$ $[M]^+$ 1741.2549; found 1741.2523.

Tetrabenzoxazines (*M*,*S*,*R*)-15a and (*P*,*S*,*S*)-15a′: Prepared according to the representative procedure from tetra-2-methylpropyl-tetramethoxyresorcinarene (1.0 g, 1.30 mmol). The suspension was heated under microwave irradiation at 150 °C for 2×10 min. The obtained orange oil was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to afford (*M*,*S*,*R*)-**15a** and (*P*,*S*,*S*)-**15a′**. *First eluting diastereomer (M,S,R)-15a:* Pale yellow foam (0.75 g, 43%). $[\alpha]_D^{25}$ –108.1 (*c* = 0.47, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2951, 2864, 2359, 1589, 1469, 1365, 1235, 1095, 942, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 10.0 Hz, 12 H), 0.96 (d, *J* = 10.0 Hz, 12 H), 1.39 (d, *J* = 6.5 Hz, 12 H), 1.52–1.61 (m, 4 H), 1.65–1.72 (m, 4 H), 1.76–1.83 (m, 4 H), 3.26 (s, 12 H), 3.80 (q, *J* = 6.5 Hz, 4 H), 3.86 (d, *J* = 17.0 Hz, 4 H), 4.17 (d, *J* = 16.9 Hz, 4 H), 4.55–4.62 (m, 12 H), 6.70 (s, 4 H), 7.17–7.35 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 22.8, 22.9, 25.9, 33.1, 44.6, 44.9, 57.2, 60.1, 79.6, 112.3, 124.7, 127.3, 127.6, 128.4, 128.7, 144.0, 150.0, 153.6 ppm. HRMS (FAB): calcd. for $C_{88}H_{108}O_8N_4$ $[M]^+$ 1348.8167; found 1348.8189. *Second eluting diastereomer (P,S,S)-15a′:* Colourless crystals, recrystallized from ethanol (0.75 g, 43%). M.p. 144–146 °C. $[\alpha]_D^{25}$ = +18.1 (*c* = 1.04, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2950, 2863, 2360, 1590, 1467, 1366, 1235, 1090, 941, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 20.2 Hz, 12 H), 0.93 (d, *J* = 20.2 Hz, 12 H), 1.39 (d, *J* = 6.5 Hz, 12 H), 1.45–1.50 (m, 4 H), 1.65–1.68 (m, 4 H), 1.77–1.83 (m, 4 H), 3.36 (s, 12 H), 3.68 (q, *J* = 6.5 Hz, 4 H), 3.95 (q, *J* = 15.2 Hz, 8 H), 4.57 (q, *J* = 7.8 Hz, 8 H), 4.97 (d, *J* = 9.9 Hz, 4 H), 6.81 (s, 4 H), 7.16–7.37 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C): δ = 21.2, 22.8, 25.9, 33.3, 45.4, 45.5, 57.7, 60.1, 79.4, 112.6, 124.8, 127.0, 127.4, 127.8, 128.3, 144.4, 150.1, 150.4, 154.1 ppm. HRMS (FAB): calcd. $C_{88}H_{108}O_8N_4$ $[M]^+$ 1348.8167; found 1348.8188.

Tetrabenzoxazines (*M*,*S*,*R*)-16a and (*P*,*S*,*S*)-16a′: Prepared according to the representative procedure from tetra-2-methylpropyl-tetraisopropyloxyresorcinarene (0.10 g, 0.11 mmol). The suspension was heated under microwave irradiation at 140 °C for 3×10 min. The obtained orange oil was placed on a column of silica gel and eluted with hexane/ethyl acetate (6:1) to afford (*M*,*S*,*R*)-**16a** and (*P*,*S*,*S*)-**16a′**. *First eluting diastereomer (M,S,R)-16a:* Yellow foam (0.062 g, 37%). $[\alpha]_D^{25}$ –136.9 (*c* = 1.3, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2953, 2361, 1457, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.85 (d, *J* = 5.6 Hz, 12 H), 0.93 (t, *J* = 6.4 Hz, 24 H), 1.06 (d, *J* = 5.6 Hz, 12 H), 1.41 (d, *J* = 6.4 Hz, 12 H), 1.45–1.56 (m, 4 H), 1.66–1.74 (m, 4 H), 1.85–1.93 (m, 4 H), 3.85 (q, *J* = 6.4 Hz, 4 H), 3.92 (d, *J* = 16.8 Hz, 4 H), 4.21 (d, *J* = 16.8 Hz, 4 H), 4.10 (m, 4 H), 4.47–4.65 (m, 12 H), 6.88 (s, 4 H), 7.22–7.39 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 21.1, 21.9, 22.5, 26.0, 34.3, 45.0, 45.4, 56.9, 73.8, 79.5, 113.0, 125.8, 127.2, 127.6, 128.4, 144.2, 149.9, 151.3 ppm. HRMS (FAB): calcd. for $C_{100}H_{132}O_8N_4$ $[M]^+$ 1464.9732; found 1464.9759. *Second eluting diastereomer (P,S,S)-16a′:* Yellow foam (0.064 g, 38%). $[\alpha]_D^{25}$ –12.0 (*c* = 1.5, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2969, 2864, 2359, 1465, 1109, 939 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.89 (t, *J* = 6.8 Hz, 24 H), 0.96 (t, *J* = 6.0 Hz, 12 H), 1.08 (d, *J* = 6.0 Hz, 12 H), 1.45 (d, *J* = 6.4 Hz, 12 H), 1.51–1.58 (m, 4 H), 1.62–1.73 (m, 4 H), 1.82–1.93 (m, 4 H), 3.75–3.91 (m, 12 H), 4.10 (m, 4 H, H7), 4.54 (t, *J* = 7.4 Hz, 4 H), 4.58 (d, *J* = 9.6 Hz, 4 H), 4.98 (d, *J* = 9.6 Hz, 4 H), 6.91 (s, 4 H), 7.21–7.39 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 22.3, 22.4, 26.0, 34.4, 45.5, 46.8, 57.8, 74.1, 78.8, 113.4, 127.0, 127.4, 128.3, 144.5, 150.1 ppm.

Tetrabenzoxazines (*M*,*S*,*R*)-17a and (*P*,*S*,*S*)-17a′: Prepared according to the representative procedure from tetrapentyl-tetracyclopentyloxyresorcinarene **9e** (0.10 g, 0.10 mmol). The suspension was heated under microwave irradiation at 140 °C for 4×10 min. The obtained orange oil was placed on a column of silica gel and eluted with hexane/ethyl acetate (9:1) to afford (*M*,*S*,*R*)-**17a** and (*P*,*S*,*S*)-**17a′**. *First eluting diastereomer (M,S,R)-17a:* Yellow foam (0.057 g, 37%). $[\alpha]_D^{25}$ –127.6 (*c* = 1.3, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2958, 2872, 1588, 1469, 1326, 1231, 1116, 939 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.87 (t, *J* = 5.8 Hz, 12 H), 1.12–1.33 (m, 40 H), 1.39 (d, *J* = 6.0 Hz, 12 H), 1.44–1.59 (m, 16 H), 1.62–1.81 (m, 4 H), 1.93–2.08 (m, 4 H), 3.84 (q, *J* = 6.5 Hz, 4 H), 3.87 (d, *J* = 17.0 Hz, 4 H), 4.18 (d, *J* = 17.0 Hz, 4 H), 4.29 (m, 4 H), 4.44 (t, *J* = 7.2 Hz, 4 H), 4.66 (m, 8 H), 6.87 (m, 4 H), 7.19–7.36 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.6, 22.7, 23.6, 23.7, 28.1, 32.1, 32.6, 32.7, 36.1, 36.7, 45.4, 57.2, 79.6, 84.5, 112.6, 125.4, 125.5, 127.2, 127.4, 128.4, 144.3, 149.9, 152.3 ppm. LRMS (ESI): *m*/*z* = 1622 $[M + H]^+$. *Second eluting diastereomer (P,S,S)-17a′:* Yellow foam (0.055 g, 35%). $[\alpha]_D^{25}$ = +6.2 (*c* = 1.8, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 2950, 2864, 1582, 1494, 1452, 1315, 1225, 941 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 0.90 (t, *J* = 6.4 Hz, 12 H), 1.18–1.40 (m, 40 H), 1.45 (d, *J* = 6.0 Hz, 12 H), 1.50–1.66 (m, 16 H), 1.68–1.81 (m, 4 H), 1.94–2.06 (m, 4 H), 3.79 (q, *J* = 6.4 Hz, 4 H), 3.86 (d, *J* = 16.8 Hz, 4 H), 3.92 (d, *J* = 16.8 Hz, 4 H), 4.29 (m, 4 H), 4.44 (t, *J* = 7.2 Hz, 4 H), 4.57 (d, *J* = 9.4 Hz, 4 H), 4.95 (d, *J* = 16.8 Hz, 4 H), 6.88 (m, 4 H), 7.15–7.46 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.2, 22.7, 23.3, 23.6, 28.0, 32.1, 32.8, 36.2, 36.6, 46.7, 57.8, 78.8, 84.6, 112.6, 127.1, 127.4, 128.5, 144.3, 150.2, 152.9 ppm. LRMS (ESI): *m*/*z* = 1622 $[M + H]^+$.

Compound 18: Anhydrous potassium carbonate (4.48 g, 32.4 mmol) was added to a solution of tetraheptyl-tetramethoxyresorcinarene **9c** (1.52 g, 1.6 mmol) and ethyl bromoacetate (2.17 g, 13.0 mmol) in dry acetone (250 mL), and the mixture was heated under reflux for 40 h. The reaction mixture was cooled to room temperature and filtered. The mother liquor was concentrated under reduced pressure to yield a mobile oil. The oil was dissolved in diethyl ether (80 mL) and washed successively with water (2×50 mL), brine (1×50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a colourless oil which crystallized from a minimum amount of methanol when cooled to 4 °C for 24 h to yield **18** as colourless crystals (1.77 g, 85%). M.p. 63.5–64.0 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2928, 1761, 1500, 1303, 1192 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (br. t, *J* = 6.7 Hz, 12 H), 1.16–1.42 (m, 52 H,), 1.76–1.90 (m, 8 H), 3.62 (s, 12 H), 4.24 (q, *J* = 7.2 Hz, 8 H), 4.03 (d, *J* = 15.9 Hz, 4 H), 4.19 (d, *J* = 15.9 Hz, 4 H), 4.52 (t, *J* = 7.4 Hz, 4 H), 6.31 (s, 4 H), 6.62 (s, 4 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.8, 14.9, 23.4, 28.7, 30.0, 30.6, 32.7, 35.3, 36.2 (CH_2 and CH), 56.2, 61.6, 69.1, 100.2, 127.0, 128.1, 128.8, 155.6, 156.2, 170.3 ppm. HRMS (FAB): calcd. for $C_{76}H_{112}O_{16}$ $[M]^+$ 1280.7950; found 1280.7685.

General Procedure for the Formation of Resorcinarene Amides: A mixture of resorcinarene (3.0 g), 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide (4.8 equiv.) and potassium carbonate (8.0 equiv.) in dry acetonitrile (80 mL) was heated under reflux overnight. The reaction mixture was then cooled and water (80 mL) added. The resulting precipitate was filtered and dried under vacuum to afford the corresponding diastereomeric mixtures. The diastereomers were separated by flash chromatography with ethyl acetate/dichloromethane (1:1) as the eluant.

Resorcinarene Amides (*M*,*R*,*R*)-20a and (*P*,*R*,*S*)-20a′: Prepared according to the general procedure from tetrapropyl-tetramethoxyresorcinarene **9b** (3.00 g, 4.2 mmol) and 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide (4.61 g, 20.2 mmol) to afford (*M*,*R*,*R*)-**20a** and

(*P*,*R*,*S*)-**20a′**. *First eluting diastereomer (M,R,R)-**20a**:* Colourless crystals, recrystallized from methanol (2.01 g, 35%). M.p. 180–181 °C, $[\alpha]_D^{25}$ –7.8 (*c* = 2.04, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3422, 2955, 2930, 2870, 1684, 1501, 1299, 1199 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 12 H), 1.23–1.41 (m, 8 H), 1.46 (d, *J* = 6.6 Hz, 12 H), 1.82–1.98 (m, 8 H), 3.34 (s, 12 H), 4.06 (d, *J* = 14.5 Hz, 4 H), 4.33 (d, *J* = 14.5 Hz, 4 H), 4.57 (t, *J* = 8.0 Hz, 4 H), 5.11–5.31 (m, 4 H), 6.03 (s, 4 H), 6.80–6.92 (m, 8 H), 7.02–7.22 (m, 20 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.9, 22.0, 22.5, 35.6, 38.0, 48.6, 56.7, 68.3, 98.0, 126.1, 126.5, 126.9, 127.0, 127.9, 129.2, 143.4, 154.1, 156.3, 168.1 ppm. HRMS (FAB): calcd. for $C_{84}H_{100}N_4O_{12}$ $[M]^+$ 1356.7338; found 1356.7129. *Second eluting diastereomer (P,R,S)-**20a′**:* Colourless crystals, recrystallized from methanol (0.67 g, 12%). M.p. 168–169 °C, $[\alpha]_D^{25}$ –13.8 (*c* = 1.31, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3419, 2955, 2931, 2870, 1682, 1499, 1298, 1197 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 12 H), 1.16–1.37 (m, 8 H), 1.49 (d, *J* = 6.6 Hz, 12 H), 1.75–1.90 (m, 8 H), 3.44 (s, 12 H), 4.20 (d, *J* = 14.8 Hz, 4 H), 4.30 (d, *J* = 14.8 Hz, 4 H), 4.58 (t, *J* = 7.2 Hz, 4 H), 5.16–5.35 (m, 4 H), 6.25 (s, 4 H), 6.81 (s, 4 H), 7.03 (d, 4 H), 7.26–7.40 (m, 20 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.9, 22.0, 22.4, 35.6, 38.1, 48.7, 57.0, 69.1, 98.8, 126.7, 126.9, 127.0, 127.8, 128.0, 129.3, 143.5, 154.3, 156.3, 168.3 ppm. $C_{84}H_{100}N_4O_{12}$ (1357.71): calcd. C 74.3, H 7.4, N 4.1; found C 73.9, H 7.3, N 4.1.

Resorcinarene Amides (*M*,*R*,*R*)-20b and (*P*,*R*,*S*)-20b′: Prepared according to the general procedure from tetraheptyl-tetramethoxyresorcinarene **9c** (3.00 g, 3.2 mmol) and 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide (3.51 g, 15.4 mmol) to afford (*M*,*R*,*R*)-**20b** and (*P*,*R*,*S*)-**20b′**. *First eluting diastereomer (M,R,R)-**20b**:* Colourless crystals, recrystallized from ethanol (1.78 g, 35%). M.p. 170–171 °C. $[\alpha]_D^{25}$ –12.6 (*c* = 4.24, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3421, 2926, 2854, 1684, 1499, 1298, 1198 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (br. t, 12 H), 1.14–1.39 (m, 40 H), 1.47 (d, *J* = 6.6 Hz, 12 H), 1.80–1.99 (m, 8 H), 3.33 (s, 12 H), 4.06 (d, *J* = 14.6 Hz, 4 H), 4.32 (d, *J* = 14.6 Hz, 4 H), 4.55 (t, *J* = 7.2 Hz, 4 H), 5.11–5.31 (m, 4 H), 6.03 (s, 4 H), 6.80–6.92 (m, 8 H), 7.01–7.22 (m, 20 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.8, 22.5, 23.3, 29.0, 30.0, 30.6, 32.7, 35.8, 36.0, 48.6, 56.8, 68.5, 98.1, 126.3, 126.6, 127.0, 127.2, 127.9, 129.2, 143.5, 154.1, 156.3, 168.1 ppm. $C_{100}H_{132}N_4O_{12}$ (1582.14): calcd. C 75.9, H 8.4, N 3.5; found C 75.6, H 8.4, N 3.5. *Second eluting diastereomer (P,R,S)-**20b′**:* Colourless crystals, recrystallized from methanol (1.28 g, 25%). M.p. 137–138 °C. $[\alpha]_D^{25}$ –14.3 (*c* = 3.72, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3418, 2926, 2854, 1685, 1500, 1297, 1198 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (br. t, 12 H), 1.13–1.36 (m, 40 H), 1.49 (d, *J* = 7.4 Hz, 12 H), 1.72–1.93 (m, 8 H), 3.44 (s, 12 H), 4.19 (d, *J* = 14.8 Hz, 4 H), 4.30 (d, *J* = 14.8 Hz, 4 H), 4.51 (t, *J* = 7.2 Hz, 4 H), 5.14–5.32 (m, 4 H), 6.21 (s, 4 H), 6.76 (s, 4 H), 6.99 (d, *J* = 8.8 Hz, 4 H), 7.22–7.35 (m, 20 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.8, 22.5, 23.3, 28.9, 30.0, 30.6, 32.6, 35.9, 36.0, 48.7, 57.0, 69.1, 98.9, 126.6, 126.9 (two coincident signals), 127.9, 128.0, 129.3, 143.5, 154.3, 156.3, 168.3 ppm. $C_{100}H_{132}N_4O_{12}$ (1582.14): calcd. C 75.9, H 8.4, N 3.5; found C 75.6, H 8.3, N 3.5.

Resorcinarene Amides (*M*,*R*,*R*)-20c and (*P*,*R*,*S*)-20c′: Prepared according to the general procedure from tetradecyl-tetramethoxyresorcinarene **9d** (3.00 g, 2.6 mmol) and 2-bromo-*N*-[(*R*)-(+)-(α-methylbenzyl)]acetamide (2.83 g, 12.4 mmol) to afford **20c** and **20c′**. *First eluting diastereomer (M,R,R)-**20c**:* Colourless crystals, recrystallized from ethanol (1.74 g, 37%). M.p. 164–165 °C. $[\alpha]_D^{25}$ –12.9 (*c* = 3.72, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3422, 2924, 2853, 1684, 1509, 1298, 1198 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (br. t, 12 H), 1.17–1.38 (m, 72 H), 1.47 (d, *J* = 7.4 Hz, 12 H), 1.80–1.98 (m, 8 H), 3.33 (s, 12 H), 4.05 (d, *J* = 14.5 Hz, 4 H), 4.32 (d, *J* = 14.5 Hz, 4 H), 4.54 (t, *J* = 7.4 Hz, 4 H), 5.11–5.31 (m, 4 H), 6.04 (s, 4 H), 6.81 (s, 4 H), 6.87 (d, *J* = 8.2 Hz, 4 H), 7.03–7.21 (m, 20 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.8, 22.6, 23.4, 29.1, 30.1, 30.4, 30.45, 30.5, 30.7, 32.6, 35.8, 36.1, 48.6, 56.7, 68.4, 98.1, 126.2, 126.6, 127.0, 127.1, 128.0, 129.2, 143.5, 154.1, 156.3, 168.1 ppm. $C_{116}H_{164}N_4O_{12}$ (1806.56): calcd. C 77.1, H 9.2, N 3.1; found C 77.2, H 9.1, N 3.1. *Second eluting diastereomer (P,R,S)-**20c′**:* Colourless crystals, recrystallized from ethanol (1.09 g, 23%). M.p. 108.5–110.0 °C. $[\alpha]_D^{25}$ –13.0 (*c* = 2.77, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3418, 2924, 2853, 1685, 1500, 1297, 1198 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (br. t, 12 H), 1.13–1.37 (m, 72 H), 1.49 (d, *J* = 6.6 Hz, 12 H), 1.76–1.95 (m, 8 H), 3.44 (s, 12 H), 4.19 (d, *J* = 14.7 Hz, 4 H), 4.29 (d, *J* = 14.7 Hz, 4 H), 4.50 (t, *J* = 7.4 Hz, 4 H), 5.12–5.31 (m, 4 H), 6.21 (s, 4 H), 6.75 (s, 4 H), 6.98 (d, *J* = 8.0 Hz, 4 H), 7.22–7.36 (m, 20 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.8, 22.5, 23.4, 29.0, 30.1, 30.39, 30.4, 30.47, 30.5, 30.7, 32.6, 35.9, 36.0, 48.7, 57.0, 69.2, 98.9, 126.6, 126.9, 127.0, 127.9, 128.0, 129.3, 143.5, 154.3, 156.3, 168.3 ppm. $C_{116}H_{164}N_4O_{12}$ (1806.56): calcd. C 77.1, H 9.2, N 3.1; found C 77.0, H 9.0, N 3.0.

Representative Procedure for the Addition of Diethyl or Dimethylzinc to Aromatic Aldehydes

1-Phenylpropanol:[52] Diethylzinc (1.0 M in hexanes, 2.2 mmol, 2.2 mL) was added to a solution of tetrabenzoxazine (*P*,*R*,*S*)-**12b** (0.017 g, 0.01 mmol) in toluene (1 mL) at 0 °C, and the solution was then cooled to –78 °C for 30 min. Benzaldehyde (0.1 mL, 1.0 mmol) was then added dropwise, and the solution was left for 12 h while ambient temperature was attained. The solution was quenched with NH_4Cl and extracted with diethyl ether (2 × 10 mL). The conversion and *ee* were calculated from the crude product (>95% conversion, 83% *ee*). IR (neat): $\tilde{\nu}$ = 3358, 2929, 2873, 1475, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 1.75–1.87 (m, 2 H), 2.40 (br. s, 1 H), 4.58 (t, *J* = 6.8 Hz, 1 H), 7.29–7.40 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1, 31.8, 75.9, 125.9, 128.3, 128.9, 144.5 ppm. GC conditions: β cyclodextrin (120 °C, isothermal), 6.28 min, 6.43 min (major isomer).

Supporting information (see footnote on the first page of this article): Synthesis and spectroscopic data for the following compounds: tetrabenzoxazines (*P*,*R*,*S*)-**2a**, (*P*,*R*,*S*)-**2b**, (*P*,*R*,*S*)-**3c**, (*P*,*R*,*S*)-**12a**/(*M*,*R*,*R*)-**12a′**, hexabenzoxazines (*M*,*R*)-**5**/(*P*,*S*)-**5′**, (*M*,*R*,*R*)-**6**/(*P*,*R*,*S*)-**6′**, tetra-*O*-methyl ether (*P*,*R*,*S*)-**3a**, 4,10,16,22-tetrahydroxy-6,12,18,24-tetramethoxy-2,8,14,20-tetrapropylresorcinarene (**9b**), 4,10,16,22-tetrahydroxy-2,8,14,20-tetraisobutyl-6,12,18,24-tetrakis(isopropyloxy)resorcinarene (**9h**), 1-phenylethanol, 2-methyl-1-phenylpropanol, (4-methoxyphenyl)propanol, (*E*)-5-phenylpent-4-en-3-ol, (4-chlorophenyl)propanol and 1,3-diphenylprop-2-yn-1-ol.

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