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

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ABSTRACT

The measurement of the pK_a of a racemic tetramethoxyresorcin[4]arene explains the failure to obtain good yields in attempted Mannich reactions of tetraalkoxyresorcin[4]arenes under classical reaction conditions. The failure is related to the lack of adequate concentrations of iminium ions that results from the reduced acid strength of tetraalkoxyresorcin[4]arenes as compared to parent octahydroxyresorcin[4]arenes. However, the preparation of a series of Mannich bases derived from racemic tetraalkoxyresorcin[4]arenes was accomplished using aprotic reaction conditions, including microwave assisted reactions, and using pre-formed iminium ion intermediates. In the case of reactions using chiral bis(aminol)ethers, the reactions gave mixtures of diastereoisomers that were separated by flash chromatography. The absolute configurations of the enantiomerically pure tetrabenzoxazine derivatives were established as (*P,R,S*) or (*M,S,R*), in some cases by X-ray crystallographic analysis, and by a comparison of nuclear magnetic resonance spectroscopic data. The alkylation of racemic tetramethoxyresorcin[4]arenes was achieved in reactions using an excess of *N*-(*R*)-(+)- α -methylbenzyl-2-bromoacetamide in acetonitrile containing potassium carbonate. Enantioselective ligand-assisted reactions of aromatic aldehydes are reported using dialkylzinc reagents both in the absence and presence of terminal alkynes.

Introduction

The chemistry of calixarenes provides a diverse range of molecular assemblies that have been used for a variety of purposes, 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 catalysed 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 which have been used under mild classical conditions with aqueous formaldehyde at an early stage,^{4a-d} even including aza-crown secondary amines,^{4e} and can lead to tetra(dialkylaminomethyl) derivatives.^{4k-p} Oxazolidines derived from secondary β -amino alcohols^{4f} and the amination of 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 not to require added protic acid. Mannich reactions that can lead to partial aminoalkylation of resorcin[4]arenes have also been reported using di-isopropylamine as the secondary amine.⁵ Mannich reactions using primary amines and formaldehyde have also been widely used and lead to tetrabenzoxazine derivatives.^{3a,6} Dissymmetry generated by the unsymmetrical substitution of calixarenes is related to the non-planar structures of the parent compounds;^{7a} it was also recognized that a number of chiral calixarene conformers are racemized thermally by processes involving 'through-the-annulus rotation'.^{7b} The depending alkyl group that is present in resorcinarenes, for example the 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, in the majority of published examples the products have been obtained as racemates that have defied resolution except by using chiral HPLC techniques.⁸ This has inevitably meant that only very small amounts of optically pure material have been available for use in other studies. An exception to this problem was provided by studies carried out by us,^{9a} and others,^{9b,c} using optically pure α -methylbenzylamines and formaldehyde that 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 using *n*-butyllithium in tetrahydrofuran at -78°C followed by reaction with methyl triflate in order to preclude diastereoisomerization as well as 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 co-workers 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 and used the *R*- and *S*-designations in this connection.^{11c} They prepared and considered cyclo-hexaalanyls and cyclo-diglycyl-tetraalanyl 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,b} was strongly recommended,^{12c} rather than the *aR/aS* descriptors that are regarded as being 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 attached to the phenolic groups, viewed from a position *above* the polar rim in the benzenoid rings, is defined as having *P* axial chirality as in the compounds (*P,R,S*)-**2a**, shown in **Figure 1**. The symbols are shown in the following sequence: axial chirality (*P*), followed by the chiral auxiliary (*R*), and finally the inter-ring stereogenic centre (*S*). In a number of other papers in this area C_4 symmetric compounds are frequently shown in an abbreviated form as in for example (*M,R,R*)-**2***, a diastereoisomer of **2a**, shown in **Figure 2** where the benzenoid ring is viewed from *within* the cavity: this places the hydrogen atom at the methine inter-ring position away from the observer for pseudo-axial *R* groups. In practice it is found that substituents at the inter-ring stereogenic centre are depending and take a pseudo-axial 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.

Figure 1. Representation of Resorcin[4]arenes, including Axial Stereochemistry

Figure 2. Abbreviated Representation of Resorcin[4]- and [6]arenes

Like other workers who used *p*-substituted α -methylbenzylamines,^{9e} we found that the resorcinarene **1** ($R = \text{C}_{11}\text{H}_{23}$) also gave a single diastereoisomer in a good yield in a Mannich reaction with formaldehyde and (*R*)-(+)-4-methoxy- α -methylbenzylamine. However, we were disappointed to find that the preparation of enantiomerically pure derivatives in high yields by the alkylation of the residual phenolic hydroxyl groups in the diastereomerically pure tetrabenzoxazine derivatives, for example **2a** and **b** (**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**, **b**, and **d** can be prepared on a multi-gram scale. For example, using a high-speed stirrer, we were able to deprotonate and then methylate the resorcinarene **2b** (18 g) and obtain the derivative **3b** in 94% yield. We have also investigated Mannich reactions of the resorcin[6]arene **4** using *N,N*-bis(methoxymethyl)-*N*-benzylamine and *N,N*-bis(methoxymethyl)-*N*- α -methylbenzylamine but found that, as expected, the former reaction gave a racemic mixture (**5** and **5'**) while in the latter reaction a 1:1 mixture of diastereoisomers **6** and **6'** was produced as shown in **Scheme 2**. We found that the

reactions using bis(aminol) ethers gave significantly higher yields than reactions carried out using the corresponding amine together with paraformaldehyde and a catalytic amount of sodium hydroxide.

Scheme 1. Alkylation of Diastereomerically Pure Tetrabenzoxazines

Scheme 2. Mannich Reactions of a Resorcin[6]arene using Bis(aminol) ethers

In addition, we have been unable to methylate the four residual hydroxy groups in the racemic tetrabenzoxazine that is obtained when using methylamine as the primary amine, presumably as a result of easy quaternization of the benzoxazine nitrogen atoms. The axially chiral non-racemic compound **7** was available from our earlier study,¹⁰ and large quantities of the racemate of resorcinarene derivatives such as **7** were required for other studies. The report of the formation of racemic tetramethoxyresorcin[4]arenes by the boron trifluoride catalysed 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 diastereoisomers to a pair of enantiomers from a single initial reaction. Reactions of iminium salts with arenes with 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 involving the use of dimethylamine and formaldehyde. The possibility of accessing a range of other tetraalkoxyresorcin[4]arene derivatives also provided an opportunity to prepare other axially chiral resorcin[4]arene derivatives on multigram scales, for example from 3-benzyloxyphenol,¹⁵ 3-*iso*-propyloxyphenol¹⁶ and 3-cyclopentyloxyphenol.¹⁷ We have recently shown¹⁷ that a wide range of 3-alkoxyphenol derivatives (**8**) is readily available starting from 3-iodophenol using alcohols and copper(I) iodide-9,10-phenanthroline catalysis,¹⁸ or from resorcinol monobenzoate using alcohols in Mitsunobu reactions,¹⁹ followed by base catalysed alcoholysis. The racemic tetraalkoxyresorcin[4]arenes **9a–9e** were prepared, in each case in good to excellent yields, using the previously reported protocol,¹³ or a modification as shown in **Scheme 3**, by the interaction of boron trifluoride (200 mol%) with 1,1-dimethoxyalkanes or aldehydes, and the 3-alkoxyphenol derivatives **8a–8d**.²⁰

Scheme 3. Formation of Racemic Tetraalkoxyresorcinarenes

The large number of reports of Mannich reactions of octahydroxyresorcin[4]arenes that have been carried out giving the products in high yields under mild reactions using 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 using aqueous formaldehyde and primary or secondary amines under a variety of reaction conditions, including the addition of toluene to ethanolic solutions of the potential co-reactants. There is some evidence that a variety of intermediates are involved in Mannich reactions, dependent on the precise reaction conditions used,²¹ but apparent failures may also result from very low equilibrium concentrations of reactive intermediates.²² For example, furan is reported not to take part in Mannich reactions carried out under classical reaction conditions.²³ However, both thiophene,²⁴ a weakly nucleophilic aromatic compound, and furan,²⁵ do give Mannich bases in good yields in reactions carried out with pre-formed iminium salts. Nuclear magnetic resonance 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 ¹³C NMR spectrum of a solution of *N,N*-dimethyl(methylene)iminium chloride in a mixture of sulfur dioxide and deuteriodichloromethane showed resonances at $\delta_C = 38.7, 49.4, 79.0,$ 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 ¹³C NMR spectra of that solid, determined in deuteriochloroform or deuterioacetonitrile, even in the presence of sulfur dioxide, did not show the presence of an iminium carbon atom; the solutions showed a resonance at $\delta_C = 78.4$ ppm that indicated that the equilibrium lay well in favour of the chloromethylamine **10**.²⁶

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

The fact that in some reactions resorcinarenes have been shown to be sufficiently acidic to undergo Mannich reactions without added 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 values for the first four phenolic hydroxyl

groups to be deprotonated in the case of the acetaldehyde derived resorcinarene (**1**, R = Me) gave a value that is two pKa units more acidic than resorcinol.²⁷ Gas phase calculation of pKa values for a number of phenols gave a value for 3-methoxyphenol of 9.5.²⁸ We therefore decided to determine the pKa value for the tetramethoxyresorcinarene **9a**, derived from 3-methoxyphenol and hexanal. We looked for a method using nuclear magnetic resonance spectroscopy that did not depend on the measurement of NMR integrals. Such a method had been used to determine the solvolysis rate of a trifluoroacetate by 2,2,2-trifluoroethanol buffered by 2,6-lutidine.²⁹ The methyl singlet in 2,6-lutidine at $\delta_{\text{H}} = 2.504$ ppm was found to shift downfield over the course of the reaction in a first order fashion. Since 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 the method for the determination of relative pKa values we carried out NMR experiments with resorcinol and 3-methoxyphenol, and obtained average values over three determinations of 9.47 and 9.71 respectively. The pKa of resorcinol in water is reported as 9.81.³⁰ The value that we obtained for the tetramethoxyresorcinarene **9a** was 10.05: that is two pKa units less acidic than a related octahydroxyresorcinarene. It is clear that in order to obtain good reactivity in Mannich reactions, more forcing reaction conditions were required in order to displace the equilibrium between an iminium ion and its precursor in favour of the iminium ion.

We have previously reported using a number of bis(aminol) ethers,^{26,31} including *N,N*-bis(methoxymethyl)-*N*-(*R*)- α -methylbenzylamine 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 using 0.1 mmol of the tetramethoxyresorcin[4]arene **9a** and a tenfold excess of *N,N*-bis(methoxymethyl)-*N*-benzylamine in which the solutions were heated under reflux. Use of toluene as the solvent resulted in the formation of the racemic tetrabenzoxazine **11a** in 75% yield when the solution of the reactants 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 using 2-methoxyethanol as the alcohol component. A 12 mmol scale reaction was complete after 96 h using the tetramethoxyresorcin[4]arene **9a** and *N,N*-bis(2-methoxyethoxymethyl)-*N*-methylamine, and gave the product **11b** in 73% yield. A similar reaction using the tetramethoxyresorcin[4]arene **9e** gave the anticipated product **11c** in 71% yield. The

reactions are shown in **Scheme 5**. The use of the higher temperature evidently succeeded in displacing the equilibrium between the precursors used and the related iminium ions in favour of the latter.

Scheme 5. Formation of Racemic Tetrabenzoxazines from Tetraalkoxyresorcinarenes

We turned our attention next to reactions designed to produce diastereoisomers by using the chiral bis(methoxymethyl)amino ethers derived from (*R*)-(+)- and (*S*)-(–)- α -methylbenzylamine.^{6m,10} We found that reactions of the racemic tetraalkoxyresorcinarenes (**9a**, **g**, **i**, and **j**) using the chiral bis(aminol) ethers also proceeded slowly, and that, when carried out by heating the reacting components under reflux using 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 diastereoisomers. The diastereoisomers 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 distinguished the two diastereoisomers in the ¹H NMR spectra of the crude reaction mixtures was the two AB systems for the O-CH₂-N residues at $\delta_{\text{H}} = 4.58$, $J = 10.0$ Hz and 4.63 , $J = 10.0$ Hz, and $\delta_{\text{H}} = 4.55$, $J = 10.0$ Hz and 4.98 , $J = 10.0$ Hz. The first diastereoisomer to be eluted from silica gel from the reaction mixture formed using the resorcinarene **9a** and (*R*)-(+)- α -methylbenzylamine was shown to be the known compound **12a**.¹⁰ In each case the first eluted diastereoisomer crystallized and was shown to be the (*P,R,S*) diastereoisomer; that is **12a**, **12b**, and **12c**: the other diastereoisomers failed to give

crystals that were suitable for X-ray crystallography but analysis of the spectroscopic data showed that they were the (*M,R,R*) compounds **12a'**, **12b'**, and **12c'** [Scheme 6]. Similarly, in the case of the products of reactions of *N,N*-bis(methoxymethyl)-*N*-(*S*)-(-)- α -methylbenzylamine, the first compound which was eluted was shown, by comparison of the ^1H NMR spectra, to be the (*M,S,R*)-diastereoisomer (Scheme 7). The ^1H NMR spectra for the compounds **15a** and **15a'** illustrate this feature and are shown below. The structures of the compounds **12c** and **13b** were also confirmed by X-ray crystallographic analysis, shown in Figures 3 and 4.

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.

Scheme 6. Formation of Diastereoisomeric Tetrabenzoxazines from Tetraalkoxyresorcinarenes and *N,N*-Bis(methoxymethyl)-*N*-(*R*)-(+)- α -methylbenzylamine

Scheme 7. Formation of Diastereoisomeric Tetrabenzoxazines from Tetraalkoxyresorcinarenes and *N,N*-Bis(methoxymethyl)-*N*-(*S*)-(-)- α -methylbenzylamine

We carried out additional reactions in order to assess the possibility that the long reaction times involved in the reactions using bis(aminol) ethers were related to the position of the equilibrium between an iminium species and its counter-ion and the iminium ion precursor. It was also possible that the polarity of the solvent system used might be important. We found that the compound **7** was formed in 93% yield when a solution of the 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 the octahydroxyresorcinarene **1** (R = *n*-C₅H₁₁) 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 reactions, and led us to conclude that reactions should be more successful if carried out using 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: the tetramethoxyresorcinarene **9a** was then added after 30 min and the mixture was stirred at room temperature for 120 h giving a very pure crystalline racemic product **7** in 98% yield (**Scheme 8**) that was suitable for X-ray structural analysis (**Figure 5**).

Scheme 8. Formation of a Mannich Base Using a Pre-formed Iminium Ion Source

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

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 $-20\text{ }^{\circ}\text{C}$ to give 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. Addition of a solution of the resorcinarene **9a** in 1,2-dichloroethane to the cold solid followed by heating the mixture under reflux for 15 h gave the tetrabenzoxazine **11a** in 80% yield.

The primary mechanism involved in the now well established microwave assisted technology is dielectric loss rather than a simple heating effect.³³ Despite our success in carrying out Mannich reactions involving tetraalkoxyresorcin[4]arenes using 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 of carrying out syntheses using microwave assistance,³⁴ including the use of environmentally benign solvent-free reactions.^{34b} A number of Mannich reactions have been carried out using microwave assistance.³⁵ However, as far as we are aware there is only one example of microwave-assisted Mannich reactions involving phenols.³⁶ We were pleased to find that experiments carried out using 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, a reaction of the tetramethoxyresorcinarene **9a** in bis(dimethylamino)methane (10 equivalents) gave, after 10 min with a power of up to 300W and cooling to 110 °C, a quantitative yield of the compound **7**. Experiments using bis(aminol) ethers are shown in the **Scheme 9** and **Table 1**. In the case of reactions using *N,N*-bis(methoxymethyl)-*N*-(*S*)-(-)- α -methylbenzylamine the first diastereoisomer to be eluted from silica gel was shown to correspond to the diastereoisomer **A**, by comparison of spectroscopic data with those obtained previously: that is having absolute configurations (*M,S,R*). The ¹H NMR spectra for the compounds **15a** and **15a'**, shown in **Figures 6** and **7**, illustrate this feature. It is of interest to note that a sequence of 2 times 10 minutes or 3 times 10 minutes, with cooling to room temperature between irradiations, gave better yields than reactions carried out for 20 or 30 minutes respectively: we have also been able to carry out reactions on a one-gram scale using these conditions.

$R^1 = \text{Me}, R^2 = n\text{-C}_5\text{H}_{11}$	$R^3 = \text{Bn}$	Racemic 11	
$R^1 = \text{Me}, R^2 = n\text{-C}_5\text{H}_{11}$	$R^3 = (S)\text{-}\alpha\text{-MeBn}$	13a	13a'
$R^1 = \text{Me}, R^2 = n\text{-C}_{11}\text{H}_{23}$	$R^3 = (S)\text{-}\alpha\text{-MeBn}$	14a	14a'
$R^1 = \text{Me}, R^2 = i\text{-Butyl}$	$R^3 = (S)\text{-}\alpha\text{-MeBn}$	15a	15a'
$R^1 = i\text{-Pr}, R^2 = n\text{-C}_5\text{H}_{11}$	$R^3 = (S)\text{-}\alpha\text{-MeBn}$	13b	13b'
$R^1 = i\text{-Pr}, R^2 = i\text{-Butyl}$	$R^3 = (S)\text{-}\alpha\text{-MeBn}$	16a	16a'
$R^1 = \text{cyclopentyl}, R^2 = n\text{-C}_5\text{H}_{11}$	$R^3 = (S)\text{-}\alpha\text{-MeBn}$	17a	17a'

Scheme 9. Microwave Assisted Mannich Reactions to Produce Tetrabenzoxazines

Table 1: Reactions of Bis(aminol) ethers with Tetraalkoxyresorcinarenes Using Focused Microwave Irradiation

R ¹	R ²	R ³	Power (W)	Temp. (°C)	Time (min.)	Product A* Yield (%)	Product B* Yield (%)
Me	<i>n</i> -C ₅ H ₁₁	Bn	<300	150	10	(11a) 82 (racemic)	–
Me	<i>n</i> -C ₅ H ₁₁	α -Me-Bn	<300	150	10	(13a) 38	(13a') 36
Me	<i>n</i> -C ₁₁ H ₂₃	α -Me-Bn	<300	150	2 x 10	(14a) 33	(14a') 31
Me	2-methyl-propyl	α -Me-Bn	<300	150	2 x 10	(15a) 43	(15a') 43
<i>i</i> -Pr	<i>n</i> -C ₅ H ₁₁	α -Me-Bn	<300	140	3 x 10	(13b) 39	(13b') 39
C ₅ H ₉	<i>n</i> -C ₅ H ₁₁	α -Me-Bn	<300	140	3 x 10	(17a) 37	(17a') 35
<i>i</i> -Pr	2-methyl-propyl	α -Me-Bn	<300	140	3 x 10	(16a) 37	(16a') 37

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

Figure 6. ¹H NMR Spectrum of Compound **15a**

Figure 7. ¹H NMR Spectrum of Compound **15a'**

We also investigated the feasibility of using (*R*)-(+)- α -methylbenzylamine as the chiral auxiliary in the formation of diastereoisomeric amides from racemic tetramethoxyresorcinarenes. The alkylation of calixarenes and resorcinarenes with ethyl-, or methyl-bromoacetate has been well documented to provide the corresponding ether-ester derivatives in high yield.³⁷ The direct conversion of esters into amides by aminolysis is well established,³⁸ and has been applied recently to a calixarene tetraester.³⁹ In the calixarene case, 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 solution of amine in ethanol at reflux, we felt that more vigorous conditions should be investigated. Thus the tetraester **18** was heated at 100 °C with neat (*R*)-(+)- α -methylbenzylamine 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 compounds that was not separated. The use of an acid chloride derived from the carboxylic acid related to the ester **18** was also investigated but an attempted reaction using (*R*)-(+)- α -methylbenzylamine again gave a complex mixture of products. The report of the formation of *N*-(*R*)- α -methylbenzyl-2-bromoacetamide from 2-bromoacetyl bromide suggested the use of that reagent.⁴⁰ When the resorcinarenes **9b**, **c**, and **d** were heated under

reflux in acetonitrile with anhydrous potassium carbonate and an excess of *N*-(*R*)-(+)- α -methylbenzyl-2-bromoacetamide for 15 h, the expected diastereoisomeric 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 the compound (*M,R,R*)-**20a** was established by a 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 reaction an ester was heated with (*S*)-(-)- α -methylbenzylamine at 160 °C.^{37b,42}

Scheme 10. Formation of Diastereoisomeric Amides from Tetramethoxyresorcinarenes and [*N*-Bromoacetyl]-(*R*)-(+)- α -methylbenzylamine

Figure 8. X-ray Structure of the 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 were interested to investigate their potential for use in ligand-assisted reactions. Our interest in the ligand assisted addition of dialkylzinc reagents to benzaldehyde using 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, in particular using 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 using alkynylzinc reagents have also been reported recently;⁴⁸ they 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 the 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 reported previously.¹⁰ The compounds that were chosen contained hydroxyl and benzylamino groups in order to establish the possible influence of

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 adding a solution of the dialkylzinc reagent in hexanes to a solution of the potential ligand in toluene: the mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ before adding the aromatic aldehyde. The reaction mixtures were allowed to warm to room temperature and after 12 h the mixture was worked up and analysed using either chiral gas chromatography or chiral HPLC followed by isolation of the product and determination of the sign of rotation of the product. The use of the tetramethoxyresorcinarene **21**, which lacked axial chirality, gave 1-phenylpropanol in 84% yield in a reaction with diethylzinc. However, the product was racemic. The ^1H NMR spectrum of the 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 an NMR time scale. As expected, when the ^1H NMR spectrum of the ligand was determined at higher temperatures the signals sharpened. A number of possible interactions between the amino- and hydroxyl- groups is possible, which suggests that that result is not unexpected. The tetra-*N,N*-dimethylbenzylamine derivative **22**, where the only chiral element is the axis of chirality gave an interesting result: 1-phenylpropanol was produced in 71% yield and an ee of 42%, with the 1-phenylpropanol having an excess of the (*R*)-(+)-enantiomer. In the case of reactions in which we used the diastereoisomers **23** and **24**, the enantiomeric excesses resulted only from the influence of the chiral auxiliaries. The 1-phenylpropanol was obtained in 80% yield with an ee of 56% of the (*S*)-(–)- enantiomer in the reaction of diethylzinc with benzaldehyde in the presence of 5 mol% of the ligand **23**. In a similar reaction using 5 mol% of the ligand **24** the 1-phenylpropanol was obtained in 75% yield with an ee of 55% of the (*R*)-(+)- enantiomer.

Figure 9. Structures of Potential Ligands

Because the overall yields and the induced enantioselectivities using the ligands **21–24** were lower than those already well established in the literature, we turned our attention to the use of some of our tetrabenzoxazine derivatives. The potential ligands investigated were the 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 used in the addition of diethylzinc to benzaldehyde to 1 mol% without affecting the conversion or enantioselectivity under standardized reaction conditions. We were pleased to find that whereas the ligand (*M,S,R*)-**13a** gave a 95% conversion with an ee of 39% in favour of the (*R*)-(+)-1-phenyl propanol, the ligand **12b** was much superior and gave a 95% conversion with an ee of 83% in favour of (*S*)-(–)-1-phenyl propanol. The ligand **12c** gave only a 65% conversion and an ee of 58% in favour of (*S*)-(–)-1-phenyl propanol. The ligands **12b'** and **12c'** evidently had their axial chirality and the chirality of their amino residues mis-matched: the ligand **12b'** gave a 95% conversion but an ee of only 5% while the ligand **12c'** gave a 63% conversion and a 5% ee.

Figure 10. Structures of Potential Ligands

The above results reveal a number of interesting features. The enantioselectivity was affected by several parameters. The steric effect of the ether moiety had a pronounced influence on the ee with the isopropyl group inducing the highest selectivity and the methyl group the lowest selectivity. The relative configurations of the ligands was also shown to be important, with only the matched systems [(*P,R,S*-) and (*M,S,R*-)] showing selectivity. The influence of the calix is also important: a reaction using the 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 diethylzinc was added to a solution of the resorcinarene derivative (*P,R,S*)-**12b** no change was observed in the resonances due to the benzoxazine moieties. The 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 proved to be an effective adjunct to catalyst systems that are based on chiral amino alcohols, diols, and sulfonamides derived from chiral primary diamines.⁵⁰ However, the absence of hydroxyl 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% 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 the 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 to the results obtained when using diethylzinc, both reduced conversions and enantioselectivities in the presence of the ligand (*P,R,S*)-**12b**. Once again the ligand **12c** gave less good results. Reactions using 4-chloro- and 4-methoxybenzaldehyde, in reactions with diethylzinc, again gave the best conversions and enantioselectivities in the presence of the ligand (*P,R,S*)-**12b** or its enantiomer (*M,S,R*)-**13b**. In a 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 was added to a solution of the ligand **13b**, and, after a reaction with benzaldehyde, gave 1,3-diphenylprop-2-yn-1-ol in an isolated yield of 59% and an ee of 64%. These results are collected together in **Table 2**.

Table 2: Reactions of Aromatic Aldehydes with Dialkylzinc Reagents in the Presence of Chiral Ligands

Ligand	Aldehyde	Dialkylzinc	% Convers.	ee	Config. of prod.
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	X = methoxy- (n = 0)	diethylzinc	95	68	(+)

13b	X = H (n = 1)	diethylzinc	95	41	(+)*
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†	64	(+)*
2	X = H (n = 0)	Methyl(phenylethynyl)zinc	73†	25	(+)*

* Rotation values for the pure enantiomers are very small and so the probable configurations were deduced from the HPLC traces

† Isolated yields

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 pKa units less acidic than the related resorcin[4]arenes, can be carried out using a number of different protocols. Microwave-assisted reactions allow the preparation of benzoxazine derivatives on a multi-gram scale, in high yields, after short reaction times. We also established that alkylation reactions can be carried out efficiently using a chiral non-racemic α -bromoacetamide derivative. The chiral non-racemic 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 using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer or a Bruker Vector 22 FTIR spectrometer, thin film spectra were acquired using sodium chloride plates. All ^1H and ^{13}C NMR spectra were measured at 250.13 and 62.86 MHz with a Bruker AC 250 MHz spectrometer, at 400.13 and 100.62 MHz with a Bruker DPX 400/Avance 400 MHz spectrometer, at 200 MHz and 50.3 MHz on a Varian Gemini 2000 spectrometer or at 500 and 125.8 MHz on a Bruker ARX-500, in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference. Mass spectra were recorded using a Jeol-SX102 instrument utilizing electron-impact (EI), fast atom bombardment (FAB), and by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilizing electrospray (ES). Analysis by GCMS utilized a Fisons GC 8000 series (AS 800), using a 15 m x 0.25 mm DB-5 column and an electron-impact low-resolution mass spectrometer. Melting points were recorded using 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, operating at $\lambda=589$ nm, corresponding to the sodium D line, at the temperatures indicated. Microanalyses were performed on 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 using 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 requiring anhydrous conditions were carried out using 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 over calcium sulfate or chloride. Dichloromethane was distilled over 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*)-2a:

A solution of tetraundecylresorcin[4]arene **1**⁵¹ (1.10 g, 1.0 mmol) and *N,N*-Bis(ethoxymethyl)-*N*-(*R*)- α -methylbenzylamine (1.04 g, 5.0 mmol) in ethanol (100 mL) was heated under reflux for 24 hours. After this time the reaction mixture was cooled in an ice bath and the resulting pale pink

precipitate collected by filtration and washed with cold methanol. Recrystallization from dichloromethane/methanol gave the *title compound* (*P,R,S*)-**2a** as colourless crystals (1.47 g, 83%). M.p. 75-79 °C; $[\alpha]_{\text{D}}^{25} +113.0$ (*c* 0.5, CHCl₃); ν_{max} (CH₂Cl₂) /cm⁻¹ 3363, 2923, 2853, 1601, 1467, 1347, 885; δ_{H} (400 MHz, CDCl₃) 0.88 (12 H, t, *J* 6.8 Hz), 1.26-1.37 (84 H, m), 2.13-2.20 (8 H, m), 3.73 (4 H, d, *J* 17.6 Hz), 3.80 (4 H, q, *J* 6.0 Hz), 3.94 (4 H, d, *J* 17.2 Hz), 4.19 (4 H, t, *J* 7.6 Hz), 4.92 (4 H, d, *J* 10.4 Hz), 5.13 (4 H, d, *J* 10.0 Hz), 6.93-7.24 (24 H, m), 7.66 (4 H, s); δ_{C} (100 MHz, CDCl₃) 14.6, 21.9, 23.1, 28.6, 29.9, 30.2, 30.2, 32.4, 33.1, 34.1, 45.0, 58.4, 81.3, 108.5, 121.5, 124.0, 124.7, 127.4, 128.6, 144.9, 149.1, 150.0. 3x, 1x obscured by other signals.

Tetrabenzoxazine (*P,R,S*)-2b:

Tetraphenylethylresorcin[4]arene⁵¹ (0.90 g, 1.0 mmol), (*S*)- α -methylbenzylamine (0.61 g, 5.0 mmol) and aqueous formaldehyde (37% aq. solution, 0.81 mL, 10.0 mmol) were heated under reflux in ethanol (150 mL). Recrystallization from dichloromethane/methanol gave the *title compound* (*P,R,S*)-**2b** as colourless crystals (1.17 g, 79%). M.p. 190-192 °C; $[\alpha]_{\text{D}}^{25} -124.0$ (*c* 0.5, CHCl₃); ν_{max} (CH₂Cl₂) /cm⁻¹ 3333, 2921, 1599, 1465, 1376, 1146, 879, 699; δ_{H} (250 MHz, CDCl₃) 1.28 (12 H, d, *J* 6.6 Hz), 2.49-2.63 (16 H, m), 3.78 (4 H, d, *J* 17.6 Hz), 3.80 (4 H, q), 3.98 (4 H, d, *J* 17.6 Hz), 4.27 (4 H, t, *J* 7.4 Hz), 4.92 (4 H, d, *J* 10.2 Hz), 5.14 (4 H, d, *J* 9.9 Hz), 6.92-7.24 (44 H, m), 7.66 (4 H, s); δ_{C} (100 MHz, CDCl₃) 21.4, 32.7, 34.6, 36.1, 44.6, 58.1, 81.0, 109.3, 120.9, 123.3, 124.1, 125.9, 127.0, 128.1, 128.5, 128.6, 141.9, 144.4, 149.0, 149.8.

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(ethoxymethyl)-*N*-(*R*)- α -methyl-(4-methoxybenzyl)amine (5.00 g, 33.0 mmol) was added in one portion. Formaldehyde (5 mL [37% solution in water], 62.0 mmol) was added in one portion and the mixture was heated under reflux overnight. After this time, the reaction was allowed to cool to room temperature and the precipitate filtered and washed with large amounts of ethanol (95%) to give the *title compound* (*P,R,S*)-**2a** as a pale pink solid (7.2 g, 73%). M.p. 80 °C (dec.); $[\alpha]_{\text{D}}^{25} +110$ (*c* 0.75, CHCl₃); C₁₁₆H₁₆₄N₄O₁₂: calcd. C, 77.12; H, 9.15; N, 3.10; found: C, 77.02; H, 9.08; N, 3.00; ν_{max} (CH₂Cl₂) /cm⁻¹ 3356, 3053, 2967, 2845, 2305, 1611, 1512, 1469, 1263, 1035, 896, 750; δ_{H} (400 MHz, CDCl₃) 0.88 (12 H, t, *J* 7.2 Hz), 1.27-1.37 (72 H, m), 2.15 (4 H, m), 2.23 (4 H, m), 3.66 (12 H, s), 3.72 (4 H, d, *J* 17.2 Hz), 3.77 (4 H, q, *J* 6.4 Hz), 3.94 (4 H, d, *J* 17.6 Hz), 4.21 (4 H, t, *J* 7.6 Hz), 4.86 (4 H, d, *J* 10.0 Hz), 5.08 (4 H, d, *J* 10.0 Hz), 6.74-6.76 (8 H, m), 7.15 (4 H, s), 7.19-7.21 (8 H, m), 7.66 (4 H, s); δ_{C} (100 MHz, CDCl₃) 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, remaining two CH₂ signals obscured.

Tetra-(*O*-methylether)-resorcinarene (*P,R,S*)-3a:

Tetrabenzoxazine (*P,R,S*)-**2a** (6.00 g, 3.6 mmol) was dissolved in dry THF (500 mL) and stirred at –78 °C. *n*-Butyllithium (1.6M solution in hexane, 8.93 mL, 14.8 mmol) was added dropwise and the resulting gelatinous precipitate stirred at –78 °C for 30 min. Methyl triflate (1.61 mL, 14.3 mmol) was added dropwise and the reaction mixture stirred at –78 °C until a homogeneous solution was observed. After this time, the reaction mixture was quenched by the addition of water, and the mixture was allowed to reach room temperature. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with water and a saturated aqueous solution of sodium chloride. The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure to yield the crude product as a pale pink oil. Purification by flash chromatography (silica gel, 30% ethyl acetate/light petroleum) furnished the *title compound* (*P,R,S*)-**3a** as a pale yellow oil (5.23 g, 84%). [α]_D²⁵ +95 (*c* 0.43, CHCl₃); C₁₁₆H₁₆₄N₄O₈ (1740): calcd. C, 79.95; H, 9.49; N, 3.21; found: C, 79.92; H, 9.49; N, 3.21; $\nu_{\max}$ (CH₂Cl₂) /cm^{–1} 2924, 2852, 1467; δ_{H} (400 MHz, CDCl₃) 0.86 (12 H, t, *J* 7.2 Hz), 1.24–1.37 (72 H, m), 1.38 (12 H, d, *J* 6.4 Hz), 1.80–1.90 (8 H, m), 3.26 (12 H, s), 3.80 (4 H, q, *J* 6.4 Hz), 3.84 (4 H, d, *J* 16.8 Hz), 4.16 (4 H, d, *J* 16.8 Hz), 4.42 (4 H, t, *J* 7.2 Hz), 4.58 (4 H, d, *J* 10.0 Hz), 4.63 (4 H, d, *J* 10.0 Hz), 6.72 (4 H, s), 7.22–7.27 (20 H, m); δ_{C} (100 MHz, CDCl₃) 14.1, 21.3, 22.7, 28.3, 29.4, 29.8, 29.8, 30.0, 30.1, 32.0, 35.4, 35.8, 44.7, 57.3, 60.1, 79.6, 112.2, 124.6, 127.3, 127.5, 127.8, 128.4, 128.8, 144.1, 150.1, 153.6, 1x obscured by other signals.

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. *n*-Butyllithium (2.5 M solution in hexanes, 24.2 mL, 60.5 mmol) was added dropwise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Methyl trifluoromethanesulfonate (10.0 g, 60.5 mmol) was added dropwise and stirred for 40 min. After this time the reaction was quenched with methanol (20 mL). The mixture was then allowed to warm to room temperature and concentrated. The residue produced was partitioned between CH₂Cl₂ (200 mL) and water (200 mL). The organic layer was washed with water (2 x 250 mL), dried and solvents were removed under reduced pressure. The residue was purified on silica gel (5% methanol/CH₂Cl₂) to afford the *title compound* (*P,R,S*)-**3b** as a pale yellow foam (17.6 g, 94%).

$[\alpha]_{\text{D}}^{25} +135.0$ (*c* 0.46, CHCl_3); $\text{C}_{104}\text{H}_{108}\text{N}_4\text{O}_8$: calcd. C, 80.80; H, 7.30; N, 3.62; found: C, 80.86; H, 6.90; N, 3.56; ν_{max} (CH_2Cl_2) $/\text{cm}^{-1}$ 3054, 2986, 1421, 1265, 896, 740; δ_{H} (400 MHz, CDCl_3) 1.39 (12 H, d, *J* 6.4 Hz), 2.11-2.31 (8 H, m), 2.69 (8 H, t, *J* 7.6 Hz), 3.21 (12 H, s), 3.81 (4 H, q, *J* 6.4 Hz), 3.87 (4 H, d, *J* 16.8 Hz), 4.19 (4 H, d, *J* 16.8 Hz), 4.53 (4 H, t, *J* 7.6 Hz), 4.57 (4 H, d, *J* 10 Hz), 4.64 (4 H, d, *J* 10 Hz), 6.84 (4 H, s), 7.12-7.22 (40 H, m); δ_{C} (100 MHz, CDCl_3) 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, remaining aromatic obscured; *m/z* (FAB) LRMS 1541; $\text{C}_{104}\text{H}_{108}\text{N}_4\text{O}_8$ (M^+) requires 1542.

Tetrabenzoxazine (*P,R,S*)-3c:

Tetrabenzoxazine (*P,R,S*)-**2b** (8.30 g, 5.6 mmol) was dissolved in dry THF (300 mL) under an atmosphere of nitrogen and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-Butyllithium (2.5 M solution in hexanes, 11.2 mL, 28.0 mmol) was added dropwise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Ethyl trifluoromethanesulfonate (5.0 g, 28.0 mmol) was added dropwise and stirred for 1 h. After this time the reaction was quenched with methanol (20 mL). The mixture was then allowed to warm to room temperature and concentrated. The residue produced was partitioned between CH_2Cl_2 (150 mL) and water (200 mL). The organic layer was washed with water (2 x 200 mL), saturated brine solution (100 mL), dried and solvents were removed under reduced pressure. The residue was purified on silica gel (30% Ethyl acetate/light petroleum) to afford the *title compound* (*P,R,S*)-**3c** as a colourless foam (5.60 g, 63%). $[\alpha]_{\text{D}}^{25} +110.0$ (*c* 0.79, CHCl_3); $\text{C}_{108}\text{H}_{116}\text{N}_4\text{O}_8$: calcd. C, 81.17; H, 7.32; N, 3.51; found: C, 81.08; H, 7.13; N, 3.39; ν_{max} (CH_2Cl_2) $/\text{cm}^{-1}$ 3054, 2982, 2305, 1602, 1468, 1266, 896, 742; δ_{H} (400 MHz, CDCl_3) 1.03 (12 H, t, *J* 6.8 Hz), 1.39 (12 H, d, *J* 6.8 Hz), 2.15 (4 H, m), 2.25 (4 H, m), 2.69 (8 H, t, *J* 7.6 Hz), 3.30 (8 H, br q), 3.83 (4 H, q, *J* 6 Hz), 3.85 (4 H, d, *J* 16.8 Hz), 4.22 (4 H, d, *J* 16.8 Hz), 4.50-4.58 (12 H, m), 6.83 (4 H, s), 7.12-7.30 (40 H, m); δ_{C} (100 MHz, CDCl_3) 15.5, 21.5, 34.7, 35.7, 37.6, 44.5, 56.9, 68.1, 79.5, 112.4, 124.6, 125.5, 127.3, 127.5, 128.2, 128.4, 128.5, 128.7, 142.7, 144.1, 150.1, 153.1, remaining aromatic signal obscured. *m/z* (FAB) LRMS 1597; $\text{C}_{108}\text{H}_{116}\text{N}_4\text{O}_8$ (M^+) requires 1598.

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 $-78\text{ }^{\circ}\text{C}$. *n*-Butyllithium (2.5 M solution in hexanes, 7.8 mL, 19.4 mmol) was added dropwise with vigorous stirring, using an overhead stirrer, and stirred for 30 min. Methyl trifluoromethanesulfonate (2.20 g, 19.4 mmol) was added dropwise and stirred for 45

min. After this time the reaction was quenched with methanol (10 mL). The mixture was then allowed to warm 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 x 150 mL), saturated brine solution (100 mL), dried and solvents were removed under reduced pressure. The residue was purified on silica gel (45% Ethyl acetate/light petroleum) to afford the *title compound* (*P,R,S*)-**3d** as a pale yellow oil (5.60 g, 78%). $[\alpha]_D^{25} +116.0$ (*c* 0.80, CHCl₃); $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3052, 2925, 2852, 2304, 1610, 1512, 1465, 1265, 1174, 1035, 943, 835, 741; δ_H (400 MHz, CDCl₃) 0.87 (12 H, t, *J* 8.0 Hz), 1.25-1.34 (72 H, m), 1.36 (12 H, d, *J* 6.4 Hz), 1.80 (4 H, m), 1.89 (4 H, m), 3.27 (12 H, s), 3.76 (4 H, q, *J* 6.4 Hz), 3.79 (12 H, s), 3.85 (4 H, d, *J* 16.8 Hz), 4.14 (4 H, d, *J* 16.8 Hz), 4.42 (4 H, t, *J* 7.6 Hz), 4.57 (4 H, d, *J* 10.0 Hz), 4.60 (4 H, d, *J* 10.0 Hz), 6.71 (4 H, s), 6.81-6.83 (8 H, m), 7.18-7.20 (8 H, m); δ_C (100 MHz, CDCl₃) 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, remaining CH₂ obscured; *m/z* (FAB) LRMS 1862; C₁₂₀H₁₇₂N₄O₁₂ (M⁺+H) requires 1862.

Hexabenzoxazines (*M,R*)-**5**/(*P,S*)-**5'**:

Hexa-ethyl-resorcin[6]arene **4** (0.50 g, 0.5 mmol) and *N,N*-bis(methoxymethyl)-*N*-benzylamine (1.30 g, 6.7 mmol) were dissolved in ethanol (20 mL) in a 50 mL round-bottomed flask under nitrogen. The reaction mixture was then heated under reflux for 3 d. The suspension was filtered and washed with ethanol (10 mL). The solid was then dried under vacuum to afford the *title compound* **5/5'** (0.59 g, 64%). M.p. >250 °C; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3486, 2957, 2922, 2360, 1619, 1601, 1468, 1350, 1170, 1130, 897, 729; δ_H (400 MHz, CDCl₃) 0.86 (18 H, t, *J* 7.2 Hz), 2.04 (6 H, m), 2.29 (6 H, m), 3.92 (12 H, s), 4.03 (12 H, s), 4.17 (6 H, dd, *J* 5.4, 9.4 Hz), 4.90 (12 H, s), 6.59 (6 H, s), 7.25-7.40 (30 H, m), 7.51 (6 H, s); δ_C (100 MHz, CDCl₃) 12.9, 28.9, 34.2, 46.6, 55.8, 82.2, 107.6, 121.8, 122.9, 124.5, 127.4, 128.5, 129.1, 137.9, 148.8, 149.4; *m/z* (FAB) LRMS 1689; C₁₀₈H₁₁₄N₆O₁₂ (M⁺+H) requires 1689 (the isotopic distribution of the observed data matched the theoretical [M+H]⁺ isotopic distribution).

Hexabenzoxazines (*M,R,R*)-**6**/(*P,R,S*)-**6'**:

Hexa-ethyl-resorcin[6]arene **4** (0.50 g, 0.5 mmol) and *N,N*-bis(methoxymethyl)-*N*-(*R*)- α -methylbenzylamine (1.70 g, 8.1 mmol) were dissolved in ethanol (20 mL) in a 100 mL round-bottomed flask under nitrogen. The reaction mixture was heated under reflux for 3 d. The suspension was filtered and washed with ethanol (10 mL). The solid was then dried under vacuum to afford an

inseparable mixture of the *title compounds 6/6'* (0.61 g, 63%). M.p.>250 °C; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3416, 3060, 3027, 2961, 2929, 2870, 1614, 1601, 1469, 1454, 930, 907, 876, 733; δ_{H} (400 MHz, CDCl₃) 0.81 (18 H, t, *J* 7.2 Hz), 0.88 (18 H, t, *J* 7.2 Hz), 1.46 (36 H, t, *J* 6.2 Hz), 2.03 (12 H, m), 2.26 (12 H, m), 3.91 (6 H, d, *J* 17.3 Hz), 3.95 (6 H, d, *J* 17.3 Hz), 3.98 (12 H, m), 4.08 (6 H, d, *J* 17.3 Hz), 4.10 (12 H, m), 4.16 (6 H, d, *J* 17.3 Hz), 4.81 (6 H, d, *J* 10.0 Hz), 4.86 (6 H, d, *J* 10.0 Hz), 5.07 (6 H, d, *J* 10.0 Hz), 6.55 (6 H, s), 6.62 (6 H, s), 7.20-7.41 (60 H, m), 7.47 (6 H, s), 7.48 (6 H, s); δ_{C} (100 MHz, CDCl₃) 12.9, 13.0, 21.6, 21.7, 28.8, 28.9, 34.2, 44.3, 44.5, 58.0, 80.9 81.0, 107.9, 108.0, 121.5, 121.7, 122.8, 123.2, 124.3, 124.5, 127.26, 127.31, 127.4, 128.5, 128.6, 144.2, 144.3, 149.1, 149.32, 149.34, 149.4; *m/z* (FAB) LRMS 1773; C₁₁₄H₁₂₆N₆O₁₂ (M⁺+H) requires 1773 (the isotopic distribution of the observed data matched the theoretical [M+H]⁺ isotopic distribution).

Tetramethoxy-tetra-(*N,N*-dimethyl)-resorcinarene 7:

K₂CO₃ (2.50 g, 18.0 mmol) and dry CH₂Cl₂ (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 mixture stirred for 30 min. Tetramethoxyresorcinarene **9a** (0.50 g, 0.6 mmol), dissolved in dry CH₂Cl₂ (10 mL), was added dropwise to the reaction and 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 x 100 mL), dried and solvents were removed under reduced pressure. The residue was taken up in diethyl ether (50 mL) and allowed to slowly evaporate, furnishing the *title compound 7* as colourless crystals (0.63 g, 98%). C₆₄H₁₀₀O₈N₄: calcd. C, 72.97; H, 9.57; N, 5.32; found: C, 72.68; H, 9.60; N, 5.14; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3424, 2954, 1641, 1602, 1462 1265, 1089, 896, 739; δ_{H} (400 MHz, CDCl₃) 0.84 (12 H, bt, *J* 6.4 Hz), 1.24-1.35 (24 H, m), 1.78 (4 H, m), 1.90 (4 H, m), 2.23 (24 H, s), 3.44 (12 H, s), 3.55 (4 H, d, *J* 14.0 Hz), 3.67 (4 H, d, *J* 14.4 Hz), 4.48 (4 H, t, *J* 7.6 Hz), 6.72 (4 H, s); δ_{C} (100 MHz, CDCl₃) 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; *m/z* (FAB) 1052.7572; C₆₄H₁₀₀O₈N₄ (M⁺) requires 1052.7541.

2,8,14,20-Tetra-*n*-propyl-4,10,16,22-tetrahydroxy-6,12,18,24-tetramethoxyresorcinarene 9b:

Boron trifluoride etherate (1.71 g, 12.1 mmol) was added to a stirred solution of 3-methoxyphenol (0.50 g, 4.0 mmol) and butanal (0.29 g, 4.0 mmol) in anhydrous dichloromethane (20 mL) and left to stand at room temperature for 2 h. The reaction mixture was then washed with water (2 x 20 mL) and brine (1 x 20 mL), dried (MgSO₄) and the solvent removed under reduced pressure to give a dark red oil. This was dissolved in a minimum amount of hot ethanol that, upon cooling, afforded pale pink plates. Recrystallization from methanol gave **19a** as off white plates (0.49 g, 68 %). M.p.

257-258 °C; C₄₄H₅₆O₈: calcd. C, 74.1; H, 7.9; found: C, 74.1; H, 7.9 %; δ_{H} (500 MHz, CDCl₃) 0.99 (12 H, t, *J* 7.4 Hz), 1.32 (8 H, hex, *J* 7.4 Hz), 2.20 (8 H, q, *J* 7.4 Hz), 3.84 (12 H, s), 4.31 (4 H, t, *J* 8.0 Hz), 6.35 (4 H, s), 7.24 (4 H, s), 7.51 (4 H, s); δ_{C} (125 MHz, CDCl₃) 14.7, 21.7, 33.4, 36.7, 56.6, 100.7, 124.5, 125.3, 125.4, 153.7, 154.4; *m/z* (FAB) 712.3986; C₄₄H₅₆O₈ (M⁺) requires 712.3975.

2,8,14,20-Tetra-isobutyl-4,10,16,22-tetrahydroxy-6,12,18,24-tetraisopropoxyresorcinarene 9h:

3-methyl-1,1-dimethoxybutane (1.11 g, 8.4 mmol) and 3-isopropoxyphenol (1.27 g, 8.4 mmol) were dissolved in dry dichloromethane (50 mL) in a 100 mL round-bottomed flask under nitrogen. The reaction mixture was cooled down to 0 °C. Boron trifluoride etherate (2.1 mL, 16.8 mmol) was then added to the solution over a period of 30 min. The flask was kept in the cold bath for a further 30 min, allowed to warm to room temperature and stirred for a further 6 h. Water (50 mL) was then added to the stirred solution and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol to give the *title compound* as a white solid (1.68 g, 91%). C₅₆H₈₀O₈ calcd. C, 76.3; H, 9.6; found: C, 75.8; H, 9.2 %; ν_{max} (CH₂Cl₂) /cm⁻¹ 3384, 2954, 2867, 1757, 1647, 1597, 1491, 1189, 944, 838, 738; δ_{H} (400 MHz, CDCl₃) 0.97 (24 H, t, *J* 6.4 Hz), 1.36 (12 H, d, *J* 6.2 Hz), 1.39 (12 H, d, *J* 6.2 Hz), 1.46 (4 H, m), 2.03 (4 H, m), 2.12 (4 H, m), 4.43 (4 H, t, *J* 7.8 Hz), 4.56 (4 H, sept, *J* 6.2 Hz), 6.35 (4 H, s), 7.23 (4 H, s), 7.72 (4 H, s); δ_{C} (100 MHz, CDCl₃) 21.8, 21.9, 22.7, 23.0, 26.0, 30.8, 43.1, 71.6, 102.3, 124.1, 125.2, 125.5, 151.7, 152.8; *m/z* (FAB) 880.5861; C₅₆H₈₀O₈ (M⁺) requires 880.5853.

Tetrabenzoxazine 11a:

Tetramethoxyresorcinarene **9a** (1.00 g, 1.2 mmol) was dissolved in toluene (90 mL). *N,N*-bis(ethoxymethyl)-*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 allowed to cool to room temperature and the solvent 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 the *title compound 11a* as a pale brown powder (1.2 g, 74%). M.p. 152-153 °C (dec.); C₈₈H₁₀₈N₄O₈: calcd. C, 78.30; H, 8.06; N, 4.15; found: C, 78.13; H, 7.95; N, 4.06; ν_{max} (CH₂Cl₂) /cm⁻¹ 2930, 2856, 2304, 1589, 1475, 1264, 1082, 947, 740; δ_{H} (400 MHz,

CDCl₃) 0.87 (12 H, b t), 1.31-1.40 (24 H, m), 1.79-1.84 (4 H, m), 1.92-1.97 (4 H, m), 3.40 (12 H, s), 3.62 (4 H, d, *J* 12.8 Hz), 3.74 (4 H, d, *J* 12.4 Hz), 3.93 (4 H, d, *J* 16.8 Hz), 4.04 (4 H, d, *J* 16.4 Hz), 4.46 (4 H, t, *J* 7.2 Hz), 4.56 (4 H, d, *J* 9.6 Hz), 4.69 (4 H, d, *J* 9.6 Hz), 6.76 (4 H, s), 7.22-7.34 (20 H, m); δ_C (100 MHz, CDCl₃) 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; *m/z* (FAB) LRMS 1348; C₈₈H₁₀₈N₄O₈ (M⁺) requires 1349.

Tetrabenzoxazine 11b:

Tetramethoxyresorcinarene **9a** (10.0 g, 12.0 mmol) was dissolved in toluene (450 mL) and *N*-Methyl-*N,N*-di([methoxy]ethyl)oxy)methylamine (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 allowed to cool to room temperature and the solvent 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 the *title compound* **11b** as a yellow powder (9.3 g, 73%). M.p. 179-181 °C (dec.); C₆₄H₉₂N₄O₈: calcd. C, 73.53; H, 8.87; N, 5.36; found: C, 73.71; H, 8.85; N, 5.25; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 2931, 2304, 1589, 1473, 1265, 1088, 895, 748; δ_H (400 MHz, CDCl₃) 0.85 (12 H, b t), 1.29 (24 H, m), 1.75-1.87 (8 H, m), 2.46 (12 H, s), 3.42 (12 H, s), 3.83 (4 H, d, *J* 16.0 Hz), 3.93 (4 H, d, *J* 16.0 Hz), 4.44 (4 H, t, *J* 8.0 Hz), 4.50 (4 H, d, *J* 8.0 Hz), 4.67 (4 H, d, *J* 8.0 Hz), 6.67 (4 H, s); δ_C (100 MHz, CDCl₃) 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; *m/z* (FAB) LRMS 1045; C₆₄H₉₂N₄O₈ (M⁺+H) requires 1045.

Tetrabenzoxazine 11c:

Tetramethoxyresorcinarene **9b** (1.00 g, 1.0 mmol) was dissolved in toluene (40 mL) and *N*-Methyl-*N,N*-di([methoxy]ethyl)oxy)methylamine (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 allowed to cool 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 the *title compound* **11c** as an off white powder (0.84 g, 71%). M.p. 178-182 °C (dec.); δ_H (400 MHz, CDCl₃) 2.12-2.20 (8 H, m), 2.47 (12 H, s), 2.64 (8 H, t, *J* 8.0 Hz), 3.37 (12 H, s), 3.86 (4 H, d, *J* 16.0 Hz), 3.94 (4 H, d, *J* 16.0 Hz), 4.53-4.57 (8 H, m), 4.68 (4 H, d, *J* 8.0 Hz), 6.79 (4 H, s), 7.07-7.17 (20 H, m); δ_C (100 MHz, CDCl₃) 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; *m/z* (FAB) LRMS 1181; C₇₆H₈₄N₄O₈ (M⁺+H) requires 1182.

Representative procedure for the reaction of bis(aminol) ethers with tetraalkoxyresorcinarenes under standard conditions under reflux:

Tetrabenzoxazines (*P,R,S*)-12a /(*M,R,R*)-12a':

Tetrapentyl-tetramethoxyresorcinarene **9a** (4.00 g, 4.9 mmol) was dissolved in toluene (100 mL). *N,N*-Bis(ethoxymethyl)-*N*-(*R*)- α -methylbenzylamine (5.10 g, 24.3 mmol) in toluene (10 mL) was added in one portion and the reaction mixture was heated under reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel (30% ethyl acetate/light petroleum) to furnish the *title compounds* (*P,R,S*)-**12a** /(*M,R,R*)-**12a'**.

First eluting diastereoisomer (*P,R,S*)-12a: Pale yellow foam (2.40 g, 35%). $[\alpha]_D^{25} +125.0$ (*c* 0.55, CHCl₃); C₉₂H₁₁₆N₄O₈: calcd. C, 78.60; H, 8.32; N, 3.99; found: C, 78.34; H, 8.26; N, 4.11; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3054, 2985, 2305, 1421, 1265, 896, 747. δ_H (400 MHz, CDCl₃) 0.88 (12 H, b t, *J* 6.8 Hz), 1.33 (24 H, m), 1.38 (12 H, d, *J* 6.4 Hz), 1.79-1.82 (4 H, m), 1.88-1.91 (4 H, m), 3.25 (12 H, s), 3.80 (4 H, q, *J* 6.8 Hz), 3.84 (4 H, d, *J* 16.4 Hz), 4.16 (4 H, d, *J* 17.2 Hz), 4.20 (4 H, t, *J* 7.2 Hz), 4.58 (4 H, d, *J* 10.4 Hz), 4.63 (4 H, d, *J* 10.4 Hz), 6.73 (4 H, s), 7.25 (20 H, m); δ_C (100 MHz, CDCl₃) 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; *m/z* (FAB) LRMS 1405; C₉₂H₁₁₆N₄O₈ (M⁺) requires 1405.

Second eluting diastereoisomer (*M,R,R*)-12a': Pale yellow foam (2.40 g, 35%). $[\alpha]_D^{25} -5.0$, (*c* 0.53, CHCl₃); C₉₂H₁₁₆N₄O₈: calcd. C, 78.60; H, 8.32; N, 3.99; found: C, 78.40; H, 8.16; N, 4.00; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3054, 2985, 2305, 1421, 1265, 896, 749; δ_H (400 MHz, CDCl₃) 0.87 (12 H, b t), 1.30 (24 H, m), 1.38 (12 H, d, *J* 6.4 Hz), 1.75-1.80 (4 H, m), 1.90-1.95 (4 H, m), 3.33 (12 H, s), 3.70 (4 H, q, *J* 6.4 Hz), 3.88 (4 H, d, *J* 16.8 Hz), 3.97 (4 H, d, *J* 17.2 Hz), 4.44 (4 H, t, *J* 7.2 Hz), 4.55 (4 H, d, *J* 10.0 Hz), 4.98 (4 H, d, *J* 10.0 Hz), 6.80 (4 H, s), 7.16-7.30 (20 H, m); δ_C (100 MHz, CDCl₃) 14.2, 21.4, 22.7, 27.8, 32.2, 35.4, 36.09, 45.4, 57.4, 60.2, 79.2, 112.3, 124.5, 127.1, 127.4, 127.8, 128.4, 128.5, 144.4, 150.3, 154.0; *m/z* (FAB) LRMS 1405; C₉₂H₁₁₆N₄O₈ (M⁺) requires 1405.

Tetrabenzoxazines (*P,R,S*)-12b /(*M,R,R*)-12b':

Prepared according to the representative procedure from tetrapentyl-tetraisopropoxyresorcinarene **9g** (2.00 g, 2.1 mmol). The residue was placed on a column of silica gel and eluted with ethyl acetate: hexane (10:9) to give the *title compounds* (*P,R,S*)-**12b** /(*M,R,R*)-**12b'**.

First eluting diastereoisomer (*P,R,S*)-12b: Colourless foam (1.20 g, 35%). $[\alpha]_D^{25} +131.4$ (*c* 1.4, CHCl₃); $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 2969, 2926, 2858, 1467, 1110, 940, 700; δ_H (400 MHz, 50 °C, CDCl₃) 0.77 (12 H, d, *J* 4.0 Hz), 0.85 (12 H, t, *J* 6.2 Hz), 0.98-1.10 (12 H, m), 1.15-1.34 (24 H, m), 1.39 (12 H, d, *J* 6.4 Hz), 1.69-1.77 (4 H, m), 1.93-2.03 (4 H, m), 3.83 (4 H, q, *J* 6.4 Hz), 3.86 (4 H, d, *J* 16.8 Hz), 4.14 (4 H, d, *J* 16.8 Hz), 4.12 (4 H, m), 4.31 (4 H, t, *J* 7.2 Hz), 4.53 (4 H, d, *J* 9.8 Hz), 4.59 (4 H, d, *J* 9.8 Hz), 6.82 (4 H, s), 7.22-7.34 (20 H, m); δ_C (100 MHz, CDCl₃) 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; *m/z* (FAB) 1517.0057; C₁₀₀H₁₃₂O₈N₄ (M⁺) requires 1517.0045.

Second eluting diastereoisomer (*M,R,R*)-12b': Colourless foam (1.10 g, 35%). $[\alpha]_D^{25} -9.1$ (*c* 1.5, CHCl₃); $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 2968, 2926, 2857, 1461, 1110, 942, 700; δ_H (400 MHz, 50 °C, CDCl₃) 0.82-0.94 (24 H, m), 1.03 (12 H, d, *J* 5.2 Hz), 1.18-1.32 (24 H, m), 1.41 (12 H, d, *J* 6.4 Hz), 1.67-1.76 (4 H, m), 1.92-2.04 (4 H, m), 3.72-3.92 (12 H, m), 4.10 (4 H, m), 4.34 (4 H, t, *J* 7.2), 4.52 (4 H, d, *J* 10.0 Hz), 4.93 (4 H, d, *J* 10.0 Hz), 6.86 (4 H, s), 7.18-7.34 (20 H, m); δ_C (100 MHz, CDCl₃) 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; *m/z* 1518.0123; C₁₀₀H₁₃₂O₈N₄ (M⁺+H) requires 1518.0144.

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 (10:9) to give the *title compounds* (*P,R,S*)-12c/(*M,R,R*)-12c'.

First eluting diastereoisomer (*P,R,S*)-12c: Colourless foam (0.13 g, 25%). $[\alpha]_D^{25} +129.8$ (*c* 1.6, CHCl₃); $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 2953, 2867, 1583, 1464, 1321, 1228, 1170, 1117, 939; δ_H (400 MHz, 50 °C, CDCl₃) 0.87 (12 H, t, *J* 5.8 Hz), 1.12-1.33 (40 H, m), 1.39 (12 H, d, *J* 6.0 Hz), 1.44-1.59 (16 H, m), 1.62-1.81 (4 H, m), 1.93-2.08 (4 H, m), 3.84 (4 H, q, *J* 6.5 Hz), 3.87 (4 H, d, *J* 17.0 Hz), 4.18 (4 H, d, *J* 17.0 Hz), 4.29 (4 H, m), 4.44 (4 H, t, *J* 7.2 Hz), 4.66 (8 H, m), 6.87 (4 H, m), 7.19-7.36 (20 H, m); δ_C (100 MHz, CDCl₃) 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; *m/z* (ESI) LRMS 1622; C₁₀₈H₁₄₀O₈N₄ (M⁺+H) requires 1622 (the isotopic distribution of the observed data matched the theoretical (M⁺+H) isotopic distribution).

Second eluting diastereoisomer (*M,R,R*)-12c': Colourless foam (0.12 g, 24%). $[\alpha]_{\text{D}}^{25} -5.0$ (*c* 1.6, CHCl₃); ν_{max} (CH₂Cl₂) /cm⁻¹ 2952, 2867, 1583, 1490, 1457, 1320, 1228, 1169, 941; δ_{H} (400 MHz, 50 °C; CDCl₃) 0.90 (12 H, t, *J* 6.4 Hz), 1.18-1.40 (40 H, m), 1.45 (12 H, d, *J* 6.0 Hz), 1.50-1.66 (16 H, m), 1.68-1.81 (4 H, m), 1.94-2.06 (4 H, m), 3.79 (4 H, q, *J* 6.4 Hz), 3.86 (4 H, d, *J* 16.8 Hz), 3.92 (4 H, d, *J* 16.8 Hz), 4.29 (4 H, m), 4.44 (4 H, t, *J* 7.2 Hz), 4.57 (4 H, d, *J* 9.4 Hz), 4.95 (4 H, d, *J* 16.8 Hz), 6.88 (4 H, m), 7.15-7.46 (20 H, m); δ_{C} (100 MHz, CDCl₃) 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; *m/z* (ESI) LRMS 1622; C₁₀₈H₁₄₀O₈N₄ (M⁺+H) requires 1622 (the isotopic distribution of the observed data matched the theoretical (M⁺+H) isotopic distribution).

Representative procedure for the reaction of bis(aminol) ethers with tetraalkoxyresorcinarenes under microwave conditions:

Tetrabenzoxazine 11a:

Tetramethoxyresorcinarene **9a** (0.50 g, 0.6 mmol) was suspended in *N,N*-bis(ethoxymethyl)-*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 orange oil obtained was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to give the *title compound* **11a** (0.66 g, 82%).

Tetrabenzoxazines (*M,S,R*)-13a /(*P,S,S*)-13a':

Prepared according to the representative procedure from tetrapentyl-tetramethoxyresorcinarene **9a** (0.46 g, 0.6 mmol) and *N,N*-Bis(ethoxymethyl)-*N*-(*S*)- α -methylbenzylamine (0.83 g, 4.5 mmol). The suspension was heated under microwave irradiation at 150 °C for 10 min (without cooling). The orange oil obtained was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to give the *title compounds* (*M,S,R*)-**13a**/(*P,S,S*)-**13a'**.

First eluting diastereoisomer (*M,S,R*)-13a: Pale yellow foam (0.29 g, 38%). $[\alpha]_{\text{D}}^{25} -107.0$ (*c* 0.50, CHCl₃); δ_{H} (400 MHz, CDCl₃) 0.88 (12 H, bt, *J* 6.8 Hz), 1.33 (24 H, m), 1.38 (12 H, d, *J* 6.8 Hz), 1.79-1.82 (4 H, m), 1.89-1.91 (4 H, m), 3.25 (12 H, s), 3.80 (4 H, q, *J* 6.4 Hz), 3.84 (4 H, d, *J* 16.8 Hz), 4.15 (4 H, d, *J* 17.2 Hz), 4.24 (4 H, t, *J* 7.6 Hz), 4.58 (4 H, d, *J* 10.0 Hz), 4.63 (4 H, d, *J* 10.4 Hz), 6.73 (4 H, s), 7.26 (20 H, m); δ_{C} (100 MHz, CDCl₃) 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; m/z (FAB) LRMS 1405; $C_{92}H_{116}N_4O_8$ (M^+) requires 1405.

Second eluting diastereoisomer (*P,S,S*)-13a': Pale yellow foam (0.27 g, 36 %). $[\alpha]_D^{25} +7.0$ (c 0.70, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (12 H, bt), 1.30 (24 H, m), 1.38 (12 H, d, J 6.4 Hz), 1.75-1.80 (4 H, m), 1.90-1.95 (4 H, m), 3.33 (12 H, s), 3.70 (4 H, q, J 6.4 Hz), 3.88 (4 H, d, J 16.8 Hz), 3.97 (4 H, d, J 17.2 Hz), 4.44 (4 H, t, J 7.6 Hz), 4.55 (4 H, d, J 10.0 Hz), 4.98 (4 H, d, J 10.0 Hz), 6.80 (4 H, s), 7.18-7.30 (20 H, m); δ_C ($CDCl_3$; 100 MHz) 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; m/z (FAB) LRMS 1405; $C_{92}H_{116}N_4O_8$ (M^+) requires 1405.

Tetrabenzoxazines (*M,S,R*)-13b/(*P,S,S*)-13b':

Prepared according to the representative procedure from tetrapentyl-tetraisopropoxyresorcinarene **9c** (0.10 g, 0.1 mmol). The suspension was heated under microwave irradiation at 140 °C for 3 x 10 min. The orange oil obtained was placed on a column of silica gel and eluted with hexane/ethyl acetate (6:1) to give the *title compounds* (*M,S,R*)-13b/(*P,S,S*)-13b'.

First eluting diastereoisomer (*M,S,R*)-13b: Yellow foam (0.063 g, 39%). $[\alpha]_D^{25} -116.0$ (c 0.32, $CHCl_3$); ν_{max} (CH_2Cl_2) / cm^{-1} 3054, 2986, 2305, 1421, 1265, 896, 749, 705; δ_H (400 MHz, 50 °C, $CDCl_3$) 0.77 (12 H, d, J 4.0 Hz), 0.85 (12 H, t, J 6.2 Hz), 0.98-1.10 (12 H, m), 1.15-1.34 (24 H, m), 1.39 (12 H, d, J 6.4 Hz), 1.69-1.77 (4 H, m), 1.93-2.03 (4 H, m), 3.83 (4 H, q, J 6.4 Hz), 3.86 (4 H, d, J 16.8 Hz), 4.14 (4 H, d, J 16.8 Hz), 4.12 (4 H, m), 4.31 (4 H, t, J 7.2 Hz), 4.53 (4 H, d, J 9.8 Hz), 4.59 (4 H, d, J 9.8 Hz), 6.82 (4 H, s), 7.22-7.34 (20 H, m); δ_C (100 MHz, $CDCl_3$) 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; m/z (FAB) LRMS 1518; $C_{100}H_{132}O_8N_4$ (M^+) requires 1518.

Second eluting diastereoisomer (*P,S,S*)-13b': Yellow foam (0.064 g, 39%). $[\alpha]_D^{25} +3.0$ (c 0.36, $CHCl_3$); ν_{max} (CH_2Cl_2) / cm^{-1} 2968, 2926, 2857, 1461, 1110, 942, 700; δ_H (400 MHz, 50 °C, $CDCl_3$) 0.82-0.94 (24 H, m), 1.03 (12 H, d, J 5.2 Hz), 1.18-1.32 (24 H, m), 1.41 (12 H, d, J 6.4 Hz), 1.67-1.76 (4 H, m), 1.92-2.04 (4 H, m), 3.72-3.92 (12 H, m), 4.10 (4 H, m), 4.34 (4 H, t, J 7.2), 4.52 (4 H, d, J 10.0 Hz), 4.93 (4 H, d, J 10.0 Hz), 6.86 (4 H, s), 7.18-7.34 (20 H, m); δ_C (100 MHz, $CDCl_3$) 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; m/z (FAB) LRMS 1518; $C_{100}H_{132}O_8N_4$ (M^+) requires 1518.

Tetrabenzoxazines (*M,S,R*)-13c/(*P,S,S*)-13c':

Tetra-*n*-butyloxyresorcinarene **9i** (1.00 g, 1.0 mmol) was dissolved in xylene (80 ml). *N,N*-Bis(ethoxymethyl)-*N*-(*S*)- α -methylbenzylamine (1.70 g, 8.0 mmol) in xylene (20 ml) was added in one portion and the reaction mixture was heated under reflux for 4 d. After this time the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified on silica gel eluting with light petroleum/ethyl acetate (7:1) to furnish the *title compounds* (*M,S,R*)-13c/(*P,S,S*)-13c'.

First eluting diastereoisomer (*M,S,R*)-13c: Pale yellow foam (0.50 g, 31%). $[\alpha]_D^{25} -105.0$ (*c* 0.23, CHCl₃); C₁₀₄H₁₄₀N₄O₈: calcd. C, 79.35; H, 8.96; N, 3.56; found C, 79.27; H, 9.03; N, 3.62; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3053, 2958, 2305, 1466, 1421, 1265, 896, 747; δ_H (400 MHz, 50 °C, CDCl₃) 0.93 (12 H, t, *J* 7.2 Hz), 0.97 (12 H, t, *J* 6.4 Hz), 1.41 (32 H, m), 1.46 (12 H, d, *J* 6.8 Hz), 1.56-1.65 (8 H, m), 1.86-1.92 (4 H, m), 1.97-2.02 (4 H, m), 3.50-3.41 (4 H, m), 3.47-3.52 (4 H, m), 3.89-3.95 (8 H, m), 4.26 (4 H, d, *J* 16.8 Hz), 4.54 (4 H, t, *J* 7.2 Hz), 4.69 (4 H, d, *J* 10.0 Hz), 4.73 (4 H, d, *J* 10.0 Hz), 6.85 (4 H, s), 7.31-7.39 (20 H, m); δ_C (100 MHz, CDCl₃, 50 °C) 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; *m/z* (FAB) 1573.0708; C₁₀₄H₁₄₀N₄O₈ (M⁺) requires 1573.0671.

Second eluting diastereoisomer (*P,S,S*)-13c': (0.50 g, 31%). $[\alpha]_D^{25} +21.0$ (*c* 0.51, CHCl₃); C₁₀₄H₁₄₀N₄O₈: calcd. C, 79.35; H, 8.96; N, 3.56; found C, 79.45; H, 9.02; N, 3.53; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3053, 2959, 2305, 1590, 1465, 1421, 1265, 896, 748; δ_H (400 MHz, CDCl₃, 50 °C) 0.77 (12 H, t, *J* 7.2 Hz), 0.86 (12 H, bt), 1.15-1.24 (8 H, m), 1.30 (24 H, m), 1.39 (12 H, d, *J* 6.4 Hz), 1.41-1.48 (8 H, m), 1.74-1.79 (4 H, m), 1.88-1.93 (4 H, m), 3.32-3.43 (8 H, m), 3.70 (4 H, q, *J* 6.8 Hz), 3.88 (8 H, 2 x bd), 4.43 (4 H, t, *J* 7.2 Hz), 4.53 (4 H, d, *J* 10.0 Hz), 4.90 (4 H, d, *J* 10.0 Hz), 6.77 (4 H, s), 7.12-7.27 (20 H, m); δ_C (100 MHz, CDCl₃, 50 °C) 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; *m/z* (FAB) LRMS 1573; C₁₀₄H₁₄₀N₄O₈ (M⁺H) requires 1574.

Tetrabenzoxazines (*M,S,R*)-14a/(*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 x 10

min. The orange oil obtained was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to give the *title compounds* (*M,S,R*)-**14a**/*(P,S,S)*-**14a'**.

First eluting diastereoisomer (*M,S,R*)-14a: Pale yellow oil (0.25 g, 33%). $[\alpha]_{\text{D}}^{25} -95.2$ (*c* 0.84, CHCl₃); ν_{max} (CHCl₃) /cm⁻¹ 3060, 2922, 2852, 2359, 1589, 1467, 1321, 1229, 1098, 944, 754; δ_{H} (400 MHz, CDCl₃) 0.80 (12 H, t, *J* 6.4 Hz), 1.17-1.27 (72 H, m), 1.31 (12 H, d, *J* 6.4 Hz), 1.55-1.82 (8 H, m), 3.18 (12 H, s), 3.72 (4 H, q, *J* 6.4 Hz), 3.76 (4 H, d, *J* 16.8 Hz), 4.08 (4 H, d, *J* 16.8 Hz), 4.34 (4 H, t, *J* 7.6 Hz), 4.53 (4 H, d, *J* 10.0 Hz), 4.63 (4 H, d, *J* 10.0 Hz), 6.65 (4 H, s), 7.08-7.29 (20 H, m); δ_{C} (100 MHz; CDCl₃) 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; *m/z* (FAB) 1742.2627; C₁₁₆H₁₆₄O₈N₄ (M⁺+H) requires 1742.2627.

Second eluting diastereoisomer (*P,S,S*)-14a': Pale yellow oil (0.24 g, 31%). $[\alpha]_{\text{D}}^{25} -15.4$ (*c* 0.63, CHCl₃); ν_{max} (CHCl₃) /cm⁻¹ 3059, 2922, 2851, 2346, 1589, 1467, 1322, 1230, 1095, 946, 751; δ_{H} (400 MHz, CDCl₃) 0.87 (12 H, t, *J* 7.2 Hz), 1.24-1.30 (72 H, m), 1.38 (12 H, d, *J* 6.4 Hz), 1.76-1.94 (8 H, m), 3.33 (12 H, s), 3.69 (4 H, q, *J* 6.4 Hz), 3.88 (4 H, d, *J* 16.8 Hz), 3.96 (4 H, d, *J* 16.8 Hz), 4.43 (4 H, t, *J* 7.2 Hz), 4.55 (4 H, d, *J* 10.0 Hz), 4.99 (4 H, d, *J* 10.0 Hz), 6.80 (4 H, s), 7.16-7.34 (20 H, m); δ_{C} (100 MHz; CDCl₃) 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; *m/z* (FAB) 1741.2523; C₁₁₆H₁₆₄O₈N₄ (M⁺) requires 1741.2549.

Tetrabenzoxazines (*M,S,R*)-15a/*(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 x 10 min. The orange oil obtained was placed on a column of silica gel and eluted with light petroleum/ethyl acetate (5:1) to give the *title compounds* (*M,S,R*)-**15a**/*(P,S,S)*-**15a'**.

First eluting diastereoisomer (*M,S,R*)-15a: Pale yellow foam (0.75 g, 43%). $[\alpha]_{\text{D}}^{25} -108.1$ (*c* 0.47, CHCl₃); ν_{max} (CHCl₃) /cm⁻¹ 2951, 2864, 2359, 1589, 1469, 1365, 1235, 1095, 942, 753; δ_{H} (400 MHz, CDCl₃) 0.94 (12 H, d, *J* 10.0 Hz), 0.96 (12 H, d, *J* 10.0 Hz), 1.39 (12 H, d, *J* 6.5 Hz), 1.52-1.61 (4 H, m), 1.65-1.72 (4 H, m), 1.76-1.83 (4 H, m), 3.26 (12 H, s), 3.80 (4 H, q, *J* 6.5 Hz), 3.86 (4 H, d, *J* 17.0 Hz), 4.17 (4 H, d, *J* 16.9 Hz), 4.55-4.62 (12 H, m), 6.70 (4 H, s), 7.17-7.35 (20 H,

m); δ_{C} (100 MHz, CDCl_3) 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; m/z (FAB) 1348.8189; $\text{C}_{88}\text{H}_{108}\text{O}_8\text{N}_4$ (M^+) requires 1348.8167.

Second eluting diastereoisomer (*P,S,S*)-15a’: Colourless crystals, recrystallized from ethanol (0.75 g, 43%). M.p. 144-146 °C; $[\alpha]_{\text{D}}^{25} +18.1$ (c 1.04, CHCl_3); ν_{max} (CHCl_3) / cm^{-1} 2950, 2863, 2360, 1590, 1467, 1366, 1235, 1090, 941, 755; δ_{H} (400 MHz, CDCl_3) 0.90 (12 H, d, J 20.2 Hz), 0.93 (12 H, d, J 20.2 Hz), 1.39 (12 H, d, J 6.5 Hz), 1.45-1.50 (4 H, m), 1.65-1.68 (4 H, m), 1.77-1.83 (4 H, m), 3.36 (12 H, s), 3.68 (4 H, q, J 6.5 Hz), 3.95 (8 H, q, J 15.2 Hz), 4.57 (8 H, q, J 7.8 Hz), 4.97 (4 H, d, J 9.9 Hz), 6.81 (4 H, s), 7.16-7.37 (20 H, m); δ_{C} (100 MHz, CDCl_3 , 55°C) 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; m/z (FAB) 1348.8188; $\text{C}_{88}\text{H}_{108}\text{O}_8\text{N}_4$ (M^+) requires 1348.8167.

Tetrabenzoxazines (*M,S,R*)-16a/(*P,S,S*)-16a’:

Prepared according to the representative procedure from tetra-2-methylpropyl-tetraisopropoxyresorcinarene (0.10 g, 0.11 mmol). The suspension was heated under microwave irradiation at 140 °C for 3 x 10 min. The orange oil obtained was placed on a column of silica gel and eluted with hexane/ethyl acetate (6:1) to give the *title compounds* (*M,S,R*)-16a/(*P,S,S*)-16a’.

First eluting diastereoisomer (*M,S,R*)-16a: Yellow foam (0.062 g, 37%). $[\alpha]_{\text{D}}^{25} -136.9$ (c 1.3, CHCl_3); ν_{max} (CH_2Cl_2) / cm^{-1} 2953, 2361, 1457, 1108; δ_{H} (400 MHz, 50 °C, CDCl_3) 0.85 (12 H, d, J 5.6), 0.93 (24 H, t, J 6.4 Hz), 1.06 (12 H, d, J 5.6 Hz), 1.41 (12 H, d, J 6.4 Hz), 1.45-1.56 (4 H, m), 1.66-1.74 (4 H, m), 1.85-1.93 (4 H, m), 3.85 (4 H, q, J 6.4 Hz), 3.92 (4 H, d, J 16.8 Hz), 4.21 (4 H, d, J 16.8 Hz), 4.10 (4 H, m), 4.47-4.65 (12 H, m), 6.88 (4 H, s), 7.22-7.39 (20 H, m); δ_{C} (100 MHz, 60 °C, CDCl_3) 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; m/z (FAB) 1464.9759; $\text{C}_{100}\text{H}_{132}\text{O}_8\text{N}_4$ (M^+) requires 1464.9732.

Second eluting diastereoisomer (*P,S,S*)-16a’: Yellow foam (0.064 g, 38%). $[\alpha]_{\text{D}}^{25} -12.0$ (c 1.5, CHCl_3). ν_{max} (CH_2Cl_2) / cm^{-1} 2969, 2864, 2359, 1465, 1109, 939; δ_{H} (400 MHz, 50 °C, CDCl_3) 0.89 (24 H, t, J 6.8 Hz), 0.96 (12 H, t, J 6.0 Hz), 1.08 (12 H, d, J 6.0 Hz), 1.45 (12 H, d, J 6.4 Hz), 1.51-1.58 (4 H, m), 1.62-1.73 (4 H, m), 1.82-1.93 (4 H, m), 3.75-3.91 (12 H, m), 4.10 (4 H, m, H7), 4.54 (4 H, t, J 7.4 Hz), 4.58 (4 H, d, J 9.6 Hz), 4.98 (4 H, d, J 9.6 Hz), 6.91 (4 H, s), 7.21-

7.39 (20 H, m); δ_{C} (100 MHz, CDCl_3) 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.

Tetrabenzoxazines (*M,S,R*)-17a/(*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 x 10 min. The orange oil obtained was placed on a column of silica gel and eluted with hexane/ethyl acetate (9:1) to give the *title compounds* (*M,S,R*)-**17a**/(*P,S,S*)-**17a'**.

First eluting diastereoisomer (*M,S,R*)-17a: Yellow foam (0.057 g, 37%). $[\alpha]_{\text{D}}^{25} -127.6$ (*c* 1.3, CHCl_3); ν_{max} (CH_2Cl_2) / cm^{-1} 2958, 2872, 1588, 1469, 1326, 1231, 1116, 939; δ_{H} (400 MHz, 50 °C, CDCl_3) 0.87 (12 H, t, *J* 5.8 Hz), 1.12-1.33 (40 H, m), 1.39 (12 H, d, *J* 6.0 Hz), 1.44-1.59 (16 H, m), 1.62-1.81 (4 H, m), 1.93-2.08 (4 H, m), 3.84 (4 H, q, *J* 6.5 Hz), 3.87 (4 H, d, *J* 17.0 Hz), 4.18 (4 H, d, *J* 17.0 Hz), 4.29 (4 H, m), 4.44 (4 H, t, *J* 7.2 Hz), 4.66 (8 H, m), 6.87 (4 H, m), 7.19-7.36 (20 H, m); δ_{C} (100 MHz, CDCl_3) 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; *m/z* (ESI) LRMS 1622; $\text{C}_{108}\text{H}_{140}\text{O}_8\text{N}_4$ ($\text{M}^+\text{+H}$) requires 1622.

Second eluting diastereoisomer (*P,S,S*)-17a': Yellow foam (0.055 g, 35%). $[\alpha]_{\text{D}}^{25} +6.2$ (*c* 1.8, CHCl_3); ν_{max} (CH_2Cl_2) / cm^{-1} 2950, 2864, 1582, 1494, 1452, 1315, 1225, 941; δ_{H} (400 MHz, 50 °C; CDCl_3) 0.90 (12 H, t, *J* 6.4 Hz), 1.18-1.40 (40 H, m), 1.45 (12 H, d, *J* 6.0 Hz), 1.50-1.66 (16 H, m), 1.68-1.81 (4 H, m), 1.94-2.06 (4 H, m), 3.79 (4 H, q, *J* 6.4 Hz), 3.86 (4 H, d, *J* 16.8 Hz), 3.92 (4 H, d, *J* 16.8 Hz), 4.29 (4 H, m), 4.44 (4 H, t, *J* 7.2 Hz), 4.57 (4 H, d, *J* 9.4 Hz), 4.95 (4 H, d, *J* 16.8 Hz), 6.88 (4 H, m), 7.15-7.46 (20 H, m); δ_{C} (100 MHz, CDCl_3) 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; *m/z* (ESI) LRMS 1622; $\text{C}_{108}\text{H}_{140}\text{O}_8\text{N}_4$ ($\text{M}^+\text{+H}$) requires 1622.

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 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 ether (80 mL) and washed successively with water (2 x 50 mL), brine (1 x 50 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford a colourless oil which crystallized from a minimum amount of methanol upon cooling to 4°C for 24 h to yield *title compound 18* as colourless crystals (1.77 g, 85 %). M.p. 63.5–64.0 °C. $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 2928, 1761, 1500, 1303, 1192; δ_{H} (500 MHz, CDCl₃) 0.86 (12 H, bt, *J* 6.7 Hz), 1.16–1.42 (52 H, m), 1.76–1.90 (8 H, m), 3.62 (12 H, s), 4.24 (8 H, q, *J* 7.2 Hz), 4.03 (4 H, d, *J* 15.9 Hz), 4.19 (4 H, d, *J* 15.9 Hz), 4.52 (4 H, t, *J* 7.4 Hz), 6.31 (4 H, s), 6.62 (4 H, s); δ_{C} (126 MHz, CDCl₃) 14.8, 14.9, 23.4, 28.7, 30.0, 30.6, 32.7, 35.3, 36.2 (CH₂ and CH), 56.2, 61.6, 69.1, 100.2, 127.0, 128.1, 128.8, 155.6, 156.2, 170.3; *m/z* (FAB) 1280.7685; C₇₆H₁₁₂O₁₆ (M⁺) requires 1280.7950.

General procedure for the formation of resorcinarene amides:

A mixture of the resorcinarene (3.0 g), *N*-bromoacetyl-(*R*)-(+)- α -methylbenzylamine (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 give the corresponding diastereoisomeric mixtures. The diastereoisomers were separated by flash chromatography eluting with ethyl acetate/dichloromethane (1:1).

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 *N*-bromoacetyl-(*R*)-(+)- α -methylbenzylamine (4.61 g, 20.2 mmol) to give the *title compounds* (*M,R,R*)-20a and (*P,R,S*)-20a’.

First eluting diastereoisomer (*M,R,R*)-20a: Colourless crystals, recrystallized from methanol (2.01 g, 35 %). M.p. 180–181 °C, $[\alpha]_{\text{D}}^{25}$ –7.8 (*c* 2.04, CHCl₃); $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3422, 2955, 2930, 2870, 1684, 1501, 1299, 1199; δ_{H} (200 MHz, CDCl₃) 0.95 (12 H, t, *J* 7.2 Hz), 1.23–1.41 (8 H, m), 1.46 (12 H, d, *J* 6.6 Hz), 1.82–1.98 (8 H, m), 3.34 (12 H, s), 4.06 (4 H, d, *J* 14.5 Hz), 4.33 (4 H, d, *J* 14.5 Hz), 4.57 (4 H, t, *J* 8.0 Hz), 5.11–5.31 (4 H, m), 6.03 (4 H, s), 6.80–6.92 (8 H, m), 7.02–7.22 (20 H, m); δ_{C} (50.3 MHz, CDCl₃) 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; *m/z* (FAB) 1356.7129; C₈₄H₁₀₀N₄O₁₂ (M⁺) requires 1356.7338.

Second eluting diastereoisomer (*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, CHCl₃); C₈₄H₁₀₀N₄O₁₂: calcd. C, 74.3; H, 7.4; N, 4.1; found: C, 73.9; H, 7.3; N, 4.1; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3419, 2955, 2931, 2870, 1682, 1499, 1298, 1197; δ_H (200 MHz, CDCl₃) 0.89 (12 H, t, *J* 7.4 Hz), 1.16-1.37 (8 H, m), 1.49 (12 H, d, *J* 6.6 Hz), 1.75-1.90 (8 H, m), 3.44 (12 H, s), 4.20 (4 H, d, *J* 14.8 Hz), 4.30 (4 H, d, *J* 14.8 Hz), 4.58 (4 H, t, *J* 7.2 Hz), 5.16-5.35 (4 H, m), 6.25 (4 H, s), 6.81 (4 H, s), 7.03 (4 H, d), 7.26-7.40 (20 H, m); δ_C (50.3 MHz, CDCl₃) 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.

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 *N*-bromoacetyl-(*R*)-(+)- α -methylbenzylamine (3.51 g, 15.4 mmol) to give the *title compounds* (*M,R,R*)-20b and (*P,R,S*)-20b’.

First eluting diastereoisomer (*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, CHCl₃). C₁₀₀H₁₃₂N₄O₁₂: calcd. C, 75.9; H, 8.4; N, 3.5; found: C, 75.6; H, 8.4; N, 3.5; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3421, 2926, 2854, 1684, 1499, 1298, 1198; δ_H (200 MHz, CDCl₃) 0.87 (12 H, bt), 1.14-1.39 (40 H, m), 1.47 (12 H, d, *J* 6.6 Hz), 1.80-1.99 (8 H, m), 3.33 (12 H, s), 4.06 (4 H, d, *J* 14.6 Hz), 4.32 (4 H, d, *J* 14.6 Hz), 4.55 (4 H, t, *J* 7.2 Hz), 5.11-5.31 (4 H, m), 6.03 (4 H, s), 6.80-6.92 (8 H, m), 7.01-7.22 (20 H, m); δ_C (50.3 MHz, CDCl₃) 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.

Second eluting diastereoisomer (*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, CHCl₃). C₁₀₀H₁₃₂N₄O₁₂: calcd. C, 75.9; H, 8.4; N, 3.5; found: C, 75.6; H, 8.3; N, 3.5; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3418, 2926, 2854, 1685, 1500, 1297, 1198; δ_H (200 MHz, CDCl₃) 0.87 (12 H, bt), 1.13-1.36 (40 H, m), 1.49 (12 H, d, *J* 7.4 Hz), 1.72-1.93 (8 H, m), 3.44 (12 H, s), 4.19 (4 H, d, *J* 14.8 Hz), 4.30 (4 H, d, *J* 14.8 Hz), 4.51 (4 H, t, *J* 7.2 Hz), 5.14-5.32 (4 H, m), 6.21 (4 H, s), 6.76 (4 H, s), 6.99 (4 H, d, *J* 8.8 Hz), 7.22-7.35 (20 H, m); δ_C (50.3 MHz, CDCl₃) 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.

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 *N*-bromoacetyl-(*R*)-(+)- α -methylbenzylamine (2.83 g, 12.4 mmol) to give the *title compounds* **20c** and **20c'**.

First eluting diastereoisomer (*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, CHCl₃). C₁₁₆H₁₆₄N₄O₁₂: calcd. C, 77.1; H, 9.2; N, 3.1; found: C, 77.2; H, 9.1; N, 3.1; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3422, 2924, 2853, 1684, 1509, 1298, 1198; δ_H (200 MHz, CDCl₃) 0.88 (12 H, bt), 1.17-1.38 (72 H, m), 1.47 (12 H, d, *J* 7.4 Hz), 1.80-1.98 (8 H, m), 3.33 (12 H, s), 4.05 (4 H, d, *J* 14.5 Hz), 4.32 (4 H, d, *J* 14.5 Hz), 4.54 (4 H, t, *J* 7.4 Hz), 5.11-5.31 (4 H, m), 6.04 (4 H, s), 6.81 (4 H, s), 6.87 (4 H, d, *J* 8.2 Hz), 7.03-7.21 (20 H, m); δ_C (50.3 MHz, CDCl₃) 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.

Second eluting diastereoisomer (*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, CHCl₃). C₁₁₆H₁₆₄N₄O₁₂: calcd. C, 77.1; H, 9.2; N, 3.1; found: C, 77.0; H, 9.0; N, 3.0; $\nu_{\max}$ (CH₂Cl₂) /cm⁻¹ 3418, 2924, 2853, 1685, 1500, 1297, 1198; δ_H (200 MHz, CDCl₃) 0.88 (12 H, bt), 1.13-1.37 (72 H, m), 1.49 (12 H, d, *J* 6.6 Hz), 1.76-1.95 (8 H, m), 3.44 (12 H, s), 4.19 (4 H, d, *J* 14.7 Hz), 4.29 (4 H, d, *J* 14.7 Hz), 4.50 (4 H, t, *J* 7.4 Hz), 5.12-5.31 (4 H, m), 6.21 (4 H, s), 6.75 (4 H, s), 6.98 (4 H, d, *J* 8.0 Hz), 7.22-7.36 (20 H, m); δ_C (50.3 MHz, CDCl₃) 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.

Representative procedure for the addition of diethyl or dimethylzinc to aromatic aldehydes:

1-phenylpropanol:⁵²

Diethylzinc (2.2 mmol, 2.2 mL, 1.0M in hexanes) was added to a solution of tetrabenzoxazine (*P,R,S*)-**12b** (0.017 g, 0.01 mmol) in toluene (1mL) at 0°C and then the solution was cooled to -78° C for 30 min. Benzaldehyde (0.1 mL, 1.0 mmol) was then added dropwise and the solution left for 12 h while attaining ambient temperature. The solution was quenched with NH₄Cl and extracted with diethyl ether (2 x 10 mL). The conversion and ee were calculated from the crude product (>95% conversion, 83% ee). $\nu_{\max}$ (neat) /cm⁻¹ 3358, 2929, 2873, 1475, 1030; δ_H (400 MHz, CDCl₃) 0.93 (3 H, t, *J* 7.2 Hz), 1.75-1.87 (2 H, m), 2.40 (1 H, bs), 4.58 (1 H, t, *J* 6.8 Hz), 7.29-7.40 (5 H, m); δ_C

(100 MHz, CDCl₃) 10.1, 31.8, 75.9, 125.9, 128.3, 128.9, 144.5; GC conditions: β cyclodextrin (120° C, isothermal), 6.28 min, 6.43 min (major isomer).

1-phenylethanol:⁵²

Colourless oil: $\nu_{\max}$ (neat) /cm⁻¹ 3365, 2929, 2870, 1472, 1031; δ_{H} (400 MHz, CDCl₃) 1.45 (1 H, d, *J* 7.8 Hz), 2.42 (1 H, bs), 4.79 (1 H, q, *J* 7.8 Hz), 7.29-7.32 (5 H, m); δ_{C} (100 MHz, CDCl₃) 25.7, 70.8, 126.1, 127.9, 129.2, 146.4; GC conditions: β cyclodextrin (110° C, isothermal), 12.0 min, 12.6 min (major isomer).

2-methyl-1-phenylpropanol:⁵³

Colourless oil: $\nu_{\max}$ (neat) /cm⁻¹ 3393, 3027, 2957, 2870, 1468, 1453, 1021, 759; δ_{H} (400 MHz, CDCl₃) 0.73 (3 H, d, *J* 6.7 Hz), 0.93 (3 H, d, *J* 6.7 Hz), 1.78 (1 H, bs), 1.90 (1 H, sept, *J* 6.7), 4.21 (1 H, d, *J* 6.9 Hz), 7.18-7.29 (5 H, m); δ_{C} (100 MHz, CDCl₃) 18.2, 18.9, 35.1, 80.0, 126.7, 127.8, 128.1, 143.6; HPLC conditions: (Chiracel OD), 95:5 Hexane:Isopropanol, r.t., 29.4 min, 32.1 min (major isomer).

(4-methoxyphenyl)propanol:⁵⁴

Colourless oil: $\nu_{\max}$ (neat) /cm⁻¹ 3390, 2960, 2932, 1611, 1513, 1247; δ_{H} (400 MHz, CDCl₃) 0.84 (3 H, t, *J* 7.2 Hz), 1.60-1.90 (2 H, m), 1.80 (1 H, bs), 3.74 (3 H, s), 4.64 (1 H, t, *J* 6.8 Hz), 6.82 (2 H, d, *J* 8.7 Hz), 7.18 (2 H, d, *J* 8.7 Hz); δ_{C} (100 MHz, CDCl₃) 10.2, 31.7, 55.2, 75.6, 113.7, 127.2, 136.7, 158.9; GC conditions: β-cyclodextrin, 125° C, r.t., 33.7 min(major isomer), 35.2 min.

(*E*)-5-Phenylpent-4-en-3-ol:⁵²

Pale yellow oil: $\nu_{\max}$ (neat) /cm⁻¹ 3356, 3057, 2962, 2929, 1448, 964; δ_{H} (400 MHz, CDCl₃) 0.86 (3 H, t, *J* 7.6 Hz), 1.46-1.61 (2 H, m), 2.2 (1 H, bs), 4.1 (1 H, dq, *J* 7.6, 0.8 Hz), 6.10 (1 H, dd, *J* 16.0, 6.8 Hz), 6.44 (1 H, d, *J* 16.0 Hz), 7.11-7.26 (5 H, m); δ_{C} (100 MHz, CDCl₃) 9.5, 29.2, 74.1, 126.1, 128.3, 129.4, 131.3, 132.3, 126.5; HPLC conditions: (Chiracel OD), 85:15 Hexane:Isopropanol, 0.8 mL/min, r.t., 17.9 min(major isomer), 23.3 min.

4-chlorophenyl propanol:⁵⁵

Pale yellow oil: $\nu_{\max}$ (CHCl₃) /cm⁻¹ 3361, 2954, 2875, 1491, 1090, 1013, 823; δ_{H} (400 MHz, CDCl₃) 0.82 (3 H, t, *J* 7.4 Hz), 1.60-1.88 (2 H, m), 2.30 (1 H, bs), 4.40 (1 H, t, *J* 6.5 Hz), 7.17-7.35 (4 H,

m); δ_{C} (100 MHz, CDCl_3) 10.0, 32.0, 75.3, 127.3, 129.4, 143.0, 151.1; GC conditions: β -cyclodextrin (125° C, isothermal), 31.5 min, 32.7 min (major isomer).

1,3-Diphenylprop-2-yn-1-ol:^{49f,56}

Dimethylzinc (3.0 mL, 3.0 mmol, 1.5M in hexane), was added to a solution of phenylacetylene (0.35 mL, 2.8 mmol) in dry toluene (2.0 mL) at room temperature under an atmosphere of nitrogen. The solution was then left to stand for 1.5 h without stirring. The solution was then transferred to a flask containing tetrabenzoxazine (*P,R,S*)-**12b** (0.075 g, 0.05 mmol) then stirred for 10 min. Benzaldehyde (0.1 mL, 1.0 mmol) was then added and the solution stirred for 48 h. The reaction was quenched (NH_4Cl), extracted with diethyl ether, then purified using column chromatography (8:1, petroleum ether: ethyl acetate). Colourless oil (59%, 64% ee). ν_{max} (neat) / cm^{-1} 3385, 3060, 2874, 1951, 1957, 1490; δ_{H} (400 MHz, CDCl_3) 2.58 (1 H, bs), 5.57 (1 H, s), 7.12-7.51 (10 H, m); δ_{C} (100 MHz, CDCl_3) 65.0, 86.6, 88.7, 122.4, 126.7, 128.2, 128.4, 128.6, 128.7, 131.8, 140.6; HPLC conditions: (Chiracel OD), 80:20 Hexane:Isopropanol, 0.6 mL/min, r.t., 32.1 min, 51.1 min (major isomer).

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Captions

Figure 1. Representation of Resorcin[4]arenes, including Axial Stereochemistry

Figure 2. Abbreviated Representation of Resorcin[4]- and [6]arenes

Scheme 1. Alkylation of Diastereomerically Pure Tetrabenzoxazines

Scheme 2. Mannich Reactions of a Resorcin[6]arene using Bis(aminol) ethers

Scheme 3. Formation of Racemic Tetraalkoxyresorcinarenes

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

Scheme 5. Formation of Racemic Tetrabenzoxazines from Tetraalkoxyresorcinarenes

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.

Scheme 6. Formation of Diastereoisomeric Tetrabenzoxazines from Tetraalkoxyresorcinarenes and *N,N*-Bis(methoxymethyl)-*N*-(*R*)-(+)- α -methylbenzylamine

Scheme 7. Formation of Diastereoisomeric Tetrabenzoxazines from Tetraalkoxyresorcinarenes and *N,N*-Bis(methoxymethyl)-*N*-(*S*)-(-)- α -methylbenzylamine

Scheme 8. Formation of a Mannich Base Using a Pre-formed Iminium Ion Source

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

Scheme 9. Microwave Assisted Mannich Reactions to Produce Tetrabenzoxazines

Table 1: Reactions of Bis(aminol) ethers with Tetraalkoxyresorcinarenes Using Focused Microwave Irradiation

Figure 6. ^1H NMR Spectrum of Compound **15a**

Figure 7. ^1H NMR Spectrum of Compound **15a'**

Scheme 10. Formation of Diastereoisomeric Amides from Tetramethoxyresorcinarenes and [*N*-Bromoacetyl]-(*R*)-(+)- α -methylbenzylamine

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

Scheme 11 The Ligand Assisted Addition of Diethylzinc to Benzaldehyde

Figure 9. Structures of Potential Ligands

Figure 10. Structures of Potential Ligands

Table 2: Reactions of Aromatic Aldehydes with Dialkylzinc Reagents in the Presence of Chiral Ligands

Tables

Table 1: Reactions of Bis(aminol) ethers with Tetraalkoxyresorcinarenes Using Focused Microwave Irradiation

R ¹	R ²	R ³	Power (W)	Temp. (°C)	Time (min.)	Product A* Yield (%)	Product B* Yield (%)
Me	<i>n</i> -C ₅ H ₁₁	Bn	<300	150	10	(11a) 82 (racemic)	—
Me	<i>n</i> -C ₅ H ₁₁	α-Me-Bn	<300	150	10	(13a) 38	(13a') 36
Me	<i>n</i> -C ₁₁ H ₂₃	α-Me-Bn	<300	150	2 x 10	(14a) 33	(14a') 31
Me	2-methyl-propyl	α-Me-Bn	<300	150	2 x 10	(15a) 43	(15a') 43
<i>i</i> -Pr	<i>n</i> -C ₅ H ₁₁	α-Me-Bn	<300	140	3 x 10	(13b) 39	(13b') 39
C ₅ H ₉	<i>n</i> -C ₅ H ₁₁	α-Me-Bn	<300	140	3 x 10	(17a) 37	(17a') 35
<i>i</i> -Pr	2-methyl-propyl	α-Me-Bn	<300	140	3 x 10	(16a) 37	(16a') 37

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

Table 2: Reactions of Aromatic Aldehydes with Dialkylzinc Reagents in the Presence of Chiral Ligands

Ligand	Aldehyde	Dialkylzinc	% Convers.	ee	Config. of prod.
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	X = methoxy- (n = 0)	diethylzinc	95	68	(+)
13b	X = H (n = 1)	diethylzinc	95	41	(+)*
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†	64	(+)*
2	X = H (n = 0)	Methyl(phenylethynyl)zinc	73†	25	(+)*

* Rotation values for the pure enantiomers are very small and so the probable configurations were deduced from the HPLC traces

† Isolated yields

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Schemes and Figures

Figure 1. Representation of Resorcin[4]arenes, including Axial Stereochemistry

Figure 2. Abbreviated Representation of Resorcin[4]- and [6]arenes

$(P,R,S)\text{-2a}$, Ar = Ph, $R^1 = n\text{-C}_{11}\text{H}_{23}$
 $(P,R,S)\text{-2b}$, Ar = Ph, $R^1 = \text{Ph.CH}_2\text{CH}_2$
 $(P,R,S)\text{-2b}$, Ar = Ph, $R^1 = \text{Ph.CH}_2\text{CH}_2$
 $(P,R,S)\text{-2c}$, Ar = 4-MeO.C₆H₄, $R^1 = n\text{-C}_{11}\text{H}_{23}$

$(P,R,S)\text{-3a}$, Ar = Ph, $R^1 = n\text{-C}_{11}\text{H}_{23}$, $R^2 = \text{Me}$, 84%
 $(P,R,S)\text{-3b}$, Ar = Ph, $R^1 = \text{Ph.CH}_2\text{CH}_2$, $R^2 = \text{Me}$, 94%
 $(P,R,S)\text{-3c}$, Ar = Ph, $R^1 = \text{Ph.CH}_2\text{CH}_2$, $R^2 = \text{Et}$, 63%
 $(P,R,S)\text{-3d}$, Ar = 4-MeO.C₆H₄, $R^1 = n\text{-C}_{11}\text{H}_{23}$, $R^2 = \text{Me}$, 78%

Scheme 1. Alkylation of Diastereomerically Pure Tetrabenzoxazines

Scheme 2. Mannich Reactions of a Resorcin[6]arene using Bis(aminol) ethers

8a, R² = Me

8a, R² = Me

8a, R² = Me

8a, R² = Me

8a, R² = Me

8a, R² = Me

8b, R² = *i*-Pr

8b, R² = *i*-Pr

8c, R² = *n*-Bu

8d, R² = cyclopentyl

9a, R¹ = *n*-C₅H₁₁, R² = Me

9b, R¹ = *n*-Pr, R² = Me

9c, R¹ = *n*-C₇H₁₅, R² = Me

9d, R¹ = *n*-C₁₁H₂₃, R² = Me

9e, R¹ = Ph.CH₂.CH₂, R² = Me

9f, R¹ = *i*-Bu, R² = Me

9g, R¹ = *n*-C₅H₁₁, R² = *i*-Pr

9h, R¹ = *i*-Bu, R² = *i*-Pr

9i, R¹ = *n*-C₅H₁₁, R² = *n*-Bu

9j, R¹ = *n*-C₅H₁₁, R² = cyclopentyl

Scheme 3. Formation of Racemic Tetraalkoxyresorcinarenes

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

Scheme 5. Formation of Racemic Tetrabenzoxazines from Tetraalkoxyresorcinarenes

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.

Scheme 6. Formation of Diastereoisomeric Tetrabenzoxazines from Tetraalkoxyresorcinarenes and *N,N*-Bis(methoxymethyl)-*N*-(*R*)-(+)- α -methylbenzylamine

Scheme 7. Formation of Diastereoisomeric Tetrabenzoxazines from Tetraalkoxyresorcinarenes and *N,N*-Bis(methoxymethyl)-*N*-(*S*)-(-)- α -methylbenzylamine

Scheme 8. Formation of a Mannich Base Using a Pre-formed Iminium Ion Source

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

Scheme 9. Microwave Assisted Mannich Reactions to Produce Tetrabenzoxazines

Figure 6. ^1H NMR Spectrum of Compound **15a**

Figure 7. ^1H NMR Spectrum of Compound **15a'**

18, R = *n*-C₇H₁₅, R' = CH₂CO₂Et

9b, R = *n*-Pr, R' = H

9c, R = *n*-C₇H₁₅, R' = H

9d, R = *n*-C₁₁H₂₃, R' = H

(*M,R,R*)-**20a**, R = *n*-Pr

(*P,R,S*)-**20a'**, R = *n*-Pr

(*M,R,R*)-**20b**, R = *n*-C₇H₁₅

(*P,R,S*)-**20b'**, R = *n*-C₇H₁₅

(*M,R,R*)-**20c**, R = *n*-C₁₁H₂₃

(*P,R,S*)-**20c'**, R = *n*-C₁₁H₂₃

Scheme 10. Formation of Diastereoisomeric Amides from Tetramethoxyresorcinarenes and [*N*-Bromoacetyl]-(*R*)-(+)- α -methylbenzylamine

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

Scheme 11 The Ligand Assisted Addition of Diethylzinc to Benzaldehyde

Figure 9. Structures of Potential Ligands

Figure 10. Structures of Potential Ligands