Molecular design of novel transition state analogues for molecular imprinting

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The synthesis and characterisation of novel polymerisable heterocycles containing boron is described. The compounds were designed to serve as transition state analogues of the enantioselective borane reduction of prochiral ketones with oxazaborolidine catalysts (CBS reduction). Preliminary results show that the heterocycles can be conveniently used as template monomers in the synthesis of molecularly imprinted polymers.

Reproducing the features of natural enzymes in artificial systems represents one of the most challenging tasks for today's chemists. The successful development of such systems contributes to the understanding of the principles and strategies of enzyme catalysis, enabling the discovery of novel non-biological catalysts as well as the targeted use of modern protein engineering techniques for the preparation of tailor-made biocatalysts with novel properties.

Since the publication of the first crystal structures of enzymes more than 40 years ago, a continuously increasing number of researchers have been working on this topic. Early attempts making use of host–guest chemistry[1] or functionalised linear polymers[2] have been paralleled by a variety of other approaches based on supramolecular complexes,[1] functionalised micelles and vescicles,[1*b*] cyclodextrins,[1,3] artificial polypeptides,[1*c*,4] catalytic antibodies,[5] and molecularly imprinted materials.[6]

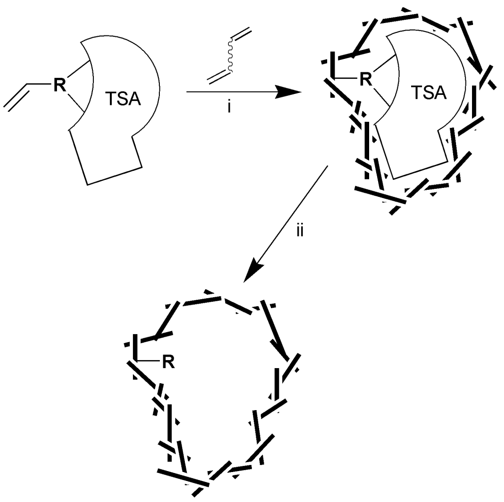
Enzymes are very efficient catalysts that usually work with high activity and selectivity. High chemo-, regio- and especially stereoelectivity is induced by specific interactions (steric effects, hydrophobic and electrostatic interactions) between the substrates and the active site of the enzyme. Co-ordination to the active site brings the reagents into particular conformations and relative positions, which allow for just one of the possible reaction patterns.

The application of a similar strategy to the catalysis of abiotic reactions of synthetic interest appears very intriguing. To achieve this, a catalytically active moiety should be positioned into artificial clefts that are able, through their size, shape and three-dimensional arrangement of functional groups, to direct the reaction towards one of the possible products. A rough but illustrative application of this principle can be seen in the well-known regioselective isomerisation and disproportionation of hydrocarbons within zeolite cavities.[7] More difficult, however, appears to be the development of general strategies for the preparation of stereoselective catalysts of this kind.

We, together with other research groups, have decided to tackle this problem by making use of molecular imprinting.[6] This technique involves the preparation of highly crosslinked polymers in the presence of molecules acting as templates. After removal of the template molecules, a solid is left possessing cavities that are complementary in size, shape and functionalisation to the template being employed; such cavities are able to recognise and selectively rebind the template molecule.

In order to prepare enzyme-like polymers by molecular imprinting, molecules that mimick the transition state of a given reaction are used as templates; furthermore, the system must be designed in such a way that a reactive moiety or a convenient precursor thereof is placed in the cavity in the course of the imprinting procedure (Scheme 1). The resulting functionalised cavities are then potentially able to accelerate the rate of a reaction taking place inside them by stabilising the transition state, and/or to impart higher selectivity by favouring the formation of one of the possible transition states.

Molecular imprinting has already proven useful in the preparation of polymer-bound reagents with unusual regio- and stereoselectivities,[8] as well as in the development of catalysts showing a certain degree of substrate selectivity.[1*c*,9]



Scheme 1 Preparation of enzyme-like reactive polymers by molecular imprinting. (i) Copolymerisation of a transition state analogue (TSA) containing a reactive group (R) with an excess of crosslinker; (ii) removal of the TSA leaving R exactly placed in the cavity.

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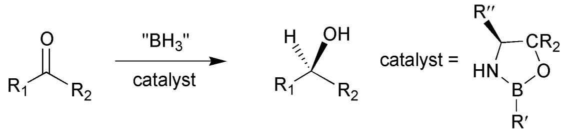
Very recently, initial attempts to improve the performance of enantioselective transition metal catalysts by molecular imprinting have also been reported.[10] Higher activities and enantioselectivities in comparison with non-imprinted polymer supports were reached with these catalysts, but their performance was never found to be superior to that of the corresponding metal complexes in homogeneous solution.

As a test reaction we have chosen the enantioselective borane reduction of prochiral ketones with a 1,3,2-oxazaborolidine as the catalyst (CBS reduction shown in Scheme 2).[11,12]

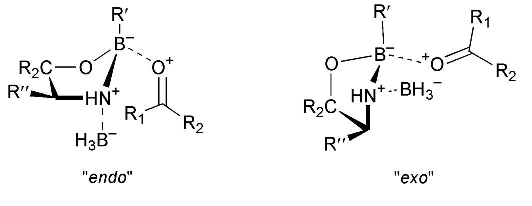


Scheme 2 The CBS reduction.

This reaction has aroused considerable interest in the last ten years due to its versatility and high enantioselectivity.[13] Although the detailed kinetics of this complex reaction are still not completely understood, there is an experimentally well-founded hypothesis about the reaction mechanism.[14] In the first step, the reagents co-ordinate to the catalyst forming a ternary complex (Scheme 3). The borane interacts with the nitrogen atom and the ketone with the boron atom; both reagents bind *anti* to the oxazaborolidine substituent R″ at the asymmetrical carbon atom, which shields one face of the ring. The co-ordination of the ketone with the larger substituent R_2 *anti* to the oxazaborolidine ring is favoured for steric reasons. However, the complex can still assume two different conformations, namely *exo* and *endo*.[15]

The key step, that is, the hydride transfer from borane to ketone, takes place intramolecularly in the complex through a cyclic six-membered transition state. Since *exo* and *endo* complexes afford products with opposite configuration, the stereochemical output of the reaction is critically dependent on the energetic differences between the two conformations. According to *ab initio* calculations, the *endo* conformation in the ternary complex is slightly more stable;[14a,15] in spite of this, the product from the *exo* conformation usually predominates, since the activation energy for the hydride transfer in the *exo* conformation is lower.[15]

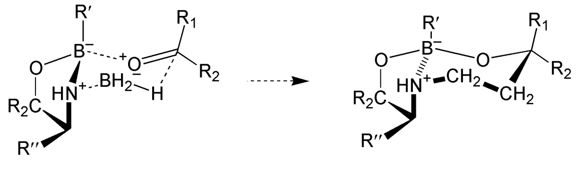
The selective stabilisation of one particular complex conformation should in principle have a profound influence on the enantioselectivity of the reaction. This can actually be achieved by molecular imprinting. Using the synthetic strategy outlined above, it is possible to prepare imprinted polymers that possess cavities complementary in size and shape to a predetermined transition state analogue. Following removal of the template molecule, oxazaborolidines can be placed within these cavities, resembling one of the possible transition states. By testing these catalysts in the CBS reduction, the cavity effect on the stereochemical outcome of the reaction can be investigated. In this paper we wish to report on the synthetic methodology for the preparation of these novel materials.



Scheme 3 Representation of the two possible conformations of the intermediate complex in the CBS reduction

Results and discussion

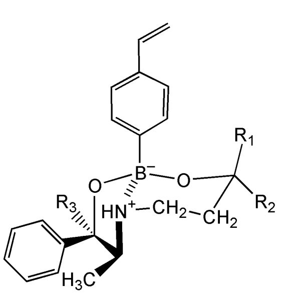
The first problem to be addressed was the choice of a transition state analogue of the CBS reduction suitable for molecular imprinting. The target molecule should be sterically and electronically similar to the transition state, and be polymerisable. Furthermore, after polymerisation it should be easily removed from the imprinted polymer, leaving functional groups in the cavities that allow the exact placement of the oxazaborolidine catalyst. These conditions can be fulfilled by using molecules of the type shown in Scheme 4. In this model compound for the *exo* conformation of the transition state, the bridging borane is substituted by two methylene groups, the coordinated ketone is simulated by an alkoxide functionality, and the B–N covalent bond is replaced by a co-ordinative intramolecular interaction.



Scheme 4 Transition state (left) and the proposed transition state analogue (right) of the CBS reduction.

The molecule can be made polymerisable through the choice of an appropriate substituent R′. After polymerisation, the dialcoholamine part of the molecule can be split off by simple hydrolysis, leaving a polymer-bound boronic acid group that can be easily converted into an oxazaborolidine catalyst by condensation with an appropriate amino alcohol. Interestingly, chiral as well as achiral oxazaborolidines, depending on the amino alcohol employed, can be bound to the polymer with this approach, making it possible on the one hand to study the cavity effect on the intrinsic enantioselectivity of the reaction and on the other to evaluate the enantioselective induction of the cavity alone.

Based on the structure shown in Scheme 4, we prepared the transition state analogues **1**–**4**. These molecules are models for the CBS reduction of acetophenone or related compounds, a standard substrate class for this reaction, with oxazaborolidines derived from the commercially available chiral amino alcohols norephedrine and diphenylalaninol.



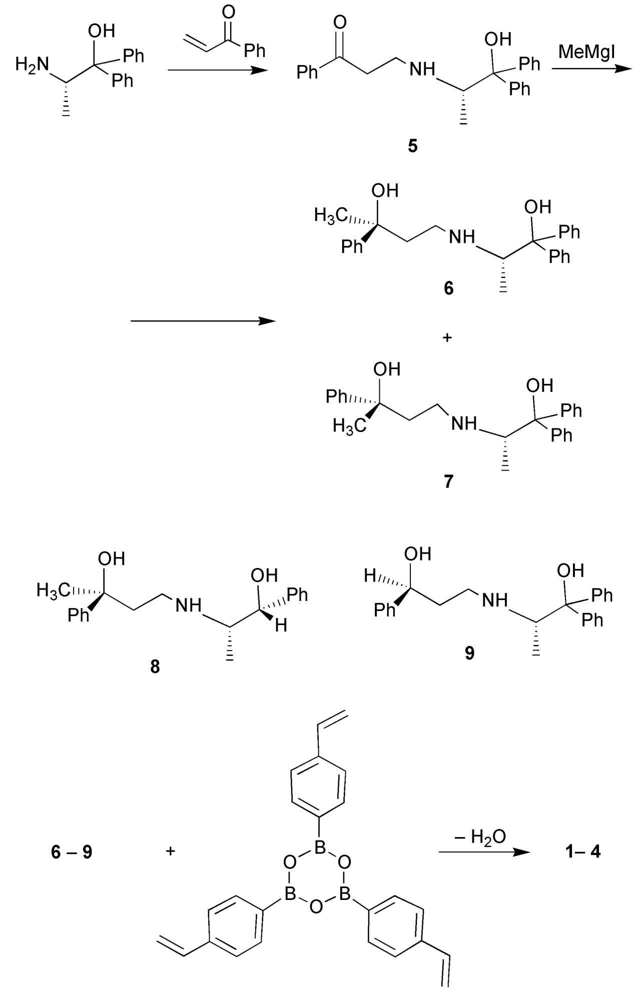
1: R_1 = methyl, R_2 = R_3 = phenyl
2: R_1 = R_3 = phenyl, R_2 = methyl
3: R_1 = methyl, R_2 = phenyl, R_3 = H
4: R_1 = H, R_2 = R_3 = phenyl

It should be noted that compounds **1**, **3** and **4** represent true transition states of the CBS reduction, whereas **2** is a model of a less-favoured transition state (diastereomeric to **1**), in which the ketone co-ordinates with the larger substituent *syn* to the oxazaborolidine. Imprinting with this template affords cavities with the "wrong" shape, whose behaviour in the CBS reduction should disclose additional information on the cavity effect. In the case of compound **4** the methyl group in the ketone-mimicking part of the molecule was substituted by a hydrogen atom to maximise the difference in the steric demand of the two ketone substituents. As a conveniently polymerisable substituent at the boron atom the *p*-vinylphenyl group was employed.

The synthesis of compounds **1** and **2** (Scheme 5) was accomplished through a Michael-type addition of phenyl vinyl ketone to diphenylalaninol, affording **5**, followed by a Grignard reaction with methylmagnesium iodide, yielding the two diastereomers **6** and **7** in comparable amounts. The diastereomers can be conveniently separated by column chromatography. Condensation of **6** or **7** with tris(*p*-vinylphenyl)boroxine **10** yields the desired products. Use of methyl vinyl ketone and phenylmagnesium bromide results in an excess of **6** (diastereomeric ratio 7 : 3) but also in lower reaction yields.

To unequivocally assign the structures **1** and **2** to the prepared compounds, the configuration at the newly formed chiral centres has to be determined. Furthermore, experimental evidence for the intramolecular B–N interaction has to be obtained.

The isolation of a definite condensation product between **6** or **7** and the anhydride **10** is already an indication of the existence of this interaction; simple nine-membered cyclic boronic acid esters are in fact usually unstable and oligomeric products are preferentially formed under the employed reaction conditions.[16a] The fragmentation pattern of the compounds in mass spectrometry is also in accordance with the postulated structures. The B–N interaction greatly stabilises the radical ion, which results from the splitting off of the *p*-vinylphenyl substituent; the resulting signal appears as the strongest fragment peak.[16] Further evidence is provided by ^{11}B-NMR. By considering the chemical shift of the boron signal, it is possible to demonstrate the existence of the B–N interaction and also to quantify its strength, that is, the degree of quaternisation at the boron atom.[17] Tricoordinate, cyclic boronic acid diesters show chemical shifts in the range 26–33 ppm.[17c] Compounds **1** and **2** exhibit instead considerably smaller values (6.15 and 6.63 ppm, respectively). These figures are in good agreement with the literature value (6.62 ppm) for the complex between *N*-(2-hydroxyethyl)-3-aminopropanol and phenylboronic acid, a non-substituted analogue of the above listed compounds with a fully quaternised boron atom.[17a]



Scheme 5 Synthesis of the TSAs **1**–**4**.

Having proved the existence of the B–N interaction, the three-dimensional structures of the molecules **1** and **2** were carefully investigated by molecular modelling. The B–N bond was treated as a covalent bond with full charge separation. The energy-minimised structures of the compounds are reported in Fig. 1. The six-membered ring orients itself in both cases *exo* to the oxazaborolidine ring, in accordance with the preferred transition state of the CBS reduction. It takes, however, a twisted boat conformation instead of the predicted chair-like conformation. In any case, it must be remarked that the slight preference of the reaction transition state for a chair-like conformation has been theoretically proved only in a limited number of cases,[14a,15] and that the change from chair to twisted boat does not significantly vary the spatial orientation of the ring substituents, which is the most important factor for the molecular imprinting procedure.

The assignment of the structures **1** and **2** to the prepared compounds was accomplished through NOE investigations. Irradiation of the 9-methyl group signal in the ^{1}H-NMR spectra of the two compounds yields, as expected in only one case, an effect on the *ortho*-protons of the *p*-vinylphenyl ring. The substitution pattern at this ring shifts the signal of the *ortho*-protons to lower fields and makes them easily

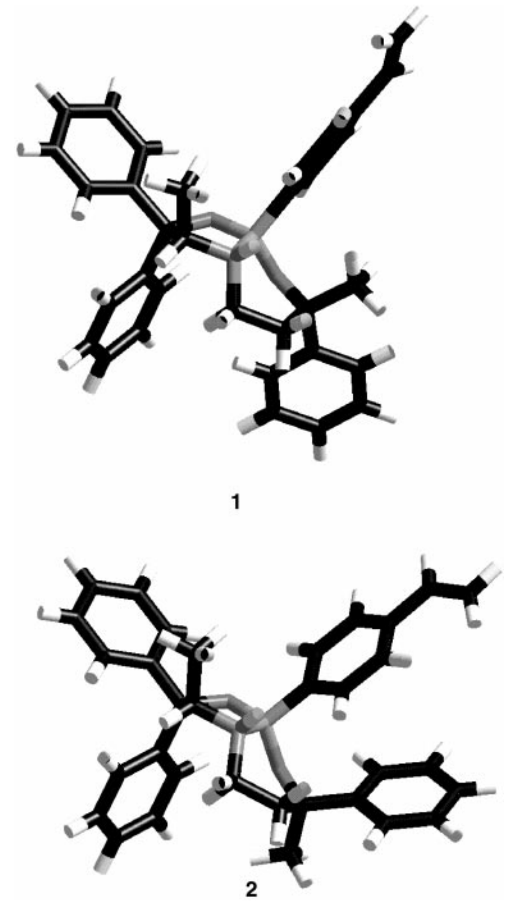


Fig. 1 Modelled structures of the transition state analogues **1** (above) and **2** (below).

distinguishable from the other phenyl protons. The NOE effect amounts to 4.8% and is reciprocal. The corresponding compound was therefore assigned the structure **1**.

Compound **3** was prepared in a similar reaction sequence starting from norephedrine. Methyl vinyl ketone and phenylmagnesium bromide were employed. One of the two diastereomeric dialcoholamine products (structure **8**) was isolated from the reaction mixture by simple crystallisation. NOE analysis of the condensation product of **8** with **10** indicated the same configuration for the new chiral carbon atom as in **1**.

The dialcoholamine **9**, the intermediate product for the synthesis of compound **4**, was synthetised by diastereoselective reduction of **5** with borane–THF. To maximise the asymmetric induction through the amino alcohol moiety, two equivalents of the borane reagent were added to the substrate solution at low temperature. In this way, the first borane equivalent builds an oxazaborolidine with the amino alcohol moiety, which subsequently catalyses the diastereoselective reaction of the keto group with the second borane equivalent through an intramolecular or intermolecular process. A diastereomeric ratio of 8 : 2 (^{1}H-NMR) was recorded. The configuration of the diastereomer produced in excess was investigated by NOE after condensation with **10**. In this case, the signal of the 9-hydrogen atom was irradiated, yielding once more a significant effect on the *ortho*-protons of the *p*-vinylphenyl ring (7%).

The structural similarity of the synthetised model compounds with the transition state of the CBS reduction is apparent. Their application to copolymerisation, as well as their ease of conversion to oxazaborolidines after polymerization, were preliminarily investigated by the synthesis of a test polymer. Monomer **3** was copolymerised with an excess of *p*-divinylbenzene as the crosslinker and THF as the porogen by radical batch polymerisation. The imprinted polymer was obtained as a stiff rod, which was subsequently ground to a particle size between 125 and 45 μm, packed in glass columns, and treated with an appropriate medium to wash out the dialcoholamine part of the template molecule. Best results were obtained by preswelling the polymer with pure THF and then washing it with 3 : 1 THF–0.01 M HCl. Under these conditions, the dissociation yield turned out to be satisfactory (86%). The polymer-bound boronic acid groups could then be converted to polymer-bound oxazaborolidines by condensation with norephedrine. Due to the heterogeneous nature of the polymeric reagent, the reaction is rather slow, but it affords the polymer-bound heterocycle in quantitative yield. A first evaluation of the catalytic performance of the resulting oxazaborolidine-containing, molecularly imprinted catalyst in the reduction of acetophenone with borane–dimethylsulfide adduct (THF, RT, 0.3 equiv. catalyst) yielded the alcohol product in quantitative yield and 77% ee, very close to the value for the corresponding free oxazaborolidine [(4*S*,5*R*)-2,5-diphenyl-4-methyl-1,3,2-oxazaborolidine] under identical conditions (82% ee).

The feasibility of the proposed synthetic strategy for the preparation of molecularly imprinted catalysts for the CBS reduction has been demonstrated. The performance of such catalysts in enantioselective reductions upon variation of parameters such as the nature of the template molecule, the nature of the co-monomers and porogen, the crosslinking degree and the polymerisation conditions are currently under investigation.

Experimental

General

Molecular modelling calculations were performed with the program Cerius^{2}, (Molecular Simulations Inc.) using the force field Dreiding 2.2.1. Melting points were determined on a Büchi 510 melting point apparatus. Optical rotations were measured on a Perkin Elmer 241 MC polarimeter. NMR spectra were recorded on Varian VXR-300 (^{1}H, ^{13}C) and Brucker DRX 500 (^{11}B) spectrometers; TMS and $BF_3 \cdot Et_2O$ were used as standards. IR spectra were recorded on a Perkin Elmer 1420 spectrophotometer. Mass spectra were obtained at the Institute of Pharmaceutical Biology, University of Düsseldorf, using a Varian MAT CH7A mass spectrometer. Elemental analyses were performed at the Institute of Pharmaceutical Chemistry, University of Düsseldorf. Silica gel 60 (Merck) was used as adsorbent for column chromatography. Diphenylalaninol,[18] *p*-divinylbenzene,[19] phenyl vinyl ketone,[20] and tris(*p*-vinylphenyl)boroxine **10**[21] were prepared according to literature procedures.

Synthesis of the transition state analogues

(*S*)-2-(3-Oxo-3-phenylpropyl)amino-1,1-diphenylpropanol 5. To a solution of vinyl phenyl ketone (7.80 g, 59 mmol) in diethyl ether (100 ml) was added a solution of diphenylalaninol (13.51 g, 59 mmol) in diethyl ether (100 ml), and the reaction mixture was stirred overnight. The product slowly separated as a white solid. The precipitation was completed by concentrating the reaction mixture to 50 ml. The product was filtered off and recrystallised from 1 : 1 $CHCl_3$–*n*-hexane. Yield 18.7 g (88%). M.p.: 103 °C. $[\alpha]^{20}_{D}$ ($c = 0.5$ in $CHCl_3$): − 38.1°. ^{1}H-NMR ($CDCl_3$, ppm): 1.00 (d, $J = 6.35$ Hz, 3H), 1.46 (br s, 1H), 2.81 (m, 1H), 3.01 (m, 3H), 3.80 (q, $J = 6.35$ Hz, 1H), 4.46 (br s, 1H), 7.11–7.59 (m, 13H), 7.87 (m, 2H). ^{13}C-NMR ($CDCl_3$, ppm): 14.81 (CH_3), 38.70, 42.14 (CH_2), 58.51 (CH), 78.75 (C), 125.81–128.57, 133.17 (CH), 136.70, 144.80, 146.46, 199.20 (C). IR (KBr, cm^{-1}): 3360 (OH), 3280 (NH), 3070, 3040, 2960, 2850, 2810 (CH), 1670 (C=O), 1480 (C=C), 1440, 1370 (CH). MS (DCI-NH_3): *m*/*z* 360 (MH^+). Anal. calc. for $C_{24}H_{25}NO_2$: C 80.19, H 7.01, N 3.90; found C 80.18, H 7.16, N 3.63%.

(2*S*)-2-[(3*S*)-3-Hydroxy-3-phenylbutyl]amino-1,1-diphenylpropanol 6 and (2*S*)-2-[(3*R*)-3-Hydroxy-3-phenylbutyl]amino-1,1-diphenylpropanol 7. A solution of methylmagnesium iodide was prepared by standard methods from magnesium turnings (7.44 g, 0.31 mol), methyl iodide (43.74 g, 0.28 mol) and dry diethyl ether (400 ml). A solution of **5** (33.5 g, 0.093 mol) in diethyl ether (200 ml) was added dropwise at room temperature. The reaction mixture was stirred for 3 h and hydrolysed with saturated NH_4Cl and water. Standard workup yielded a crude oil that was purified by column chromatography over silica (eluent: *n*–hexane–ethyl acetate–triethylamine 20 : 10 : 1).

The fractions with **6** ($R_f = 0.35$) were evaporated to dryness and the residue taken up in hot *n*-hexane. The product forms colourless crystals upon slow cooling to room temperature. M.p.: 105 °C. $[\alpha]^{20}$ ($c = 0.5$ in $CHCl_3$): − 67.5 (589), − 70.1 (578), − 79.3 (546), − 147.1 (435), − 255.6°(365 nm). ^{1}H-NMR ($CDCl_3$, ppm): 0.95 (d, $J = 6.32$ Hz, 3H), 1.38 (s, 3H) 1.72 (m, 1H), 1.93 (m, 1H), 2.26 (m, 1H), 2.85 (m, 1H), 3.49 (q, $J = 6.32$ Hz, 1H), 3.50 (br s, 1H), 7.12–7.49 (m, 15H). ^{13}C-NMR ($CDCl_3$, ppm): 13.98 (CH_3), 31.54 (CH_3), 42.13, 44.22 (CH_2), 59.06 (CH), 75.14, 80.07 (C), 125.00–128.41 (CH), 145.28, 145.80, 148.12 (C). IR (KBr, cm^{-1}): 3460, 3290 (OH), 3265 (NH), 3070, 3040, 3010, 2960, 2830 (CH), 1490, 1470 (C=C), 1440, 1375 (CH). MS (DCI-NH_3): *m*/*z* 376 (MH^+). Anal. calc. for $C_{25}H_{29}NO_2$: C 79.96, H 7.78, N 3.73; found C 79.71, H 7.81, N 3.77%.

The fractions with **7** ($R_f = 0.45$) were concentrated and the residue chromatographed again with the same eluent. The fractions were evaporated to dryness and the residue treated with hot *n*-hexane. As for its diastereomer, **7** crystallised upon cooling to room temperature. M.p.: 90 °C. $[\alpha]^{20}$ ($c = 0.5$ in

$CHCl_3$): +8.8 (589), +9.0 (578), +9.8 (546), +12.8 (435), +11.4° (365 nm). ^{1}H-NMR ($CDCl_3$, ppm): 0.82 (d, $J = 6.32$ Hz, 3H), 1.41 (s, 3H) 1.78 (m, 1H), 1.94 (m, 1H), 2.53 (m, 2H), 3.22 (br s, 1H), 3.52 (q, $J = 6.32$ Hz, 1H), 7.11–7.53 (m, 15H).^{13}C-NMR ($CDCl_3$, ppm): 14.18, 31.31 (CH_3), 42.23, 44.02 (CH_2), 59.22 (CH), 75.34, 79.73 (C), 124.96–128.58 (CH), 144.53, 145.53, 148.02 (C). IR (KBr, cm^{-1}): 3500, 3310 (OH), 3260 (NH), 3070, 3040, 3010, 2950, 2910, 2830 (CH), 1492 (C=C), 1445, 1370 (CH). MS (DCI-NH_3): *m/z* 376 (MH^+). Anal. calc. for $C_{25}H_{29}NO_2$: C 79.96, H 7.78, N 3.73; found C 79.63, H 7.79, N 3.78%.

(1*R*,2*S*)-*N*-(3-Oxobutyl)norephedrine. To a solution of norephedrine (9.6 g, 63 mmol) in $CHCl_3$ (100 ml) cooled to 0 °C was added dropwise a solution of freshly distilled methyl vinyl ketone (4.45 g, 63 mmol) in $CHCl_3$ (50 ml). The solution was stirred overnight and allowed to reach room temperature. The solvent was evaporated and the resulting solid was used without further purification. The yield is practically quantitative. M.p. 72 °C. $[\alpha]^{20}_D$ ($c = 0.5$ in $CHCl_3$): −3.3°. ^{1}H-NMR ($CDCl_3$, ppm): 0.81 (d, $J = 6.53$ Hz, 3H), 2.15 (s, 3H), 2.63 (t, $J = 6.21$ Hz, 2H), 2.88 (m, 2H), 2.97 (dq, $J = 6.53$ Hz and 3.78 Hz, 1H), 4.74 (d, $J = 3.78$ Hz, 1H), 7.30 (m, 5H).^{13}C-NMR ($CDCl_3$, ppm): 14.50, 30.20 (CH_3), 41.52, 43.87 (CH_2), 58.48, 73.05, 126.03, 126.99, 128.05 (CH), 141.46, 208.34 (C). IR (KBr, cm^{-1}): 3280 (NH), 3110 (OH), 3060, 3040, 3010, 2970, 2890 (CH), 1705 (C=O), 1485 (C=C), 1425, 1365 (CH). MS (DCI-NH_3): *m/z* 222 (MH^+). Anal. calc. for $C_{13}H_{19}NO_2$: C 70.66, H 8.65, N 6.33; found C 70.82, H 8.85, N 6.11%.

(1*R*,2*S*)-2-[(3*S*)-3-Hydroxy-3-phenylbutyl]amino-1-phenylpropanol 8. A solution of phenylmagnesium bromide was prepared by standard methods from magnesium turnings (5.36 g, 0.22 mol), bromobenzene (31.49 g, 0.20 mol) and dry diethyl ether (200 ml). A solution of 1(*R*,2*S*)-*N*-(3-oxobutyl)norephedrine (14.8 g, 0.067 mol) in diethyl ether (200 ml) was added dropwise at room temperature. The reaction mixture was stirred for 3 h and hydrolysed with saturated NH_4Cl and water. After standard workup the crude product was crystallised twice from 1 : 1 $CHCl_3$–*n*-hexane. Yield: 3.84 g (19%). M.p.: 140 °C. $[\alpha]^{20}$ ($c = 0.5$ in $CHCl_3$): −66.9 (589), −69.7 (578), −79.2 (546), −138.5 (435), −225.7° (365 nm). ^{1}H-NMR ($CDCl_3$, ppm): 0.85 (d, $J = 6.53$ Hz, 3H), 1.48 (s, 3H), 1.93 (m, 2H), 2.34 (m, 1H), 2.66 (dq, $J = 6.53$ Hz and 3.84 Hz, 1H), 2.91 (m, 1H), 4.66 (d, $J = 3.84$ Hz, 1H), 7.17–7.38 (m, 10H).^{13}C-NMR $CDCl_3$, ppm): 13.66, 31.52 (CH_3), 41.50, 43.90 (CH_2), 59.00, 75.20 (CH), 75.68 (C), 124.91–128.21 (CH), 142.03, 148.36 (C). IR (KBr, cm^{-1}): 3310 (OH), 3250 (NH), 3040, 2960, 2900, 2840 (CH), 1490, 1470 (C=C), 1440, 1365 (CH). MS (DCI-NH_3): *m/z* 300 (MH^+). Anal. calc. for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found C 76.42, H 8.45, N 4.95%.

(2*S*)-2-[(3*S*)-3-Hydroxy-3-phenylpropyl]amino-1,1-diphenylpropanol 9. A solution of **5** (3.6 g, 10 mmol) in 100 ml dry THF was cooled to −60 °C under an inert atmosphere. A 1 M solution of borane in THF (20 ml) was added with stirring during 30 min with a syringe pump. After the addition, the solution was stirred overnight and allowed to slowly reach room temperature. The solution was hydrolysed by cautious dropwise addition of methanol and evaporated to dryness. The residue was taken up in diethyl ether (100 ml) and washed two times with 0.2 M NaOH (50 ml) and two times with water (50 ml). The solution was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (eluent: *n*-hexane–ethyl acetate–triethylamine 20 : 10 : 1; $R_f = 0.23$). The fractions were evaporated to dryness and the oily residue crystallised upon standing at room temperature. The solid was washed with *n*-hexane and dried. Yield: 1.9 g (53%). M.p.: 76–77 °C. $[\alpha]^{20}$ ($c = 0.5$ in $CHCl_3$): −16.2 (589), −16.7 (578), −19.8 (546), −38.1 (435), −70.8° (365 nm). ^{1}H-NMR ($CDCl_3$, ppm): 0.98 (d, $J = 6.32$ Hz, 3H), 1.74 (m, 2H), 2.57 (m, 1H), 2.83 (m, 1H), 3.69 (q, $J = 6.32$ Hz, 1H), 3.87 (br s, 1H), 4.66 (m, 1H), 7.13–7.56 (m, 15H). ^{13}C-NMR ($CDCl_3$, ppm): 14.50 (CH_3), 38.58, 44.96 (CH_2), 59.02 (CH), 73.85, 79.46 (C), 125.63–128.40, 144.54 (CH), 144.82, 146.02 (C). IR (KBr, cm^{-1}): 3414 (OH), 3060, 3020, 2960, 2935, 2810 (CH), 1490 (C=C), 1450, 1380 (CH). MS (DCI-NH_3): *m/z* 362 (MH^+). Anal. calc. for $C_{24}H_{27}NO_2$: C 79.74, H 7.53, N 3.87; found C 79.63, H 7.24, N 3.81%.

(5*S*,9*S*)-Perhydro-5,9-dimethyl-4,4,9-triphenyl-2-(*p*-vinylphenyl)-1,3,6,2-dioxazaboronine 1. A solution of **6** (5.00 g, 13.3 mmol) and **10** (1.73 g, 4.4 mmol) in benzene (200 ml) was heated in a round-bottomed flask fitted with a Dean–Stark trap and a condenser. The solution was refluxed for 4 h and then cooled to room temperature. The solvent was evaporated and the residue was purified by column chromatography (eluent: *n*-hexane–ethyl acetate 2 : 1; $R_f = 0.55$). The product (4.41 g, 68%) was obtained as a colorless foam. $[\alpha]^{20}_D$ ($c = 0.5$ in $CHCl_3$): −112.2°. ^{1}H-NMR ($CDCl_3$, ppm): 1.04 (d, $J = 6.72$ Hz, 3H), 1.23 (s, 3H), 1.93 (m, 2H), 3.35 (m, 1H), 3.98 (m, 1H), 4.33 (dq, $J = 6.72$ Hz and 10.22 Hz, 1H), 5.21 (dd, $J = 10.87$ Hz and 1.04 Hz, 1H), 5.78 (dd, $J = 17.62$ Hz and 1.04 Hz, 1H), 6.77 (dd, $J = 10.87$ Hz and 17.62 Hz, 1H), 7.08–7.52 (m, 17H), 7.60 (d, $J = 7.93$ Hz, 2H).^{13}C-NMR ($CDCl_3$, ppm): 16.44, 30.33 (CH_3), 34.43, 42.86 (CH_2), 62.95 (CH), 73.33, 85.07 (C), 112.44 (CH_2), 124.91–128.09, 131.32 (CH), 135.51 (C), 137.40 (CH), 144.39, 147.01, 150.09 (C). ^{11}B-NMR ($CDCl_3$, ppm): 6.15. IR (KBr, cm^{-1}): 3040, 3010, 2950 (CH), 1625 (vinyl-C=C), 1595, 1490 (C=C), 1440, 1390, 1365 (CH). MS (DCI-NH_3): *m/z* 505 ($M^+ + NH_3$), 488 (MH^+), 384 (MH^+ −vinylphenyl). Anal. calc. for $C_{33}H_{34}BNO_2$: C 81.31, H 7.03, N 2.87; found C 80.93, H 6.95, N 2.78%.

General procedure for the synthesis of the template monomers 2–4. A solution of one of the dialcoholamines **7**–**9** (10–20 mmol) and **10** (0.33 equiv.) in benzene (200 ml) was heated in a round-bottomed flask fitted with a Dean–Stark trap and a condenser. The solution was refluxed for 1 h. During this time, the Dean–Stark trap was periodically emptied so that about 150 ml of the solvent were distilled off. The product (about 80% yield) separated from the solution as a white amorphous solid upon cooling.

(5*S*,9*R*)-Perhydro-5,9-dimethyl-4,4,9-triphenyl-2-(*p*-vinylphenyl)-1,3,6,2-dioxazaboronine 2. M.p.: 205 °C. $[\alpha]^{20}_D$ ($c = 0.5$ in $CHCl_3$): −38.0°. ^{1}H-NMR ($CDCl_3$, ppm): 0.95 (s, 3H) 0.97 (d, $J = 6.92$ Hz, 3H), 2.07 (m, 2H), 3.08 (m, 1H), 3.27 (m, 1H), 3.53 (m, 1H), 4.33 (dq, $J = 6.92$ Hz and 3.70 Hz, 1H), 5.11 (dd, $J = 10.86$ Hz and 1.16 Hz, 1H), 5.65 (dd, $J = 17.66$ Hz and 1.16 Hz, 1H), 6.53 (dd, $J = 10.86$ Hz and 17.66 Hz, 1H), 7.02–7.53 (m, 17H), 7.82 (d, $J = 7.12$ Hz, 2H).^{13}C-NMR ($CDCl_3$, ppm): 18.60, 32.77 (CH_3), 34.23, 44.61 (CH_2), 63.75 (CH), 72.25, 85.51 (C), 111.95 (CH_2), 124.90–128.31, 131.96 (CH), 134.91 (C), 137.50 (CH), 145.53, 147.27, 149.72 (C). ^{11}B-NMR ($CDCl_3$, ppm): 6.63. IR (KBr, cm^{-1}): 3280 (NH), 3050, 3020, 2970 (CH), 1625 (vinyl-C=C), 1595, 1490 (C=C), 1440, 1390, 1365 (CH). MS (DCI-NH_3): *m/z* 505 ($M^+ + NH_3$), 488 (MH^+), 384 (MH^+ −vinylphenyl). Anal. calc. for $C_{33}H_{34}BNO_2$: C 81.31, H 7.03, N 2.87; found C 80.98, H 7.14, N 2.78%.

(4*R*,5*S*,9*S*)-Perhydro-5,9-dimethyl-4,9-diphenyl-2-(*p*-vinylphenyl)-1,3,6,2-dioxazaboronine 3. M.p.: 202 °C. $[\alpha]^{20}_D$ ($c = 0.5$ in $CHCl_3$): −69.1°. ^{1}H-NMR ($CDCl_3$, ppm): 0.76 (d, $J = 6.92$

Hz, 3H) 1.45 (s, 3H), 1.89–2.19 (m, 2H), 2.87 (m, 1H), 3.18–3.32 (m, 2H), 3.72 (m, 1H), 5.19 (dd, $J = 10.85$ Hz and 1.07 Hz, 1H), 5.40 (d, $J = 4.95$ Hz, 1H), 5.75 (dd, $J = 17.61$ Hz and 1.07 Hz, 1H), 6.74 (dd, $J = 10.85$ Hz and 17.61 Hz, 1H), 7.16–7.41 (m, 12H), 7.69 (d, $J = 7.97$ Hz, 2H).^{13}C-NMR ($CDCl_3$, ppm): 15.68, 32.29 (CH_3), 36.14, 44.63 (CH_2), 62.93 (CH), 72.84 (C), 76.60 (CH), 112.56 (CH_2), 125.34–128.06, 132.17 (CH), 135.90 (C), 137.36 (CH), 139.97, 149.87 (C). ^{11}B-NMR ($CDCl_3$, ppm): 6.67. IR (KBr, cm^{-1}): 3260 (NH), 3040, 2950, 2900, 2830 (CH), 1625 (vinyl-C=C), 1595, 1490 (C=C), 1440, 1390, 1365 (CH). MS (DCI-NH_3): *m/z* 429 ($M^+ + NH_3$), 412 (MH^+), 308 ($MH^+ -$ vinyl- phenyl). Anal. calc. for $C_{27}H_{30}BNO_2$: C 78.84, H 7.35, N 3.41; found C 79.05, H 7.33, N 3.21%.

(5*S*,9*S*)-Perhydro-5-methyl-4,4,9-triphenyl-2-(*p*-vinylphenyl)-1,3,6,2-dioxazaboronine 4. M.p.: 195 °C. $[\alpha]^{20}_D$ ($c = 0.5$ in $CHCl_3$): $-34.1°$. ^{1}H-NMR ($CDCl_3$–*d*-DMSO 7:1, ppm): 0.99 (d, $J = 7.08$ Hz, 3H) 1.55–1.70 (m, 2H), 2.75 (m, 1H), 3.27 (m, 1H), 4.20 (q, $J = 7.08$ Hz, 1H), 4.46 (dd, $J = 10.25$ Hz and 2.65 Hz, 1H), 5.13 (dd, $J = 10.86$ Hz and 1.07 Hz, 1H), 5.69 (dd, $J = 17.58$ Hz and 1.07 Hz, 1H), 5.95 (m, 1H), 6.68 (dd, $J = 10.86$ Hz and $= 17.58$ Hz, 1H), 7.09–7.78 (m, 17H), 7.88 (d, $J = 7.26$ Hz, 2H).^{13}C-NMR ($CDCl_3$–*d*-DMSO 7:1, ppm): 18.11 (CH_3), 33.94, 48.08 (CH_2), 65.32, 70.68 (CH), 84.74 (C), 111.84 (CH_2), 124.62–128.19, 133.26 (CH), 134.92 (C), 137.50 (CH), 146.14, 146.74, 149.84 (C). ^{11}B-NMR ($CDCl_3$–*d*-DMSO 7:1, ppm): 7.09. IR (KBr, cm^{-1}): 3260 (NH), 3060, 3030, 2960, 2810 (CH), 1627 (vinyl-C=C), 1600, 1491 (C=C), 1449, 1391 (CH). MS (DCI-NH_3): *m/z* 491 ($M^+ + NH_3$), 474 (MH^+), 370 ($MH^+ -$ vinylphenyl). Anal. calc. for $C_{32}H_{32}BNO_2$: C 81.19, H 6.81, N 2.96; found C 80.87, H 6.72, N 3.04%.

Preparation of an imprinted polymer catalyst

A solution of **3** (4.32 g), *p*-divinylbenzene (10.10 g) and AIBN (0.15 g) in dry THF (14.40 g) was placed in a polymerisation vial. The solution was degassed three times through freeze–thaw cycles, the vial was sealed and the mixture polymerised at 65 °C for 70 h. The resulting polymer rod was crushed in a mortar, ground in a laboratory mill and sieved. The fraction between 125 and 45 μm was dried, weighed and packed in a small chromatographic column. The polymer was swollen overnight with THF, washed with 3 : 1 THF–0.01 M HCl (100 ml per g polymer), rinsed with 3 : 1 THF–water and vacuum-dried. The splitting percentage was determined on the wash solution as follows: the THF was evaporated, and the water solution neutralised with 0.1 M NaOH. The resulting suspension was evaporated to dryness and taken up in 100 ml $CHCl_3$. The concentration of **8** in the $CHCl_3$ solution was measured polarimetrically; the specifical optical rotations are given above.

To synthesise the polymer-bound oxazaborolidine catalysts, the washed polymer (5.04 g), norephedrine (2.00 g, 3 equiv.) and benzene (200 ml) were placed in a round-bottomed flask fitted with a Soxhlet extractor filled with 4 Å molecular sieves. The mixture was refluxed under nitrogen for 90 h. The suspension was cooled to room temperature and the polymer was filtered under nitrogen. The polymer was vacuum-dried, poured into a Soxhlet extractor, and extracted with dry benzene for 24 h under nitrogen to wash out excess amino alcohol. The solutions were combined and evaporated to dryness. The residue was taken up in 100 ml $CHCl_3$ and the concentration of norephedrine was measured polarimetrically. $[\alpha]^{20}$ ($c = 1$ in $CHCl_3$): –32.2 (589), -33.5 (578), -37.6 (546), -60.4 (435), $-86.4°$ (365 nm).

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References

1 (*a*) A. J. Kirby, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707; (*b*) Y. Murakami, J. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721; (*c*) W. B. Motherwell, M. J. Bingham and Y. Six, *Tetrahedron*, 2001, **57**, 4663.

2 W. K. Fife, *Trends Polym. Sci.*, 1995, **3**, 214.

3 R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997.

4 K. Johnsson, R. K. Allemann, H. Widmer and S. A. Benner, *Nature (London)*, 1993, **365**, 530.

5 G. M. Blackburn and A. Garcon, in *Biotechnology*, ed. D. R. Kelly, Wiley–VCH, Weinheim, Germany, 2nd edn., 2000, vol. 8b, p. 403.

6 *Molecularly Imprinted Polymers*, ed. B. Sellergren, Elsevier, Amsterdam, 2001.

7 See, for example: B. C. Gates, *Catalytic Chemistry*, Wiley, New York, 1992, p. 285.

8 (*a*) S. E. Byström, A. Börje and B. Akermark, *J. Am. Chem. Soc.*, 1993, **115**, 2081; (*b*) G. Wulff and J. Vietmeier, *Makromol. Chem.*, 1989, **190**, 1727.

9 M. J. Whitcombe, C. Alexander and E. N. Vulfson, *Synlett.*, 2000, **6**, 911 and references cited therein

10 (*a*) K. Severin, *Curr. Opin. Chem. Biol.*, 2000, **4**, 710; (*b*) F. Locatelli, P. Gamez and M. Lemaire, *J. Mol. Catal. A.*, 1998, **135**, 89.

11 (*a*) A. Hirao, S. Itsuno, S. Nakahama and N. Yamazaki, *J. Chem. Soc., Chem. Commun.*, 1981, 315; (*b*) S. Itsuno, A. Hirao, S. Nakahama and N. Yamazaki, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1673; (*c*) S. Itsuno, K. Ito, A. Hirao and S. Nakahama, *J. Org. Chem.*, 1984, **49**, 555; (*c*) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2039; (*e*) S. Itsuno, Y. Sakurai, K. Ito, A. Hirao and S. Nakahama, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 395.

12 (*a*) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551; (*b*) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.

13 (*a*) E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1986; (*b*) L. Deloux and M. Screbnik, *Chem. Rev.* 1993, **93**, 763; (*c*) S. Wallbaum and J. Martens, *Tetrahedron: Asymmetry*, 1992, **3**, 1475.

14 (*a*) D. K. Jones, D. C. Liotta, I. Shinkai and D. J. Mathre, *J. Org. Chem.*, 1993, **58**, 799; (*b*) L. P. Linney, C. R. Self and I. H. Williams, *J. Chem. Soc., Chem. Commun*, 1994, 1651; (*c*) A. W. Douglas, D. M. Tschaen, R. A. Reamer and Y.-J. Shi, *Tetrahedron: Asymmetry*, 1996, **7**, 1303.

15 G. J. Quallich, J. F. Blake and T. M. Woodall, *J. Am. Chem. Soc.*, 1994, **116**, 8516.

16 (*a*) U. W. Gerwarth, *Z. Naturforsch., B*, 1977, **32**, 1408; (*b*) I. B. Mazheika, A. P. Gaukhman, I. P. Urtane, G. I. Zelchan and E. Lukevits, *Zh. Obshch. Khim.*, 1979, **49**, 2528.

17 (*a*) R. Csuk, H. Hönig and C. Romanin, *Monatsh. Chem.*, 1982, **113**, 1025; (*b*) H. Nöth and B. Wrackmeyer, *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*, Springer, Berlin, 1978; (*c*) W. V. Dahlhoff and R. Köster, *Liebigs Ann. Chem.*, 1975, 1625.

18 F. Dammast and H.-U. Reißig, *Chem. Ber.*, 1993, **126**, 2449.

19 (*a*) T. W. Campbell and R. N. McDonald, *J. Org. Chem.*, 1959, **24**, 1246; (*b*) G. Wulff and A. Akelah, *Makromol. Chem.*, 1979, **179**, 2647.

20 A. F. Popov, Z. Piskunova and V.N. Matvienko, *J. Org. Chem. USSR*, 1986, **22**, 1299.

21 (*a*) W. J. Dale and J. E. Rush, *J. Org. Chem.*, 1962, **27**, 2598; (*b*) W. Vesper, Ph.D. Dissertation, Universität Bonn, Germany, 1978.