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A study of some molecularly imprinted polymers as protic catalysts for the isomerisation of α-pinene oxide to *trans*-carveol

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Abstract—A range of acidic Molecularly Imprinted Polymers (MIPs) were synthesised using the imprint molecule *trans*-carvyl amine as a transition state analogue for the selective isomerisation of α-pinene oxide to *trans*-carveol. The amine functionality of the imprint molecule was used to selectively position a sulfonic acid group in the MIP binding pocket utilising 4-styrene sulfonic acid as the functional monomer. Co-polymerisation with varying ratios of styrene and divinylbenzene afforded a range of MIPs which were tested for their ability to effect selective formation of *trans*-carveol from α-pinene oxide. Although successful imprinting was demonstrated in binding studies, it was shown that solvent effects were dominant in effecting selective formation of *trans*-carveol. Using DMF as solvent, up to 70% of the products from acid catalysed isomerisation of α-pinene oxide with the polystyrene MIPs were obtained via the necessary *para* menthyl tertiary carbocation, and industrially important *trans*-carveol was obtained in 45% yield.

1. Introduction

The conceptually elegant polymerization technique of molecular imprinting,[1] as encapsulated in Figure 1, produces macroporous polymers which contain binding sites capable of selective molecular recognition of the original imprint molecule or template around which they were constructed. The enormous potential of this method has not gone unrecognized and, in consequence, molecularly imprinted polymers (MIPs) have been used as separation and extraction materials,[2] as microreactors containing reagents for selective reductions,[3] as biomimetic sensors,[4] as specific adsorbents capable of shifting the equilibrium of a thermodynamically unfavourable enzymatic reaction,[5] and as 'protecting groups' using an external reagent.[6] The selection of an imprint molecule which can be regarded as a transition state mimic for a given reaction then leads on to the idea that the preparation of such shape selective polymers can be used in catalyst design, as in the seminal studies of Lerner and Schultz on catalytic antibodies.[7] Even though selective binding of a transition state mimic represents only one facet of enzyme like catalysis, several recent studies[8] testify to the potential of MIPs as selective catalysts, and therefore stimulated our interest in using this approach for proton mediated rearrangements.

From the outset, it is important to recognise both the advantages and the limitations of the process of molecular imprinting as outlined below (Fig. 1). In the first step, monomers containing functional groups which can interact with the imprint molecule, are pre-organised around the imprint molecule **1**. A mixture of standard monomer and cross-linker is then co-polymerised around this imprint moleculemonomer complex **2** in a radical polymerisation process, to form a macroporous polymer which contains sites at which the imprint molecule is bound **3**. Finally, the imprint molecule is removed from the polymer to leave well defined, shape specific cavities **4** which are spatially and functionally compatible with the imprint molecule **1**.

The interactions between the imprint molecule **1** and the functional monomers can be electrostatic, covalent or non-covalent. In the latter case the description pre-organisation is a slight misnomer, since the combination of weak intermolecular forces involved leads rather to a dynamic associated complex **2** in constant exchange with solution. This, along with other factors, leads to the inherent heterogeneity of the molecular recognition sites produced within the polymer. This has proven to be one of the major sticking points in catalytic applications of MIPs. Despite this drawback, the manifest stability of MIPs when compared to natural enzymes or other artificial analogues, means that the realisation of catalytic MIPs remains a highly desirable goal.

With the above principles in mind, the present paper describes our initial studies towards the application of this

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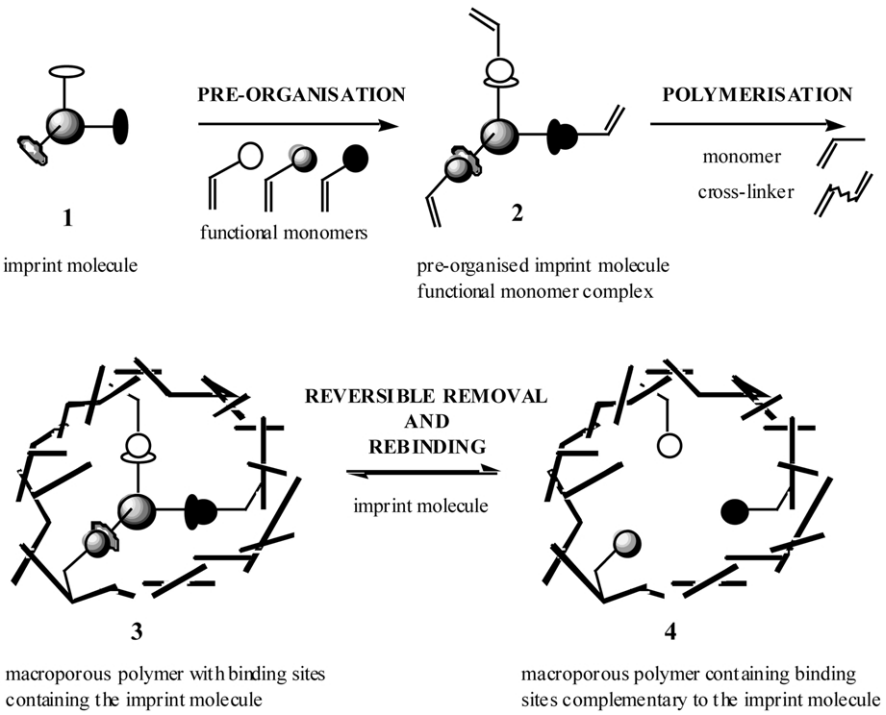


Figure 1.

technology for the selective isomerisation of α-pinene oxide to *trans*-carveol. (−)-*trans*-Carveol **5**,[9] one of the constituents of the Valencia orange essence oil, is an important compound for the fragrance chemical industry. It is usually commercially available as an expensive mixture of isomers. A selective and efficient solid-phase procedure to obtain it from α-pinene oxide **6** is therefore an important objective (Fig. 2).

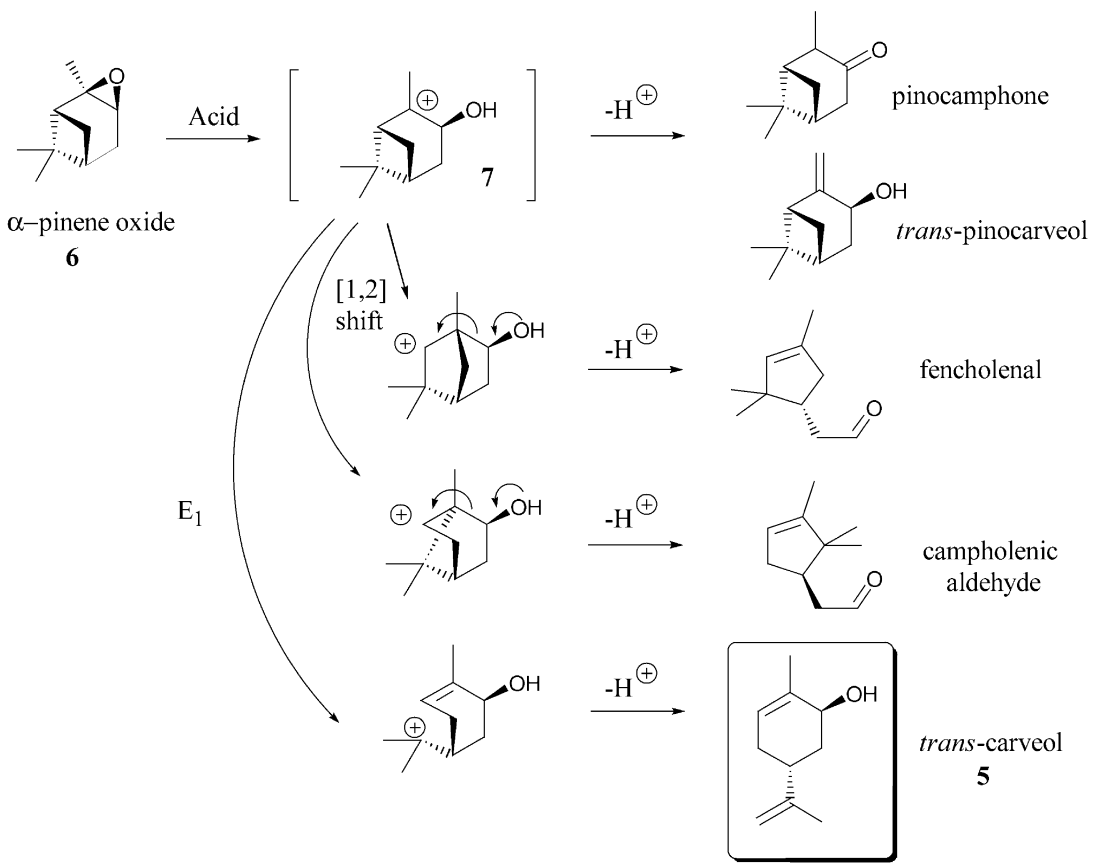


Figure 2. Representative major products arising from the acid-catalysed opening of α-pinene oxide.

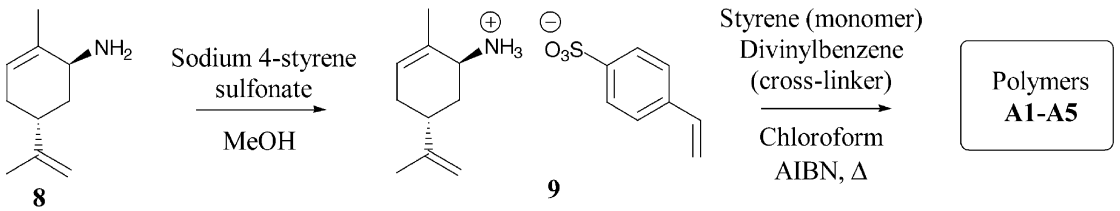


Figure 3.

The acid-catalysed opening of α-pinene oxide **6** (Fig. 2) is well documented and typical of the structural rearrangements often encountered within terpenoid chemistry. In this instance, the initially formed carbocation **7** can undergo several competing processes, including 1,2 hydride migration to give pinocamphone, proton loss to give *trans*-pinocarveol, and no less than three alkyl shifts to release the strain inherent in the four membered ring. Remarkably, both the [1,2] shift which leads to campholenic aldehyde and the 'E_1 elimination' leading to *trans*-carveol **5** both require movement of the same pair of electrons from the same σ bond. In general, Lewis acids usually display a high selectivity in favour of cyclopentenic aldehydes,[10] while in the presence of Brönsted acids, various amounts of *trans*-carveol **5** and other *para*-menthenic compounds are also produced.[11] When solid catalysts are used, campholenic aldehyde, fencholenal, pinocamphone and *trans*-pinocarveol are usually the major products and only small amounts of **5** are observed.[12] It is worthy of note that Noyori et al. achieved a 72% yield of *trans*-carveol **5** from **6** by treatment with a mixture of trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine followed by addition of DBU.[13] Such a combination of reagents is not however, a practical proposition for industrial application.

Given these previous studies and with the goal of trying to achieve selectivity towards the formation of **5**, it therefore appeared logical to focus our attention onto the design of Brönsted acid-supported imprinted polymers.

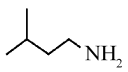
2. Results and discussion

2.1. Preparation of imprinted polystyrenes

In the first instance we elected to conduct our preliminary studies with imprinted styrene/divinylbenzene polymers since their synthesis and use as MIPs was already well precedented in the literature.[14] In the choice of the imprint molecule, we hoped to achieve two goals. The strategic location of an acidic group in the active site which could initiate the conversion of **6** to **5** was of course the primary objective. Moreover, in order to obtain selectivity, we also wished to use a molecule which would create a shape selective site capable of influencing the product ratio in favour of the product **5**. The identification of a good transition-state analogue for the transformation of α-pinene oxide **6** into **5** was far from obvious. The mechanisms are still under debate,[15] but carbonium ion **7** is generally accepted to be the preliminary intermediate. Although formation of this carbocation should be the rate-determining step, the selectivity of the transformation is determined during the subsequent collapse of this reactive intermediate **7** since most of the products derive from this common species. For our work, we therefore selected the crude imprint molecule **8**[16] (Fig. 3) in the hope that this molecule would both locate the acidic group in the binding site and produce a cavity in the polymer which was complementary to the desired product **5**, thus affecting the product distribution in its favour. In these early studies we were more concerned with selectivity than turnover, thus a product like binding site was considered acceptable.

Five polymers **A1**-**A5** of varying monomer to crosslinker ratio's were synthesised with various loadings of imprint molecule-monomer complex **9** (Fig. 3) by co-polymerising styrene and divinylbenzene with the pre-formed salt **9**[17] under radical conditions. The relative quantities of the reagents are reflected in the degree of crosslinking and have important consequences on the physical and molecular recognition properties of the MIPs produced[18] (vide infra). A reference polymer **R**, imprinted with 3-methyl-butylamine instead of carvylamine **8**, was also synthesised (Table 1).

Table 1.

Polymer	Imprint molecule	Cross-linker monomer ratio[a]	Loading[b]
R		6	1/35
A1	**8**	6	1/35
A2	**8**	3	1/35
A3	**8**	2	1/35
A4	**8**	2	1/15
A5	**8**	3	1/10

[a] Crosslinker monomer ratio. The crosslinker:monomer ratio is the ratio of moles of divinylbenzene to styrene. A higher ratio indicates a higher level of crosslinking.

[b] Loadings. Loadings refer to the ratio of the number of moles of salt **9** to the total number of moles of polymerisable molecules. A higher loading indicates more sites per unit volume of polymer.

The imprint molecules were removed by washing with triethylamine and the sulfonic acid functions of these polymers were then regenerated with HCl:diethyl ether followed by exhaustive washing to neutral pH. Five polymer catalysts **A1***–**A5*** were thus obtained (Fig. 4). A reference catalyst **R*** was also produced from polymer **R** using the same experimental protocol.

2.2. Catalysis studies

The acid-catalysed α-pinene oxide ring-opening reactions were carried out at room temperature in toluene using stoichiometric amounts of MIP. The selectivities in the presence of *p*-toluene sulfonic acid (*p*-TSA) and polymers **R***, **A1***–**A4*** are displayed in Table 2.

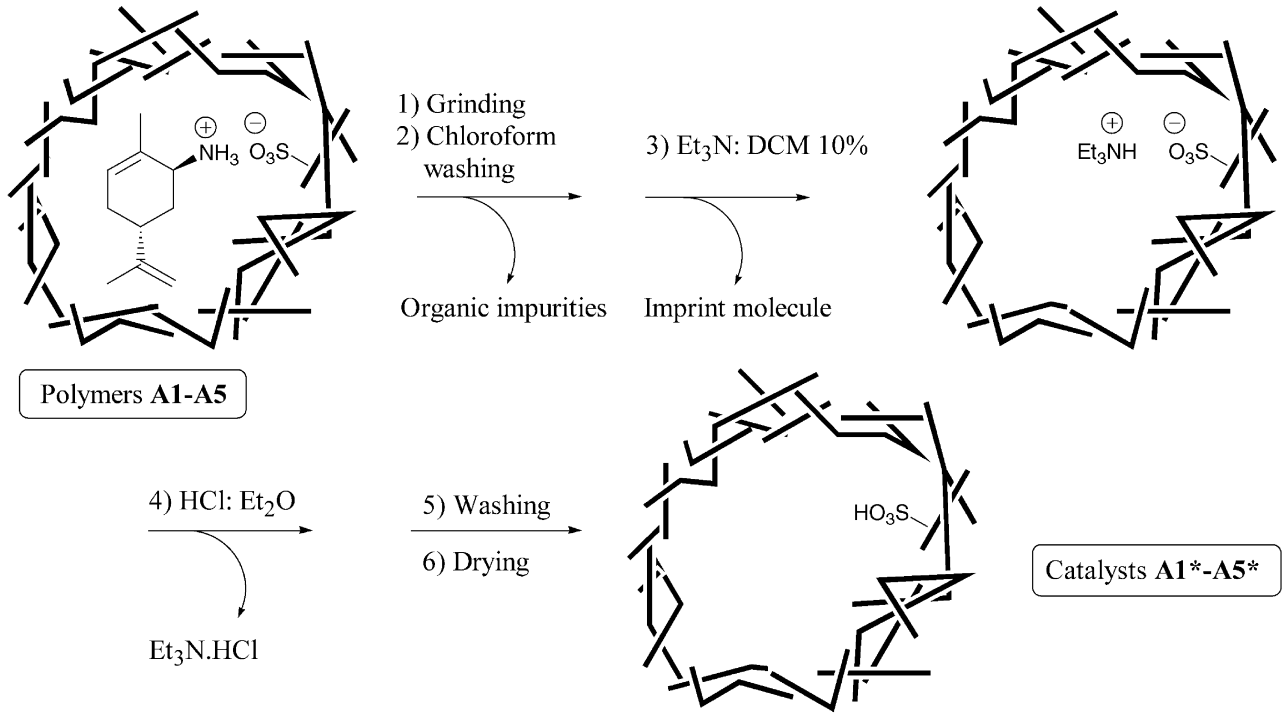


Figure 4.

In the event, it was particularly striking that all the polymer catalysts exhibited a much better selectivity for the formation of **5** than was observed in the homogeneous reaction with *para*-toluene sulfonic acid. However, the polymers **A1***–**A4*** imprinted with (−)-*trans*-carvyl amine **8** did not appear to be better than the reference polymer **R***. Indeed, all the polymers tested led to similar product distributions. This suggested that the shape of the polymer site had little effect on selectivity and the main influence seemed to be local media effects in the vicinity of the sulfonic acid group. This was interesting, since toluene had been specifically selected as the solvent since it closely resembled the hydrophobic environment expected in the polystyrene binding site. It was therefore logical to further study the influence of the nature of the solvent.

Although we had initially avoided protic solvents due to the potential complication of specific acid catalysis, we next turned to methanol as the solvent. The data obtained are presented in Table 3.

These results show that the choice of solvent can profoundly affect the selectivity of this isomerisation reaction. The compounds **5**, **15** and **16**, derived from cation **18** (Fig. 5), a secondary intermediate in the isomerisation to *trans*-carveol, are now the major products, accounting for as much as 54% of the reaction mixture. As before, all polymers displayed more or less equivalent selectivities for **5** and were significantly better than *p*-TSA.

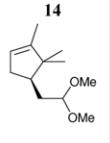
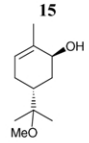
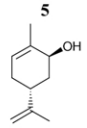
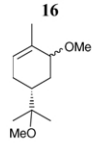
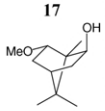
Since these results indicated that the use of a more polar solvent was promoting the reaction pathway via the carbocation **18**, we turned our attention towards DMF, in the belief that this solvent would also favour the formation of **18** without acting as a nucleophilic trap, thereby increasing the amount of **5** produced. These expectations were verified as can be seen in Table 4.

In this case no significant differences between all the catalysts, including *p*-TSA, were observed. However, in all cases, *trans*-carveol **5** became the major product. Although this result was not encouraging in terms of selective MIP

Table 2. Product distribution in the isomerisation of α-pinene oxide in toluene at room temperature. Product distributions were determined by GC analysis using authentic samples of **10**, **11**, **5**, and **12** for comparison

Catalyst	Product distribution				
	10	**11**	**5**	**12**	Total Yield
p-TSA.H_2O	59%	11%	5%	5%	80%
R*	60%	8%	22%	3%	93%
A1*	54%	9%	16%	13%	92%
A2*	60%	9%	20%	4%	93%
A3*	59%	10%	20%	4%	93%
A4*	62%	12%	11%	5%	90%

Table 3. Product distribution in the opening of α-pinene oxide in methanol at room temperature. Product distributions were determined by GC analysis using authentic samples of **14**, **15**, **5**, **17** and **16** for comparison

Catalyst	Product distribution					
	14 	**15** 	**5** 	**16** 	**17** 	Total Yield
p-TSA.H_2O	23%	17%	6%	13%	10%	69%
R*	26%	40%	12%	2%	10%	90%
A1*	27%	41%	11%	-	11%	90%
A2*	32%	36%	10%	4%	11%	93%
A3*	29%	38%	12%	3%	10%	92%
A4*	31%	36%	12%	-	11%	90%
A5*	27%	40%	10%	2%	11%	90%

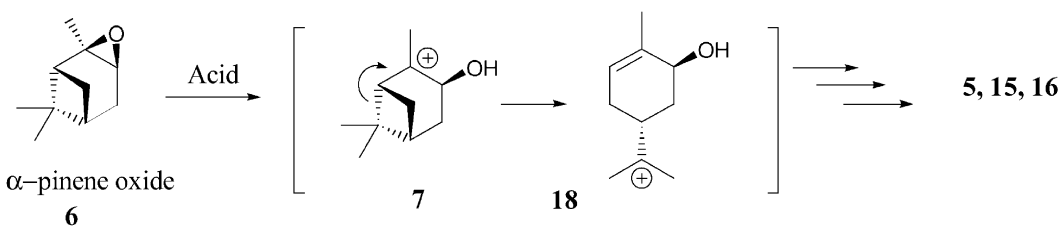
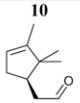
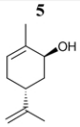
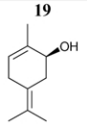


Figure 5.

Table 4. Product distribution in the isomerisation of α-pinene oxide in DMF at room temperature. Product distributions were determined by GC analysis using authentic samples of **10**, **5**, and **19** for comparison

Catalyst	Product distribution			
	10 	**5** 	**19** 	Total Yield
p-TSA.H_2O	21%	42%	24%	87%
R*	23%	42%	23%	88%
A1*	24%	45%	25%	94%
A2*	29%	41%	24%	94%
A3*	39%	38%	20%	97%
A4*	31%	41%	21%	93%
A5*	32%	39%	21%	92%

recognition it does represent a simple method for the formation of **5** from commercially available α-pinene oxide.

Two primary explanations may be considered for the similar reactivity profiles of the polymers prepared. The first is that the imprinting process was inefficient and the second possibility is that specific acid catalysis was operating, although this would tend to predicate the same product distribution with both *p*-TSA and the polymers. In order to eliminate the first possibility we therefore studied the binding characteristics of the polymers **A1***–**A5***, in order to check the quality of their molecular imprinting. Their molecular recognition properties were assessed using a simple modification of the filtration protocol as described in the experimental section.

When polymers **A1***–**A5*** and **R*** were suspended in a solution containing the imprint molecule **8**, polymer **R*** proved to be the least efficient at reabsorbing amine **8** (Fig. 6), which is consistent with the fact that an amine other than **8** was used to imprint this reference polymer. It should be noted that in all cases, the rebinding process was very sluggish, with equilibration taking more than 15 h. Accordingly, the extraction of **8** from the polymers using DCM and then 10% *n*-$PrNH_2$: DCM was also slow, as illustrated in Figure 6(b).

Competitive rebinding studies were also performed on polymers **A1***, **A4*** and **R*** using equimolar mixtures of (−)-*trans*-carvyl amine **8** and α-methyl benzylamine **20** (Fig. 7) in DCM. Although selectivities were modest, after 15 h, **A1*** and **A4*** had absorbed more imprint molecule **8** than competitor **20**, while the converse was observed with reference polymer **R*** (Table 5). Given however, that the dominant interaction of **8** involves electrostatic interactions through salt formation and that 'shape selectivity' can only involve very modest π–π interactions between the alkene residues and the aromatic rings of the polymer, the observed selectivities for preferential binding of **8** are very encouraging.

Nevertheless, from all of the foregoing results, it can be concluded that various different binding characteristics were observed depending on the MIPs tested. Polymer **A4*** displayed the fastest and most selective recognition for the imprint molecule **4**. In contrast, the reference polymer **R*** clearly exhibited much poorer performances than all the other polymers **A1***–**A5***. This constitutes strong evidence

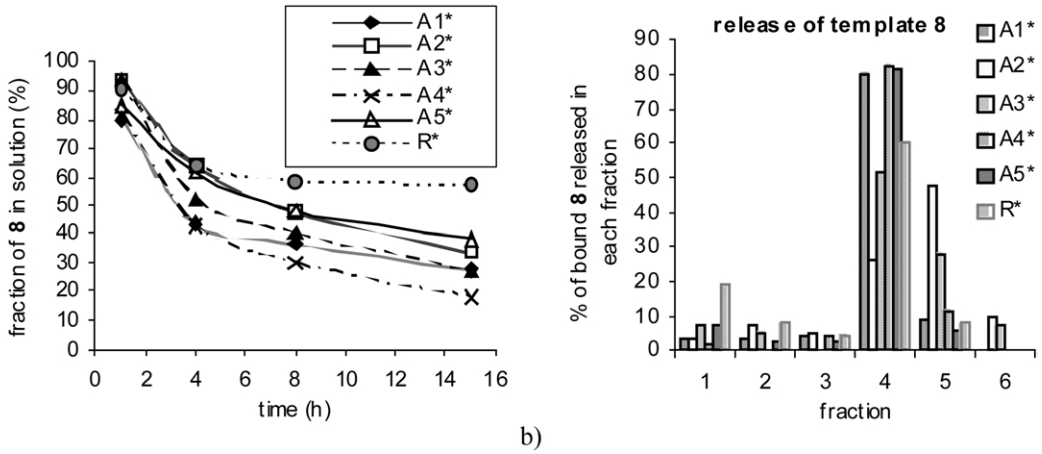


Figure 6. (a) Rebinding of **8** by polymers **A1***–**A5*** and **R*** in DCM. (b) Release of template **8** from MIPs **A1**-**A5** and **R**, using DCM (3 fractions) and then 10% *n*-$PrNH_2$:DCM (3 fractions).

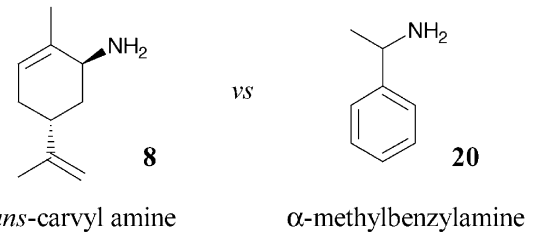


Figure 7.

Table 5. Competitive binding of equimolar amounts of **4** and **7** by polymers **A1***, **A4*** and **R*** in DCM

Polymer	**A1***	**A4***	**R***
Molar ratio **8**:**20** left in solution after 15 h	47:53	44:56	53:47

that the molecular imprinting process had per se been effective.

On considering that all of the imprinted polymers tested, including the reference polymer **R***, exhibited similar behaviours towards α-pinene oxide, despite their differing binding behaviour towards imprint molecule **8** one may wonder if the reactions did indeed proceed within the imprinted sites at all. The pK_a values of the species involved (Table 6) may suggest that none of our reactions were actually catalysed by the acidic groups of the polymers, but rather by protonated methanol, protonated DMF or by the hydronium ion.

Table 6. pK_a values for the species involved[19]

Acid	Base	Approximate pK_a
$ArSO_3H$	$ArSO_3^-$	−6.5
$MeOH_2^+$	MeOH	−2
H_3O^+	H_2O	−1.74
$DMF{\cdot}H^+$	DMF	−0.5

The actual catalytic entity would therefore be the same with all polymers and thus specific acid catalysis could occur outside the polymeric framework, which is consistent with the uniformity of the results obtained. It remains to be explained why *p*-TSA gave different results in methanol and toluene when compared with the MIPs. If the reaction were truly occurring in the bulk solvent there should be no difference between the MIPs and *p*-TSA since it is unlikely that a proton transfer process is the rate determining step.

There are two possible explanations for this phenomenon. It is possible that the reactions are occurring in a heterogeneous fashion and that although no selectivity is exerted on the reaction by the differing shapes in the different MIPs, the local media effects are such as to favour formation of the desired product. It is not unusual in enzyme systems for the local environment in the active site to modify the pK_a of the functional groups involved in enzyme catalysis and hence influence the product outcome.[20] Indeed Kirby and Tawfik have recently highlighted the importance of these local media effects in a study of modified PEI synzymes,[21] and have shown that local microenvironments alone 'in the absence of efficient positioning of the catalytic amine base relative to the substrate, can give rate accelerations as high as 10^5'. The other possibility is that the reaction is occurring within the polymer, but the sites are poorly accessible, consistent with the slow kinetics observed in the binding studies, and thus diffusion of the reactant into the binding site becomes the rate limiting step. Thus the improved yield of the desired product is due rather to a more sluggish reaction resulting in less product decomposition, than to effective selective catalysis.

Notwithstanding these subtleties, it seems clear that the collapse of carbonium **7** into **18** rather than the [1,2] shift to afford campholenic aldehydes **10** (Fig. 2), is favoured when a nucleophilic trap, either reversible or irreversible is present. Indeed, much higher yields of *trans*-carveol-derived products were observed in solvents such as methanol or DMF. Future efforts directed towards exploiting this observation should hopefully provide an efficient, cheap and commercially viable one step synthesis of *trans*-carveol **5**.

In conclusion, the results described herein, have shown that it is possible to prepare a polystyrene based sulfonic acid polymer which can channel up to 70% of the products from acid catalysed isomerisation of α-pinene oxide via the

necessary *para* menthyl tertiary carbocation and produce industrially important *trans*-carveol **5** in 45% yield. However, in spite of evidence that several of the polymers used were successfully imprinted with *trans*-carvyl amine **8** as a potential transition state mimic for the desired reaction, the nature of the solvent chosen clearly played the determining role in the final outcome. The present study should therefore also serve as a caveat as to the perfidious and promiscuous behaviour of the proton which evidently did not wish to return to its sulfonate counterion in the imprinted polymers.

3. Experimental

3.1. General

All reactions were performed under an inert atmosphere. Chloroform was distilled from calcium hydride, toluene was distilled over sodium, and methanol was distilled from magnesium turnings. DMF was dried with $MgSO_4$(s) and distilled over Linde type 4 Å molecular sieves under reduced pressure. Styrene (inhibitor 10–15 ppm *p*-*t*butylcatechol) and 80% divinylbenzene tech. (mixture of *cis* and *trans*-isomers, inhibitor 1000 ppm *p*-*t*butylcatechol) were supplied by Aldrich and were distilled from hydroquinone at low pressure prior to use. A.I.B.N. was recrystallised from DCM and all amine reagents were distilled before use. ^{1}H NMR Spectra were recorded at 500 MHz on a Bruker Avance 500, at 400 MHz on a Varian VXR-400 or a Bruker AMX-400 or at 300 MHz on a Bruker AMX-300. ^{13}C NMR spectra were recorded at 125.8, 100.6 MHz or 75.4 MHz on the instruments above. Infrared spectra were recorded as thin films on KBr plates or as KBr discs on a Perkin–Elmer FT-IR 1605 instrument Gas Chromatography was performed on a Hewlett–Packard 5890A machine (flame ionisation detector) with a 25 m×0.50 mm BPX5 column using hydrogen as the carrier gas.

3.1.1. Synthesis of (1*R*,5*R*)-*trans*-carvyl amine 8. (1*R*,5*R*)-*trans*-Carvyl amine- **8**, was prepared according to literature procedure from (*R*)-(−)-carvone.[16]

Bp: 95–98 °C/0.75 mbar; $[\alpha]_D^{25}$: −182.4 (CH_2Cl_2, c=1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.40 (1H, m), 4.68 (1H, s-), 4.67 (1H, s), 3.15 (1H, s(br)), 2.23–1.57 (5H, m), 1.72 (3H, s-), 1.69 (3H, s), 1.29 (2H, s(br)-); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 149.5, 136.2, 122.8, 108.7, 49.8, 37.5, 35.1, 31.0, 21.2, 20.9. IR (neat): $\tilde{\nu}_{max}$ 3293 (w), 3217 (w), 3074 (w), 2959 (m), 2914 (s), 1648 (m), 1441 (s), 1375 (m), 1150 (w), 1046 (w), 942 (w), 883 (s), 806 (m); LRMS (FAB) *m*/*z*: 152 $[M+H]^+$, 135, 119, 107.

3.1.2. Synthesis of 4-styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt 9. A solution of acetyl chloride:MeOH (1:20 v/v, 6.0 mL) was made up under nitrogen at 0 °C and added dropwise with stirring to (1*R*,5*R*)-*trans*-carvyl amine **8** (500 mg, 3.3 mmol, 1 equiv.) at 0 °C. After 20 min the solution was concentrated in vacuo to afford the amine hydrochloride. This was immediately dissolved in methanol (25 mL) and added to a solution of 4-styrenesulfonic acid, sodium salt (680 mg, 3.3 mmol, 1 equiv.) in methanol (125 mL). The solution was stirred for 4 h, then concentrated in vacuo to afford an off white solid. Chloroform (30 mL) was added and any remaining solid was removed by suction filtration. The filtrate was concentrated in vacuo to afford a pale yellow solid (1.05 g) containing a mixture of (1*R*,5*R*)-*trans*-carvyl amine hydrochloride **21** and 4 styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**. The ratio **9**:**21**, 1.4:1 was determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 8.11 (3H, s(br)), 7.69 (2H, AA′BB′, d, J=12.5 Hz), 7.40 (2H, AA′BB′, d, J=12.5 Hz), 6.69 (1H, dd, J=17.5, 11.0 Hz), 5.72 (1H, d, J_{trans}=17.5 Hz), 5.63 (1H, m), 5.30 (1H, d, J_{cis}=11.0 Hz,), 4.68 (1H, s), 4.64 (1H, s), 3.60 (1H, m(br)), 2.49 (1H, m(br)), 2.10 (2H, m), 1.79 (3H, s), 1.63 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 147.8, 143.2, 139.5, 135.9, 129.3, 128.4, 126.2, 126.0, 115.5, 109.5, 50.1, 34.3, 31.7, 30.3, 20.9; LRMS (FAB) *m*/*z*: 336 $[M_{salt}+H]^+$; (CI negative) *m*/*z*: 182.8 $[M_{acid}-H]^-$; (CI positive) *m*/*z*: 151.9 $[M_{amine}+H]^+$.

3.1.3. Synthesis of 4-styrenesulfonic acid, isoamylamine salt 22. HCl:diethyl ether (5 mL) was added dropwise to a stirred solution of isoamylamine (436 mg, 50 mmol, 1 equiv.) in diethyl ether (15 mL) to produce a white precipitate. The solvent was removed in vacuo and the residue taken up in MeOH (60 mL) and stirred at room temperature. 4-Styrenesulfonic acid, sodium salt (1.02 g, 60 mmol, 1.2 equiv.) was added and the solution stirred for 18 h. The solvent was removed in vacuo, the residue taken up in chloroform (70 mL), filtered, and concentrated in vacuo to afford a pale yellow solid (776 mg) containing a mixture of 4-styrenesulfonic acid, isoamylamine salt **22** and isoamylamine hydrochloride **23**. The ratio **22**:**23** 1.3:1 was determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.77 (2H, AA′BB′, d, J=12.5 Hz), 7.71 (3H, s(br)), 7.38 (2H, AA′BB′, d, J=12.5 Hz, 6.66 (1H, dd, J=17.5, 11.0 Hz), 5.74 (1H, d, J_{trans}=17.5 Hz, 5.28 (1H, d, J_{cis}=11.0 Hz), 2.84 (1H, m), 1.49 (4H, m(br)), 0.75 (6H, d, J=3.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 143.0, 139.7, 135.7, 126.1, 115.8, 38.4, 35.9, 25.5, 22.0; LRMS (CI negative) *m*/*z*: 183 $[M_{acid}-H]^-$; (CI positive) *m*/*z*: 88, $[M_{amine}+H]^+$.

3.2. General procedure for the synthesis of polystyrene MIPs

Styrene, divinylbenzene, 4-styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**, and AIBN (2 mol% per polymerisable double bond) were dissolved in chloroform (1.7 v/v of polymerisable molecules) in a Schlenk flask of diameter 3.0 cm. Three freeze thaw cycles were carried out and the polymerisation mixture was placed in a preheated bath at 70 °C and heated under nitrogen with stirring (300 rpm) for 40 min. The bath was cooled to 60 °C and the polymerisation mixture was incubated for a further 23 h 20 min. The flask was cooled to room temperature and the solvent removed under vacuum. The resultant polymer monolith was ground.

3.2.1. Synthesis of polystyrene A1. Loading: 1/35, cross-linker-monomer ratio 6:1. 4-Styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**[22] (200 mg, 0.43 mmol), styrene (224 mg, 246 μL, 2.15 mmol), divinylbenzene

(1.68 g, 1.84 mL, 12.9 mmol), AIBN. (92 mg, 0.6 mmol) and chloroform (3.55 mL) were polymerised according to the general procedure.

3.2.2. Synthesis of polystyrene A2. Loading: 1/35, cross-linker-monomer ratio 3:1. 4-Styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**[22] (200 mg, 0.43 mmol), styrene (329 mg, 430 μL, 1.3 mmol), divinylbenzene (1.47 g, 1.61 mL, 3.8 mmol), AIBN (86.5 mg, 0.53 mmol) and chloroform (3.47 mL) were polymerised according to the general procedure.

3.2.3. Synthesis of polystyrene A3. Loading: 1/35, cross-linker-monomer ratio 2:1. 4-Styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**[22] (200 mg, 0.43 mmol), styrene (523 mg, 575 μL, 5.0 mmol), divinylbenzene (1.31 g, 1.43 mL, 10.0 mmol), AIBN (82 mg, 0.5 mmol) and chloroform (3.41 mL) were polymerised according to the general procedure.

3.2.4. Synthesis of polystyrene A4. Loading: 1/15, cross-linker-monomer ratio 2:1. 4-Styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**[22] (200 mg, 0.43 mmol), styrene (224 mg, 246 μL, 2.15 mmol), divinylbenzene (560 mg, 612 μL, 4.3 mmol), AIBN (35 mg, 0.22 mmol) and chloroform (1.46 mL) were polymerised according to the general procedure.

3.2.5. Synthesis of polystyrene A5. Loading: 1/10, cross-linker-monomer ratio 3:1. 4-Styrenesulfonic acid, (1*R*,5*R*)-*trans*-carvyl amine salt **9**[22] (184 mg, 0.43 mmol), styrene (115 mg, 126 μL, 1.1 mmol), divinylbenzene (417 mg, 456 μL, 3.2 mmol), AIBN (24.6 mg, 0.15 mmol) and chloroform (1.0 mL) were polymerised according to the general procedure.

3.2.6. Synthesis of the reference polystyrene R. Styrene (224 mg, 246 μL, 2.1 mmol), divinylbenzene (1.68 g, 1.84 mL, 12.9 mmol), 4-styrenesulfonic acid, isoamylamine salt **22** (158 mg, 0.43 mmol) and AIBN (92 mg, 0.6 mmol, 2 mol% per polymerisable double bond) were dissolved in chloroform (3.55 mL, 1.7 v/v of polymerisable molecules) in a Schlenk flask of diameter 3.0 cm. Three freeze thaw cycles were carried out and the polymerisation mixture was placed in a preheated bath at 70 °C and heated under nitrogen with stirring (300 rpm) for 40 min. The bath was cooled to 60 °C and the polymerisation mixture was incubated for a further 23 h 20 min. The flask was cooled to room temperature and the solvent removed under vacuum. The resultant polymer monolith was ground.

3.3. Procedure for the washing and generation of acid sites in the crude polystyrenes A1*–A5* and R*

The ground crude polymer was placed in a sintered glass funnel and washed with chloroform (5×10 mL). The solvent was removed in vacuo and the residue analysed by ^{1}H NMR, which identified AIBN decomposition products and trace amounts of unreacted reagents as determined by comparison with reference spectra. The polymer was washed with 10% Et_3N:DCM (5×10 mL) to remove the bound (1*R*,5*R*)-*trans*-carvyl amine **8**, as determined by ^{1}H NMR analysis of the filtrate, then DCM (10 mL). The polymer was stirred in HCl:diethyl ether (20 mL) for 3 h at 0 °C, filtered, then washed with diethyl ether (2×20 mL), DCM (2×20 mL), water (2×20 mL), methanol (2×20 mL or until pH 7), and DCM (5×10 mL). The polymer was then dried in vacuo to give the active polymer **A1***–**A5*** and **R***.

Polymer **A1*** 1/35 6:1. Elemental analysis: found C 88.16, H 7.85, N 0.18, S 0.70.

Polymer **A2*** 1/35 3:1. Elemental analysis: found C 86.92, H 7.74, N 0.32, S 0.85

Polymer **A3*** 1/35 2:1. Elemental analysis: found C 88.02, H 8.01, N 0.27, S 0.82.

Polymer **A4*** 1/15 2:1. Elemental analysis: found C 86.04, H 7.76, N 0.24, S 0.93.

Polymer **A5*** 1/10 3:1. Elemental analysis: found C 85.04, H 7.72, N 0.38, S 0.92.

Polymer **R*** 1/35 6:1. Elemental analysis: found C 88.25, H 7.82, N 0.24, S 0.75.

3.4. General method for binding studies

The dried polymer **A1***–**A5*** was placed in a sealed soxhlet extraction thimble and suspended in a beaker containing a known quantity of DCM (60 mL). The solution was stirred for 20 min at 0 °C, the level of the solvent was marked and the soxhlet thimble was removed (slowly, allowing residual non-absorbed solvent to drip from the soxhlet back into the beaker). The amount of solvent absorbed by the polymer was measured using the difference between the volume of DCM remaining and the original volume of DCM (60 mL). (1*R*,5*R*)-*trans*-Carvyl amine **8** (65 mg, 0.43 mmol, 1 equiv.) was then added to the beaker, the extraction thimble was suspended as previously and DCM was added up to the mark[†] (vide supra). The solution was stirred and, at specific intervals, the thimble was raised, the remaining solvent removed in vacuo, and the quantity of (1*R*,5*R*)-*trans*-carvyl amine **8** remaining in solution was determined. After each measurement the (1*R*,5*R*)-*trans*-carvyl amine **8** was redissolved in DCM to the previously marked level.

3.5. General method for determining the percentage of imprint molecule: (1*R*,5*R*)-*trans*-carvyl amine 8 bound in the polymer

In the binding studies carried out according to the general method above there is always a certain quantity of (1*R*,5*R*)-*trans*-carvyl amine **8** present in the polymer due to non-specific binding (i.e., the solvent absorbed by the polymer will naturally contain a certain amount of (1*R*,5*R*)-*trans*-carvyl amine **8**). The approximation we have made is that

[†] An important distinction between adding DCM (60 mL) and adding the solvent up to the mark is necessary here. The polymers absorb significant quantities of solvent which they retain for a considerable time. If one adds another (60 mL) of solvent then there will be more solvent present due to preabsorbed DCM in the polymer. In order to avoid lengthy drying procedures in between steps the marked level is used. This is the level at which the total of the DCM absorbed in the polymer and in the rest of the beaker is equal to 60 mL.

the percentage of (1*R*,5*R*)-*trans*-carvyl amine **8** bound due to 'non-specific binding' is equal to the percentage of DCM absorbed by the polymer. To avoid overestimating the level of binding, the calculation of the amount of template bound in the polymer at each point in the binding study includes a correction factor to account for this phenomenon (Eq. 1).

$$\mathbf{8}\ \text{bound/mg} : M = y - x(a/b) \quad (1)$$

percentage of **8** remaining in solution

$$= M(\text{mg})/\text{original weight}(65.0\ \text{mg}) \quad (2)$$

Where y=original weight of **8** (65.0 mg, 0.43 mmol, 1 equiv.), x=weight of **8** in remaining in solution, (a/b)= correction factor: original volume of DCM (60 mL)/ (original volume of DCM (60 mL)−volume of DCM absorbed by polymer).

3.6. Binding studies on MIPs A1*–A5*, and R*

Binding studies were carried out on the polymers **A1***–**A5***, and **R*** according to the general method. The amount of solvent absorbed by each MIP was determined according to this general method, and the corrected percentage (Eq. 2) of (1*R*,5*R*)-*trans*-carvyl amine **8** remaining in solution was determined after 1, 4, 8, and 15 h for each of the MIPs

MIP	Volume of solvent absorbed (mL)	% of **8** bound					15 h mmol of **8** bound
		0 h	1 h	4 h	8 h	15 h	
A1*	12.0	0	20	56	63	72	71%
A1* (repeat)[a]	12.0	0	34	50	62	70	0.31
A2*	14.0	0	7	36	52	66	0.28
A3*	13.0	0	6	48	60	73	0.31
A4*	8.0	0	19	57	70	82	0.35
A5*	7.5	0	15	39	52	62	0.27
R*	14.0	0	10	36	42	43	0.13

The percentage of **8** bound after 15 h was taken to be the amount of **8** required for saturation of the all the available sulfonic acid sites in the MIP, and was used to calculate the number of mmol of active sites in each polymer. These values were used to calculate the number of equivalents used in the subsequent catalytic studies.

3.7. General method for the debinding studies of polystyrene–divinylbenzene MIPs A1*–A5*, and R*

The apparatus used was the same as for the binding studies. The beaker was filled up to the mark with DCM (vide supra). The solution was stirred at 0 °C for 1 h before the soxhlet was removed, the remaining solvent reduced in vacuo and the residue analysed by ^{1}H NMR. This was carried out three times. The beaker was then filled with 10% *n*-$PrNH_2$:DCM (60 mL), stirred at 0 °C for 2 h, then reduced in vacuo and the residue analysed by ^{1}H NMR. This was carried out three times. The amount of (1*R*,5*R*)-*trans*-carvyl amine **8** in each fraction was calculated from the weight and the molar ratio of **8**: *n*-$PrNH_3(CO_3)_2$: *n*-$PrNH_2$ as observed by ^{1}H NMR. In each case the mass balance of (1*R*,5*R*)-*trans*-carvyl amine **8** over the entire binding-debinding experiment was in the region of 90%.

In each case the ratios were determined by comparing the integration of the following peaks.

^{1}H NMR ($CDCl_3$, 300 MHz): δ_H (1*R*,5*R*)-*trans*-carvyl amine **8** 5.40 (1H, m, =C*H*R) and/or 4.67 (2H, 2s, =CH_2); *n*-$PrNH_3(CO_3)_2$ 0.79 (3H, t, J=7.5 Hz, CH_3);. *n*-$PrNH_2$ 0.68, (3H, t, J=7.5 Hz, CH_3)

MIP	Amount of **8** removed in each washing (mg)					
	DCM	DCM	DCM	*n*-$PrNH_2$ DCM	*n*-$PrNH_2$ DCM	*n*-$PrNH_2$ DCM
A1*	1.9	1.9	2.2	41.2	4.5	0
A2*	1.2	2.4	1.6	8.4	15.3	3.1
A3*	3.0	2.1	0.0	20.4	11.2	3.0
A4*	0.7	0.1	1.9	38.8	5.5	0.0
A5*	3.1	1.0	0.9	34.2	2.5	0
R*	7.6	3.1	1.8	24.0	3.3	0

3.8. General method for competitive binding studies

The apparatus used was the same as for the binding studies. The amount of solvent absorbed by the polymer was determined as previously. (1*R*,5*R*)-*trans*-carvyl amine **8** (1 equiv. of the calculated number of binding sites in the polymer, vide supra) and α-methyl benzylamine **20** (1 equiv.) were added to the beaker and the 1:1 ratio was confirmed by ^{1}H NMR. DCM (60 mL) was added up to the mark (vide supra) and the solution was stirred at 0 °C for 15 h. The solution was then concentrated in vacuo and the ratio **8**:**20** of the amines not bound by the polymer was determined by ^{1}H NMR.

In each case the ratio's were determined by comparing the integration of the following peaks.

^{1}H NMR ($CDCl_3$, 300 MHz): δ_H α-methyl benzylamine **20**, 4.27 (1H, q, J=6.5 Hz, CH_3CHN); (1*R*,5*R*)-*trans*-carvyl amine **8**, 5.40 (1H, m, =C*H*R) and/or 4.67 (2H, 2s, =CH_2)

Competitive binding of equimolar amounts of **8** and **20** by polymers **A1***, **A4*** and **R*** in DCM

Polymer	**A1***	**A4***	**R***
Molar ratio **8**:**20** left in solution after 15 h	47:53	44:56	53:47

3.9. General method for polymer regeneration

Polymers were regenerated after the binding studies. The apparatus used was the same as for the binding studies. The polymer was washed with DCM (2×60 mL/1 h/0 °C) to remove any excess *n*-$PrNH_2$ and then stirred with HCl:diethyl ether (60 mL/1 h/0 °C) to regenerate the acid sites. The polymer was washed with ether (3×60 mL), methanol (*n*×60 mL until pH neutral) and DCM (2×60 mL).

3.10. General procedure for the reaction of α-pinene oxide 6 with polystyrenedivinylbenzene MIPs in toluene

α-Pinene oxide **6** was added to a stirred suspension of the polystyrene–divinylbenzene MIP (1 equiv.) in toluene (0.015 M to **6**) at room temperature. An example of the reaction scale is α-pinene oxide **6** (22.9 mg, 24 μL, 0.15 mmol, 1 equiv.), **A1*** (913 mg, 0.15 mmol, 1 equiv.), and toluene (10.0 mL). The reaction was stirred for 1 h and analysed by GC comparison with authentic samples. The polymer was then filtered off, washed with DCM (3×10 mL) and the filtrate concentrated in vacuo and analysed by ^{1}H and ^{13}C NMR.

3.11. General procedure for the reaction of α-pinene oxide 6 with polystyrene–divinylbenzene MIPs in methanol

α-Pinene oxide **6** was added to a stirred suspension of the polystyrene–divinylbenzene MIP (1 equiv.) in methanol (0.015 M to **6**) at room temperature. An example of the reaction scale is α-pinene oxide **6** (22.9 mg, 24 μL, 0.15 mmol, 1 equiv.), **A1*** (913 mg, 0.15 mmol, 1 equiv.), and methanol (10.0 mL). The reaction was stirred for 1 h and analysed by GC comparison with authentic samples. The polymer was then filtered off, washed with DCM (3×10 mL) and the filtrate concentrated in vacuo and analysed by ^{1}H and ^{13}C NMR.

3.12. General procedure for the reaction of α-pinene oxide 6 with polystyrene–divinylbenzene MIP's in DMF

α-Pinene oxide **6** was added to a stirred suspension of the polystyrene–divinylbenzene MIP (1 equiv.) in DMF (0.015 M to **6**) at room temperature. An example of the reaction scale is α-pinene oxide **6** (22.9 mg, 24 μL, 0.15 mmol, 1 equiv.), **A1*** (913 mg, 0.15 mmol, 1 equiv.), and DMF (10.0 mL). The reaction was stirred until consumption of all the starting material was observed by GC comparison with authentic samples (3–7.5 h). The polymer was then filtered off, and washed with DCM (3×10 mL). The organic layer was washed with distilled water (5×10 mL), dried over $MgSO_4$(s), concentrated in vacuo and analysed by ^{1}H and ^{13}C NMR.

3.13. Solution reactions of *p*-TSA monohydrate with α-pinene oxide 6

α-Pinene oxide **6** (24 μL, 0.15 mmol, 1 equiv.) was added to a stirred solution of *p*-toluenesulfonic acid (28.5 mg, 0.15 mmol, 1 equiv.) in toluene (10.0 mL) and the reaction stirred at room temperature for 1 h and analysed by GC comparison with authentic samples.

3.13.1. 2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-ol, or *trans*-carveol 5.[23] R_f 0.3 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.59 (1H, dm, J=5.5 Hz), 4.11 (1H, s), 4.09 (1H, s), 4.02 (1H, s(br)), 2.32 (1H, m), 2.14 (1H, dm, J=13.5 Hz), 2.03–1.55 (4H, m), 1.80 (3H, s), 1.75 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 149, 134.3, 125.4 109.0, 68.6, 36.7, 35.2, 31.0, 20.9. IR (neat): $\tilde{\nu}_{max}$ 3333 (s, OH), 3082 (w), 2966 (s), 2916 (s), 1645 (m, C=C), 1438 (s), 1375 (m), 1264 (m), 1156 (m), 1164 (m), 1054 (s), 1032 (s), 962 (s), 944 (m), 887 (s); LRMS (EIMS) *m*/*z*: 152 [$M^{+\cdot}$], 109, 84, 69, 54, 38.

3.13.2. (2,2,4-Trimethyl-cyclopent-3-enyl)-acetaldehyde, or campholenic aldehyde 10.[24] R_f 0.7 (SiO_2, 20% EtOAc:petrol 40–60 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.80 (1H, t, J=2.5 Hz), 5.29 (1H, m), 2.55–2.25 (4H, m), 1.89 (1H, m), 1.61 (3H, d(br), J=2.5 Hz), 1.00 (3H, s), 0.79 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 201.8, 147.8, 121.5, 46.8, 45.0, 44.3, 35.4, 25.5, 19.9, 12.5. IR (neat): $\tilde{\nu}_{max}$ 3038 (w), 2957 (s), 2716 (w, CHO), 1726 (s, C=O), 1463 (m), 1437 (w), 1384 (w), 1362 (m), 1016 (w), 794 (m); LRMS (EIMS) *m*/*z*: 152 [$M^{+\cdot}$], 108, 93, 82, 67, 57.

3.13.3. 4,4,7-Trimethyl-6-oxa-bicyclo[3.2.1]oct-3-ene 11.[25] R_f 0.7 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 5.16 (1H, m), 3.95 (1H, d, J=5.0 Hz), 2.22–2.19 (2H, m), 2.18 (1H, dd, J=10.5, 5.0 Hz), 2.10 (1H, m,), 1.80 (1H, d, J=10.5 Hz), 1.67 (3H, m), 1.28 (3H, s), 1.16 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 139.5, 120.2, 82.7, 76.6, 41.8, 34.5, 30.4, 30.3, 25.4, 21.4. IR (neat): $\tilde{\nu}_{max}$ 2968 (s), 2874 (m), 2840 (m), 1441 (m), 1358 (m), 1297 (w), 1209 (m), 1114 (m), 1033 (m), 1006 (s); LRMS (CI) *m*/*z*: 153 $[M+H]^+$, 135, 107, 93.

3.13.4. 6,6-Dimethyl-2-methylene-bicyclo[3.1.1]heptan-3-ol, or *trans*-pinocarveol 12.[26] R_f 0.3 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.97 (1H, s), 4.80 (1H, s), 4.40 (1H, d, J=7.5 Hz), 2.49 (1H, t, J=5.5 Hz), 2.36 (1H, m), 2.22 (1H, d, J=14.5, 7.5 Hz), 1.97 (1H, m), 1.82 (1H, dd, J=14.5, 4.0 Hz), 1.69 (1H, d, J=10 Hz), 1.25 (3H, s), 0.62 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 156.3, 111.8, 67.2, 51.0, 40.8, 40.2, 34.9, 28.6, 26.3, 21.5. IR (neat): $\tilde{\nu}_{max}$ 3383 (s, b, OH), 3071 (w), 2974 (s), 2921 (s), 2869 (s), 1646 (m, C=C), 1452 (m), 1384 (s), 1387 (m), 1340 (w), 1296 (m), 1145 (m), 1106 (w), 1086 (w), 1022 (m), 1002 (m), 895 (m); LRMS (CI) *m*/*z*: 153 $[M+H]^+$, 135, 107 93, 79.

3.13.5. (2,2,3-Trimethyl-cyclopent-3-enyl)-acetaldehyde dimethyl acetal, or campholenic aldehyde dimethyl acetal 14.[27] R_f 0.5 (SiO_2, 20% EtOAc:petrol 40–60 °C); mp (petrol 30–40 °C/EtOAc): 76–78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H: 5.23 (1H, m), 4.43 (1H, dd, J=7.5, 4.0 Hz), 3.34 (3H, s), 3.31 (3H, s), 2.31 (1H, m), 1.90–1.76 (3H, m), 1.61 (3H, d, J=1.5 Hz), 1.54 (1H, m), 0.99 (3H, s), 0.76 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C/ppm: 148.5, 121.7, 104.0, 53.0, 52.0, 46.8, 45.9, 35.5, 32.8, 25.6, 19.7, 12.7. IR (neat): $\tilde{\nu}_{max}$ 3036 (w), 2953 (s), 2830 (m), 1464 (m), 1382 (m), 1361 (m), 1193 (w), 1138 (m), 1124 (s), 1059 (s), 1016 (m), 965 (m), 937 (w), 795 (m); LRMS (FABS) *m*/*z*: 198 $[M]^+$, 133.

3.13.6. 5-(1-Methoxy-1-methyl-ethyl)-2-methyl-cyclohex-2-enol, or Sobrerol-monomethyl ether 15.[28] R_f 0.1 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.57 (1H, dm, J=5.0 Hz), 4.01 (1H, m), 3.19 (3H, s), 2.04–1.89 (3H, m), 1.78 (3H, s), 1.74 (1H, s(br)), 1.38 (1H, td, J=13.0, 4.0 Hz), 1.1 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 134.3, 125.4, 76.2, 68.5, 48.7, 35.3, 32.7, 27.0, 22.4, 22.1, 20.9. IR (neat): $\tilde{\nu}_{max}$ 3394 (s, b, OH), 2970 (s), 2919 (s), 1456 (m), 1380 (m), 1364 (m), 1252 (w), 1158 (m), 1140 (m), 1075 (s), 1035 (m), 961 (w), 805 (w).

3.13.7. *trans*-2-Methyl-5-(1methoxy,1-methylethyl)-2-cyclohexenmethyl ether, or Sobrerol dimethyl ether 16.[29] R_f 0.4 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.59 (1H, m), 3.50 (1H, m), 3.40 (3H, s), 3.19 (3H, s), 2.11 (1H, dd, J=15.5, 2.0 Hz), 1.98 (2H, m), 1.76 (3H, d, J=1.5 Hz), 1.761.69 (2H, m), 1.12 (3H, s), 1.11 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 133.2, 125.8, 79.7, 76.1, 57.1, 48.6, 34.7, 27.2, 26.8, 22.7, 22.5, 21.0. IR (neat): $\tilde{\nu}_{max}$ 2972 (s), 2921 (s), 2834 (s), 1455 (m), 1381 (m), 1384 (m), 1333 (w), 1250 (m), 1189 (m), 1157 (m), 1140 (m), 1078 (s), 914 (m), 807 (w).

3.13.8. 1,7,7-Trimethyl-6-*exo*-methoxy bicyclo[2.2.1]-heptan-2-*endo*-ol 17. R_f 0.3 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 4.79 (1H, d, J=10.5 Hz, OH), 4.02 (1H, m), 3.79 (1H, dt, J=9.5, 3.0 Hz), 3.32 (3H, s), 2.38 (1H, m), 2.27 (1H, m), 1.73 (1H, t, J=5.0 Hz), 1.32 (1H, dd, J=13.0, 3.5 Hz), 1.20 (1H, dd, J=13.5, 4.0 Hz), 1.03 (3H, s), 0.80 (3H, s), 0.81 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 89.9, 79.0, 58.2, 50.1, 48.8, 43.2, 39.8, 36.0, 20.0, 19.7, 12.1. IR (neat): $\tilde{\nu}_{max}$ 3483 (s, OH), 2986 (m), 2952 (s), 2877 (m), 1450 (m), 1369 (m), 1298 (w), 1190 (m), 1230 (s), 1190 (m), 1130 (s), 1086 (s), 1062 (m), 1004 (w), 970 (w), 899 (w).

3.13.9. 5-Isopropylidene-2-methyl-cyclohex-2-enol 19. R_f 0.4 (SiO_2, 20% EtOAc:petrol 40–60 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 5.47 (1H, m), 3.97 (1H, m), 2.85 (1H, d(br), J=20 Hz), 2.65 (1H, dd, J=13.5, 4.0 Hz), 2.31 (1H, dm, 24 Hz), 1.77 (3H, m), 1.71 (3H, s), 1.66 (3H, s), 1.44 (1H, s(br)); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_c 135.9, 125.8, 124.3, 123.1, 70.4, 35.9, 29.8, 20.4, 20.2, 19.9. IR (neat): $\tilde{\nu}_{max}$ 3257 (s, OH), 3160 (m), 2966 (m), 2935 (m), 2884 (m), 1607 (w), 1436 (w), 1366 (w), 1320 (w), 1058 (w), 1014 (s), 912 (w), 803 (w); LRMS (FABS) *m/z*: 152 $[M]^+$, 149, 133, 107.

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