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Receptors functionalized with chiral aza-crown ether rings. Attempted enantioselective catalysis of a Michael addition reaction

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Abstract. A series of receptors functionalized with chiral aza-crown ether rings was synthesized. These compounds were studied as enantiopure catalysts for the addition of benzenethiols to cyclohex-2-en-1-one. Binding of 4-hydroxybenzenethiol in these molecules allows for the orientation of the thiol with respect to an asymmetric catalytic site. This orientation was, however, found to be counterproductive for enantioselective catalysis.

Introduction

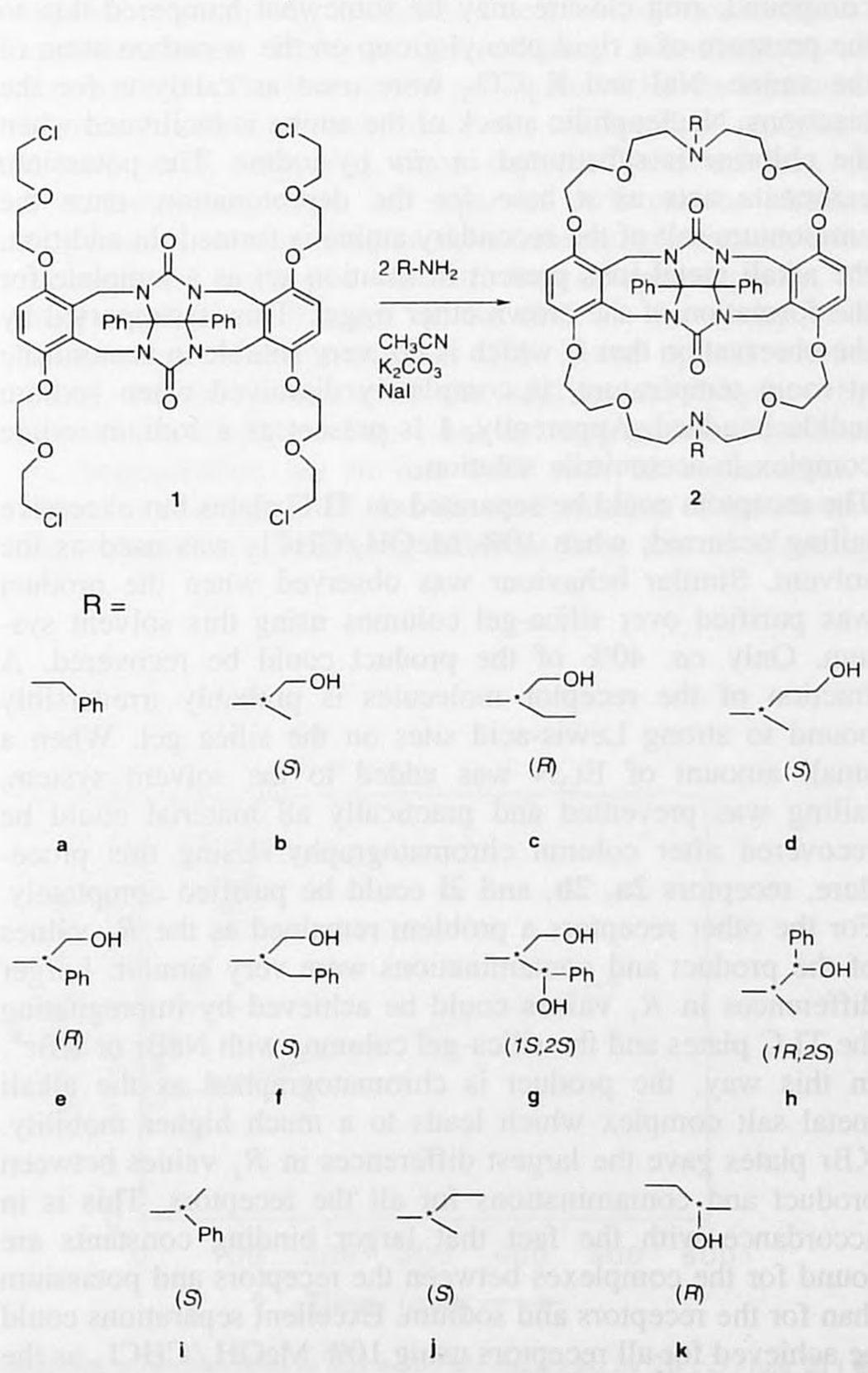
One of the challenging goals of host-guest chemistry[1,2,3] is the development of synthetic receptor molecules that are able to function as stereoselective catalysts for organic reactions. The design of such artificial catalysts is inspired by nature's enzymes. These biomacromolecules have a well-defined three-dimensional structure with a cavity or cleft. The bond-making or -breaking reaction catalyzed by enzymes is preceded by the formation of an enzyme-substrate complex. Substrates can be bound by hydrogen bonds, electrostatic interactions, and Van der Waals forces. The three-dimensional structure of an enzyme is not rigid but exhibits some flexibility, allowing for an adjustment of the shape of the active site such that, upon binding, a better fit is obtained between enzyme and substrate. After the initial binding a stereoselective conversion is achieved due to a specific ordering of catalytic groups at the active site. In addition to being stereoselective, enzymatic reactions are very fast. Compared to uncatalyzed reactions, acceleration by a factor of 10^9 or more is very common.

In this paper we focus on mimicking one of the features of enzymatic catalysis, *viz.* the stereoselective modification of a substrate. This is attempted with the help of synthetic receptors derived from the concave molecule **1** (Scheme 1). If **1** reacts with two chiral or achiral primary amines, basket-shaped receptors **2a-k** are obtained. These receptors possess: (*i*) a cavity in which a substrate can be bound, (*ii*) a tertiary amine group which can act as a basic catalyst, (*iii*) a hydroxyl substituent which may function as an activating and/or orientating group, and (*iv*) a chiral structure (except **2a**). Here we report on our efforts to use novel receptors **2** as enantiopure catalysts for the enantioselective addition of benzenethiols to cyclohexenones.

Results and discussion

Synthesis of receptors

The synthetic methods used to prepare **1** have already been published[4]. Previously, receptor **2a** was synthesized from **1** and benzylamine by applying 0.02M solutions of **1** in DMSO[5]. Under these conditions several by-products were obtained that could only be removed by tedious separation procedures on relatively small samples using long Sephadex columns. These



Scheme 1.

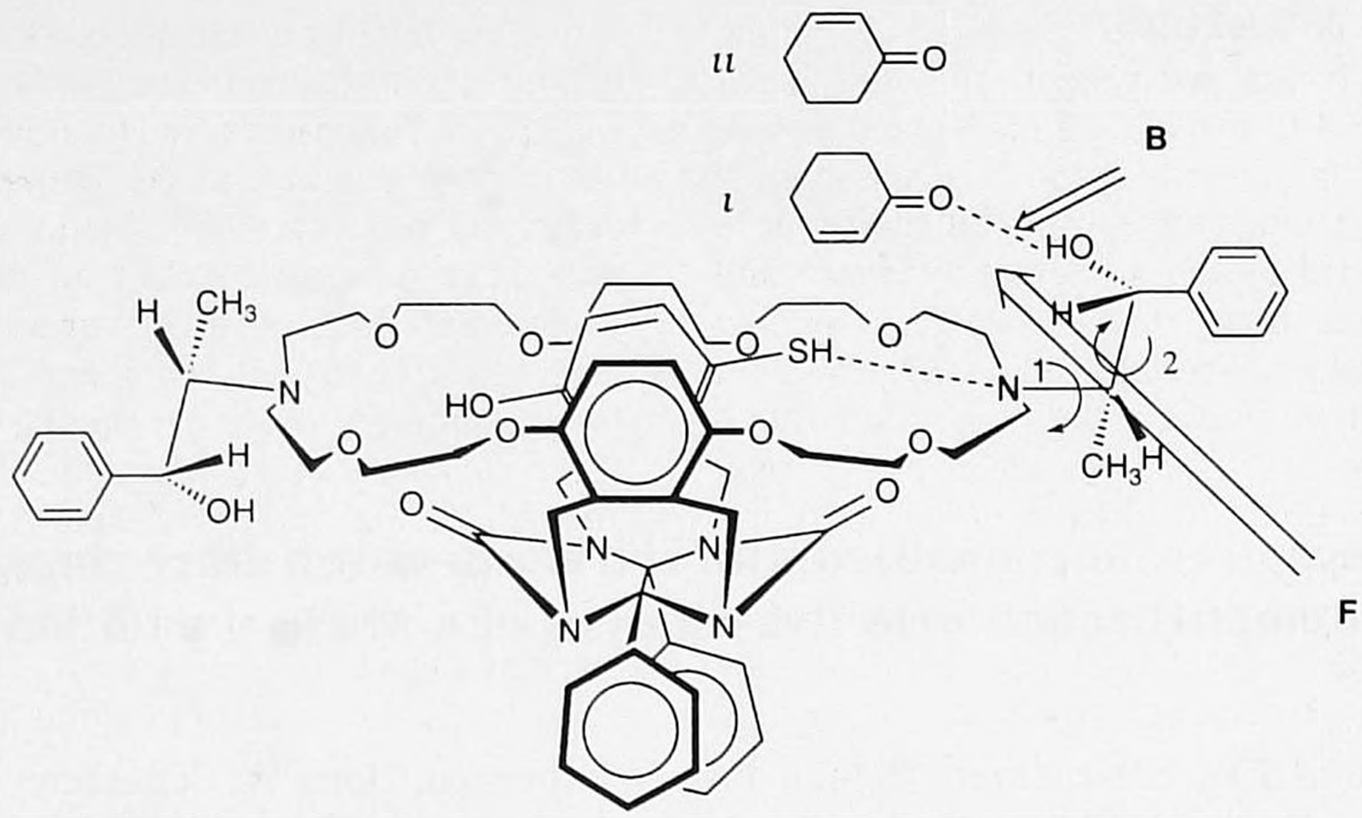


Figure 1. Schematic model showing how the addition of 4-hydroxybenzenethiol to cyclohex-2-en-1-one may be catalyzed by **2h**.

by-products are formed because additional molecules of the amine react with **1** to give secondary amines, which prevents the ring-closure reaction going to completion. We also suspected that the oxidative properties of the solvent DMSO caused the formation of by-products. We therefore developed an alternative method based on the procedure used by *Dale*[6]. The reaction was performed in acetonitrile under dilute conditions (*e.g.* solutions containing 0.01–0.001 M of **1**), and the amine was added to the reaction mixture over a period of days. This procedure yielded much cleaner products in high yields. Only in the case of **2e** was a substantial amount of by-product containing three amine moieties obtained. For this compound, ring closure may be somewhat hampered due to the presence of a rigid phenyl group on the α-carbon atom of the amine. NaI and K_2CO_3 were used as catalysts for the reactions. Nucleophilic attack of the amine is facilitated when the chlorine is substituted *in situ* by iodine. The potassium carbonate acts as a base for the deprotonation, once the ammonium salt of the secondary amine is formed. In addition, the alkali metal ions present in solution act as a template for the formation of the crown ether rings[7]. This is supported by the observation that **1**, which is not very soluble in acetonitrile at room temperature, is completely dissolved when sodium iodide is added. Apparently, **1** is present as a sodium iodide complex in acetonitrile solution.

The receptors could be separated on TLC plates but excessive tailing occurred, when 10% $MeOH/CHCl_3$ was used as the solvent. Similar behaviour was observed when the product was purified over silica-gel columns using this solvent system. Only *ca.* 40% of the product could be recovered. A fraction of the receptor molecules is probably irreversibly bound to strong Lewis-acid sites on the silica gel. When a small amount of Et_3N was added to the solvent system, tailing was prevented and practically all material could be recovered after column chromatography. Using this procedure, receptors **2a, 2h**, and **2i** could be purified completely. For the other receptors a problem remained as the R_f values of the product and contaminations were very similar. Larger differences in R_f values could be achieved by impregnating the TLC plates and the silica-gel columns with NaBr or KBr[8]. In this way, the product is chromatographed as the alkali metal salt complex which leads to a much higher mobility. KBr plates gave the largest differences in R_f values between product and contaminations for all the receptors. This is in accordance with the fact that larger binding constants are found for the complexes between the receptors and potassium than for the receptors and sodium. Excellent separations could be achieved for all receptors using 10% $MeOH/CHCl_3$ as the solvent system. A drawback of this procedure is that only 40–60% of the material can be recovered after chromatography.

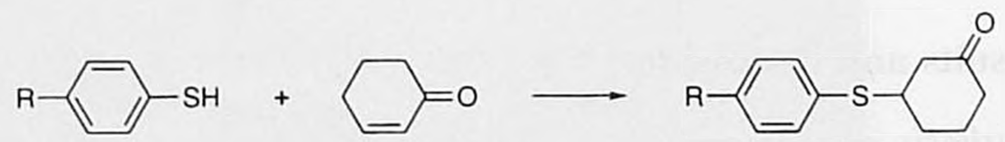
Binding of substrates

It was shown previously that dihydroxy-substituted aromatic molecules are bound by molecular baskets of type **2**[9,10]. The guests are wedged between the cavity walls of these receptors. For **2a**, binding constants between 50 and 300000 M^{-1} were found for various benzenediols[10]. The guest's hydroxyl groups form (probably bi-furcated) hydrogen bonds with the crown-ether nitrogen atoms and/or carbonyl groups of the receptor. The complexes are further stabilized by $\pi-\pi$ stacking interactions between the guest and the walls of the receptor.

To test whether the above-mentioned binding interactions can be used to orientate reactants with respect to an asymmetric catalytic site, we performed binding studies with benzenethiol (**3**) and 4-hydroxybenzenethiol (**4**). When **3** was added to **2i**, no upfield shifts were observed in the ^{1}H-NMR spectrum for the cavity-wall protons of the receptor, indicating that **3** is not bound by **2i**. Also, the host NCH_2 protons displayed negligible shifts, suggesting that no ion pair is formed with the thiol. In the case of substrate **4**, the cavity wall protons of **2i** were found to shift upfield, indicating that complex formation does take place, but no shifts of the NCH_2 protons were observed. Apparently, host-guest complex formation involves hydrogen-bond interaction between the hydroxyl function of **4** and a carbonyl group of the receptor as well as $\pi-\pi$ stacking interactions. The binding constant of the complex between **4** and **2i** was determined to be $K_a = 82\ M^{-1}$ at 298K, which corresponds to a ΔG of binding of -10.9 kJ/mol. For host **2h** a binding constant of 127 M^{-1} was found, indicating that incorporation of a hydroxyl function in the side-chain of the basket does not interfere with the binding process. The stronger complexation of the guest by **2h** may be a result of the nitrogen atoms being involved in the binding process. This is suggested by downfield shifts found for this receptor's NCH_2 protons upon complexation.

Addition of aromatic thiols to cycloalkenones catalyzed by receptors **2**

To investigate whether or not the binding properties of **2** can be used to achieve selectivity in a reaction, we studied the



3, R=H
4, R=OH

Scheme 2.

addition of **4** to cyclohex-2-en-1-one (Scheme 2) in the presence of receptors **2b-k**. For comparison, the addition of the non-bonding substrate **3** to cyclohex-2-en-1-one was also studied. The reactions of thiols with cyclic α,β-unsaturated ketones catalyzed by cinchona and ephedra alkaloids have been thoroughly investigated by the groups of *Wynberg* and *Kellogg*[11,12,13]. They demonstrated that the reaction is first order in catalyst, first order in benzenethiol, and also first order in cyclohex-2-en-1-one. Furthermore, it was found that amines possessing a β-hydroxyl function act as bifunctional catalysts. During the reaction, the thiol function becomes activated, because it forms an ion pair with the tertiary nitrogen function of the chiral catalyst. The double bond of cyclohex-2-en-1-one is made reactive via the formation of a hydrogen bond between the carbonyl group of this reagent and the hydroxyl group of the catalyst. In this way, both reactants are oriented by the catalyst in the correct position for a stereoselective reaction. This resulted in *ee* (enantiomeric excess) values for this reaction of up to 75%. We envisaged that the same bifunctional interactions as found for the alkaloids, could be present in the reaction catalyzed by receptors **2**. In addition, a third interaction, schematically illustrated in Figure 1, may be operative. The position of the phenyl ring of the 4-hydroxybenzenethiol could be fixed by complexation in the cavity of the receptor, and the orientation of the thiol function could be controlled by formation of an ionpair with the nitrogen atom of the crown-ether ring. In the model of Figure 1, the position of the double bond of the alkenone is determined by the hydrogen bond between the carbonyl group in this molecule and the hydroxyl function of the receptor. If the three-point attachment model is valid, an enantioselective reaction would be achieved, if the thiol function attacks preferentially at either the *Re* or the *Si* face of the cyclohex-2-en-1-one. This leaves open the following possibilities: (*i*) attack of the thiol on cyclohex-2-en-1-one with the double bond of the latter molecule facing the crown-ether ring (see Figure 1), (*ii*) idem with the double bond turned away from the crown-ether ring, (*iii*) and (*iv*), as in (*i*) and (*ii*) but with the attack of the thiol function at the ''front'' (**F**) instead of the ''back'' (**B**) side of the catalyst. If one of these four possibilities is energetically favoured (or two if the same enantiomer is produced), enantioselective catalysis can be expected. The above-mentioned requirements can be fulfilled, if there are local minima for rotations around bonds 1 and/or 2 (in Figure 1). *Dijkstra* has shown that, for β-amino alcohols, such discrete minima in energy do indeed exist[14]. Extensive variation of the subsituent in the side-chain of the receptor may enhance the chance that the requirements are met.

We first tested our receptors as catalysts for the addition of benzenethiol to cyclohex-2-en-1-one. Toluene was initially chosen as the reaction medium because the highest *ee* values have been reported in the literature with this solvent[12]. All catalysts were carefully dried before use, because moisture can have a negative effect on the asymmetric induction, as pointed out by *Dijkstra*[14]. For all receptors we found that the reaction is essentially complete after 15 hours. This result is in agreement with similar findings of *Hiemstra* et al.[12] for the alkaloid catalysts. For most receptors the optical purity values of the reaction products were negligible. Some asymmetric induction occurred in the presence of hosts **2c** and **2d**, for which the reaction products were found to have optical purities of 5 and 9% respectively. Because the solvent toluene may prevent binding of the thiol in the cavity of our receptors, we also performed some reactions in dichloromethane. However, the optical purity values were also very small in this solvent.

In a second series of experiments we tested 4-hydroxybenzenethiol, which was shown to be bound in the cavity of our receptors, as the reactant. Because this thiol had not been studied before, we first determined the rate of its addition to cyclohex-2-en-1-one in the absence of a catalyst. After 4 hours, no product could be detected by ^{1}H-NMR. Product formation in the catalyzed reaction turned out to be almost quantitative for all receptors within several hours. The optical rotations of the formed products were very low. As the absolute rotation of enantiomerically pure 3-(4-hydroxyphenylthio)-cyclohexanone is not known, no optical-purity values could be calculated. However, comparison of the optical rotations with those of a series of aryl-substituted 3-phenylthiocyclohexanones[12] reported in the literature suggested that the optical purities are probably negligible.

The experiments described above show that the receptors are capable of catalyzing the addition reaction of benzenethiols to cyclohexenones. However, the obtained enantioselectivities are very low. The low optical purity found for the addition of benzenethiol to cyclohex-2-en-1-one catalyzed by receptor **2h** is particularly surprising, since *Dijkstra*[14] showed that, with *N*-methylephedrine, an *ee* value of 36% can be obtained. Apparently, incorporating an ephedrine moiety into our receptor molecule leads to a dramatic loss of optical purity. This suggests that the fixation of the thiol in the cavity of the receptor is counterproductive. The lower optical rotations found for the products of the addition of 4-hydroxybenzenethiol to cyclohex-2-en-1-one as compared to those found for benzenethiol, are in line with such an explanation. A second reason might be that the conformation of ephedrine in the receptor is substantially different from that of *N*-methyl-

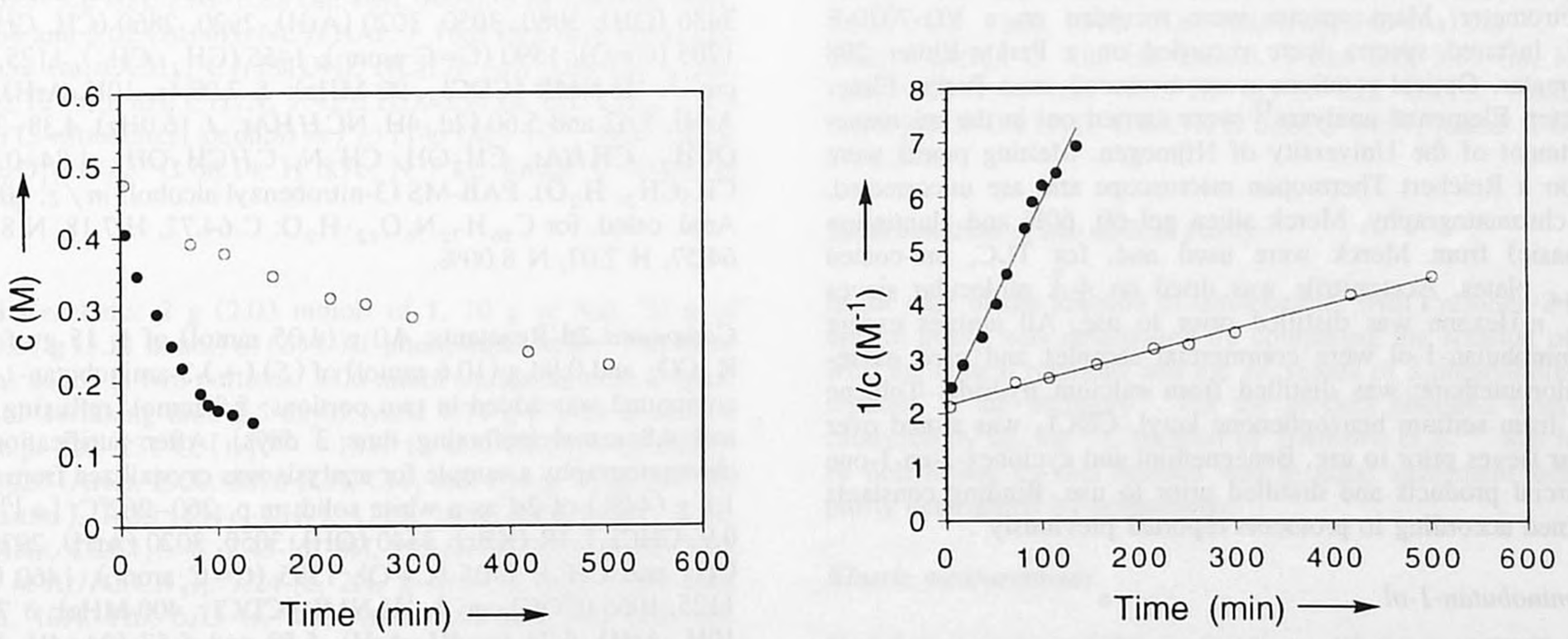
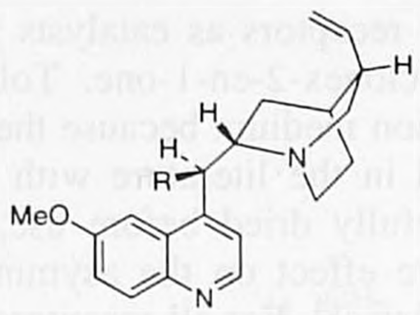


Figure 2. Left: concentration of cyclohex-2-en-1-one as function of time for the addition of benzenethiol to this molecule catalyzed by **2b** (○) *and* **2j** (●). *Right: second-order plots for this reaction.*



5 a,R=OH
b,R=OAc

ephedrine. The hydroxyl function of the ephedrine moiety in **2h** may not be available for catalysis because it is involved in hydrogen bonding, *viz.* with hydrogen-bond acceptor sites present in the receptor. The ^{1}H-NMR spectra of compounds **2b-k** indicate that such a hydrogen bond may be present[15].

Kinetics of the thiol-addition reaction catalyzed by receptors **2b** *and* **2j**

Hiemstra et al.[12] have shown that, in the presence of quinine (**5a**) as a catalyst, the thiol addition reaction follows pseudo-second-order kinetics, if the concentration of the base is kept constant. The reaction is first order in thiol and in cyclohexenone. They found that the rate decreases by a factor of 250 when acetylquinine (**5b**) is used instead of quinine.

To test whether or not the hydroxyl functions of our receptors are involved in the catalysis, we measured the rates of the addition of benzenethiol to cyclohex-2-en-1-one in the presence of **2b** and **2j**. These receptors are structurally similar, except that **2j** contains an ethyl group instead of a hydroxymethyl group in its side-chain. The reactions were performed in $CDCl_3$ and monitored by ^{1}H-NMR following the decrease of cyclohex-2-en-1-one as a function of time relative to an internal standard. The results are depicted in Figure 2. Up to approximately 70% conversion, plots of the reciprocal of the concentration of cyclohex-2-en-1-one *vs.* time gave straight lines, indicating that the reaction follows pseudo-second-order kinetics. Remarkably, receptor **2j** (k_{obs} 0.11) was found to be a better catalyst than **2b** (k_{obs} 0.016). Thus, for our catalysts, omission of an hydroxyl function leads to a higher rate. This suggests that the hydroxyl function of the receptor is not involved in the catalysis and even may hamper the reaction. To elucidate this point further a detailed study of the conformation of receptors **2a-2k** has been performed, which will be published in due course[15].

Experimental

General

^{1}H-NMR spectra[16] were recorded on a Bruker AM-400 or a Bruker WH-90 spectrometer. Mass spectra were recorded on a VG-7070-E spectrometer. Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. Elemental analyses[17] were carried out in the microanalytical department of the University of Nijmegen. Melting points were determined on a Reichert Thermopan microscope and are uncorrected. For column chromatography, Merck silica gel 60, 60H and aluminium oxide 60 (basic) from Merck were used and, for TLC, pre-coated silica-gel F_{254} plates. Acetonitrile was dried on 4-Å molecular sieves prior to use. *n*-Hexane was distilled prior to use. All amines except (*S*)-(+)-3-aminobutan-1-ol were commercial samples and used as received. Dichloromethane was distilled from calcium hydride. Toluene was distilled from sodium benzophenone ketyl. $CDCl_3$ was stored over 4-Å molecular sieves prior to use. Benzenethiol and cyclohex-2-en-1-one were commercial products and distilled prior to use. Binding constants were determined according to protocols reported previously[8].

(S)-(+)-3-Aminobutan-1-ol

This compound was synthesized from (*S*)-(-)-1-phenylethanamine and ethyl-(*E*)-but-2-enoate as described in the literature[18] with the exception that EtOAc/*n*-hexane (1/2, v/v) was used as eluent to separate the diastereomers of ethyl(*S*)-3-(methylbenzylamino)butanoate by column chromatography. (*S*)-(+)-3-aminobutan-1-ol: R_f 0.05 (EtOAc/*n*-hexane; 1/1, v/v); $[\alpha]_D^{20}$ 12.0° (*c* 1.4, EtOH). Spectral data were in agreement with reported values for racemic 3-aminobutan-1-ol[18].

Compound **1** *was synthesized according to a method published previously*[4].

General procedure for the synthesis of the receptors

NaI was added to a suspension of *x* mmol of **1** in acetonitrile. The mixture was stirred for several minutes until a clear solution resulted. K_2CO_3 and 1.5*x* mmol of the amine were added and the suspension was placed under nitrogen. Subsequently, it was refluxed for several days while being monitored by TLC. The rest of the amine (*x* mmol) was added, when **1** had disappeared. After additional refluxing for several days, the reaction mixture was filtered. The filtrate was washed with 100 ml of chloroform and the combined extracts were concentrated *in vacuo*. Chloroform (100 ml) was added and the solution was filtered again. The receptors **2a** and **2i** were purified on silica gel using $MeOH/Et_3N/CHCl_3$(2/1/97) as the eluent. Receptor **2h** was purified using silica gel and Et_3N/CH_2Cl_2(1/99). After purification Et_3N was removed by co-distillation with toluene. The other receptors were purified over a silica-gel column saturated with KBr. This column was prepared by pouring silica-gel into a 10% aqueous KBr solution. The silica gel was filtered off and dried prior to use. As eluent, 10% MeOH in $CHCl_3$ was used. After chromatography the product was dissolved in $CHCl_3$, washed with a 1M solution of K_2CO_3 (2 times) and with demineralized water (5 times). After evaporation of the solvent, the product was dissolved in a minimum amount of $CHCl_3$ and added dropwise to stirred *n*-hexane. The precipitate was filtered off, washed with *n*-hexane, and dried *in vacuo*.

Compound **2a** Reactants: 1 g (1.01 mmol) of **1**, 5 g of NaI, 15 g of K_2CO_3, and 0.24 g (2.24 mmol) of benzylamine. The latter compound was added in two portions: 1.22 mmol (refluxing time 2 days) and 1.02 mmol (refluxing time 2.5 days); yield 85% of **2a** as a white solid; m.p. 214–216°C. Spectral data were in agreement with previously reported data[5].

Compound **2b** Reactants: 4 g (4.05 mmol) of **1**, 15 g of NaI, 36 g of K_2CO_3 and 0.83 g (11.06 mmol) of (*S*)-(+)-2-aminopropan-1-ol. The latter compound was added in two portions: 6.14 mmol (refluxing time 3 days) and 4.92 mmol (refluxing time 2.5 days); yield 0.8 g (20%) of **2b** as a white solid; mp 235–237°C; $[\alpha]^{20D}$ +35.4° (*c* 0.5, $CHCl_3$). IR (KBr): 3440 (OH), 3080, 3060, 3020 (ArH), 2910, 2860 (CH, CH_2 and CH_3), 1710 (C = O), 1590 (C = C arom.), 1445 (CH_2, CH_3), 1125, 1060 (COC) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24–6.98 (m, 10H, ArH), 6.72 (s, 4H, ArH), 5.63 and 5.60 (2d, 4H, NC*H*HAr, *J* 16.1 Hz), 4.19–3.36 (m, 34H, CH_2O, NCH*H*Ar, CH_2OH), 3.30–2.29 (br m, 14H, CH_2N, NC*H*CH_3, H_2O), 0.96 (d, 6H, CH_3, *J* 6.1 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / z:* 993 $(M + H)^+$. Anal. calcd. for $C_{54}H_{68}N_6O_{12} \cdot 2H_2O$: C 63.02, H 7.05, N 8.17; found: C 63.26, H 6.69, N 8.04%.

Compound **2c** Reactants: 2 g (2.03 mmol) of **1**, 10 g of NaI, 30 g of K_2CO_3 and 0.54 g (6.06 mmol) of (*R*)-(-)-2-aminobutan-1-ol. The latter compound was added in two portions: 3.03 mmol (refluxing time 2 days) and 3.03 mmol (refluxing time 2.5 days); yield 0.95 g (46%) of **2c** as a white solid; m.p. 237–239°C; $[\alpha]^{20D}$ +17.2° (*c* 1.0, $CHCl_3$). IR (KBr): 3430 (OH), 3080, 3050, 3020 (ArH), 2920, 2860 (CH, CH_2 and CH_3), 1705 (C=O), 1590 (C=C arom.), 1455 (CH_2, CH_3), 1125, 1060 (COC) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 7.09 (s, 10H, ArH), 6.73 (s, 4H, ArH), 5.62 and 5.60 (2d, 4H, NC*H*HAr, *J* 16.0Hz), 4.38–2.47 (m, 44H, OCH_2, CH*H*Ar, CH_2OH, CH_2N, C*H*CH_2OH), 1.84–0.71 (m, 12H, CH_3CH_2, H_2O). FAB-MS (3-nitrobenzyl alcohol) *m / z*: 1021 $(M+H)^+$. Anal. calcd. for $C_{56}H_{72}N_6O_{12} \cdot H_2O$: C 64.72, H 7.18, N 8.09; found: C 64.57, H 7.07, N 8.00%.

Compound **2d** Reactants: 4.0 g (4.05 mmol) of **1**, 15 g of NaI, 36 g of K_2CO_3 and 0.94 g (10.6 mmol) of (*S*)-(+)-3-aminobutan-1-ol. The latter compound was added in two portions: 5.8 mmol (refluxing time 4 days) and 4.8 mmol (refluxing time 3 days). After purification by column chromatography a sample for analysis was crystallized from $CHCl_3$; yield 1.8 g (44%) of **2d** as a white solid; m.p. 260–262°C; $[\alpha]^{20D}$ +21.1° (*c* 0.9, $CHCl_3$). IR (KBr): 3440 (OH), 3050, 3020 (ArH), 2920, 2860 (CH, CH_2 and CH_3), 1705 (C=O), 1595 (C=C arom.), 1460 (CH_2, CH_3), 1125, 1065 (COC) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.15–7.02 (m, 10H, ArH), 6.74 (s, 4H, ArH), 5.58 and 5.57 (2d, 4H, NC*H*HAr, *J* 16.0Hz), 4.20–3.60 (m, 34H, OCH_2, NCH*H*Ar, CH_2OH), 3.17–2.91 and 2.70–2.53 (2m, 10H, CH_2N, NC*H*CH_3), 1.84–1.73 (m, 2H, C*H*-

HCH_2OH), 1.48–1.39 (m, 2H, $CHHCH_2OH$), 1.01 (d, 6H, CH_3, *J* 6.5 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / z*: 1021 $(M+H)^+$. Anal. calcd. for $C_{56}H_{72}N_6O_{12}\cdot CHCl_3$: C 60.02, H 6.45, N 7.37; found: C 59.74, H 6.15, N 7.21%.

Compound **2e** Reactants: 4.0 g (4.05 mmol) of **1**, 15 g of NaI, 36 g of K_2CO_3 and 1.57 g (11.5 mmol) of (*R*)-(-)-2-amino-2-phenylethanol. The latter compound was added in two portions: 6.4 mmol (refluxing time 4 days) and 5.1 mmol (refluxing time 3 days); yield 1.85 g (41%) of **2e** as a white solid; m.p. 237–240°C; $[\alpha]^{20D}$ −27.8° (*c* 0.5, $CHCl_3$). IR (KBr): 3430 (OH), 3060, 3030 (ArH), 2920, 2860 (CH and CH_2), 1710 (C=O), 1595 (C=C arom.), 1455 (CH_2), 1140, 1070 (COC) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.50–6.94 (m, 20H, ArH), 6.74 (s, 4H, ArH), 5.63 (d, 4H, NC*H*HAr, *J* 16.0 Hz), 4.32–3.52 (m, 34H, OCH_2, NCH*H*Ar, CH_2OH), 3.26–2.21 (m, 10H, CH_2N and NC*H*ArCH_2OH). FAB-MS (3-nitrobenzyl alcohol) *m / e*: 1117 $(M+H)^+$. Anal. calcd. for $C_{64}H_{72}N_6O_{12}\cdot 2H_2O$: C 66.65, H 6.64, N 7.29; found: C 66.45, H 6.20, N 7.16%.

Compound **2f** Reactants: 1.5 g (1.52 mmol) of **1**, 10 g NaI, 35 g K_2CO_3 and 0.51 g (3.4 mmol) (*S*)-(-)-2-amino-3-phenylpropan-1-ol. The latter compound was added in two portions: 2.0 mmol (refluxing time 2 days) and 1.4 mmol (refluxing time 2.5 days); yield 40% of **2f** as a white solid; m.p. 246–248°C; $[\alpha]^{20D}$ +28.8°(*c* 0.3, $CHCl_3$). IR (KBr): 3405 (OH), 360, 3030 (ArH), 2920, 2870 (CH, CH_2 and CH_3), 1710 (C=O), 1595 (C=C arom.), 1460 (CH_2), 1130, 1070 (COC) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.38–6.91 (m, 20H, ArH), 6.73 (s, 4H, ArH), 5.63 and 5.58 (2d, 4H, NC*H*HAr, *J* 16.1 Hz), 4.43–2.24 (m, 48H, OCH_2, NCH*H*Ar, CH2(OH), CH_2Ph, CH_2N and NC(*H*)CH_2OH). FAB-MS (3-nitrobenzyl alcohol) *m / z*: 1145 $(M+H)^+$. Anal. calcd. for $C_{66}H_{76}N_6O_{12}\cdot H_2O$: C 68.14, H 6.76, N 7.22; found: C 68.49, H 6.60, N 7.14%.

Compound **2g** Reactants: 4 g (4.05 mmol) of **1**, 15 g of NaI, 36 g of K_2CO_3 and 2.05 g (12.3 mmol) of (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol. The latter compound was added in two portions: 6.1 mmol (refluxing time 2 days) and 6.2 mmol (refluxing time 2 days); yield 2.14 g (45%) of **2g** as a white solid; m.p. 238–240°C; $[\alpha]^{20D}$ +31.0 (*c* 0.7, $CHCl_3$). IR (KBr): 3400 (OH), 3060, 3025 (ArH), 2920, 2860 (CH, CH_2 and CH_3), 1705 (C=O), 1595 (C=C arom.), 1460 (CH_2), 1125, 1070 (COC) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.50–6.82 (m, 20H, C(OH)*ArH*, ArH), 6.69 (s, 4H, ArH), 5.73 (d, 4H, NC*H*HAr, *J* 16.1 Hz), 4.97–2.83 (m, 48H, OCH_2, NCH*H*Ar, CH(OH)Ph, CH_2OH, CH_2N and NC*H*CH_2OH). FAB-MS (3-nitro-benzyl alcohol) *m / e*:1177 $(M+H)^+$. Anal. calcd. for $C_{66}H_{72}N_6O_{12}\cdot H_2O$: C 66.32, H 6.58, N 7.03; found: C 66.29, H 6.35, N 6.97%.

Compound **2h** Reactants: 4.5 g (4.6 mmol) of **1**, 20 g of NaI, 30 g of K_2CO_3 and 2.09 g (13.8 mmol) of (1*R*,2*S*)-(-)-2-amino-1-phenylpropan-1-ol. The latter compound was added in two portions: 6.9 mmol (refluxing time 2 days) and 6.9 mmol (refluxing time 2.5 days); yield 3.95 g (75%) of **2h** as a white solid; m.p. 240–242°C; $[\alpha]^{20D}$ -35.7 (*c* 1.3, $CHCl_3$). IR (KBr): 3420 (OH), 3080, 3055, 3020 (ArH), 2920, 2860 (CH, CH_2 and CH_3), 1710 (C=O), 1595 (C=C arom.), 1460 (CH_2), 1125, 1070 (COC) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 [d, 4H, *o-H*-ArC(OH), *J* 7.4 Hz] 7.27 [m, 4H, *m-H*-ArC(OH)], 7.18 [d, 2H, *p-H*-ArC(OH), *J* 7.2 Hz], 7.08–6.88 (m, 10H, ArH), 6.65 (2d, 4H, ArH, *J* 9.6 Hz), 5.68 and 5.62 (2d, 4H, NC*H*HAr, *J* 16.0 Hz), 4.78 (br s, 2H, OH), 4.19–3.52 (m, OCH_2, C*H*Ph(OH), NCH*H* Ar), 3.09 (br s, 2H, NC*H*(CH_3), 2.72 (br t, 8H, CH_2N, *J* 42.6 Hz), 0.91 (d, 6H, CH_3, *J* 6.4 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / e*: 1145 $(M+H)^+$. Anal. calcd. for $C_{66}H_{76}N_6O_{12}\cdot H_2O$: C 68.14, H 6.76, N 7.22; found: C 68.39, H 6.58, N, 7.17%.

Compound **2i** Reactants: 2 g (2.03 mmol) of **1**, 10 g of NaI, 30 g of K_2CO_3 and 0.67 g (5.51 mmol) of (*S*)-(-)-1-phenylethanamine. The latter compound was added in two portions: 3.06 mmol (refluxing time 2 days) and 2.45 mmol (refluxing time 2.5 days); yield 1.71 g (79%) of **2i** as a white solid; m.p. 229–231°C; $[\alpha]^{20D}$ +15.6° (*c* 0.5, $CHCl_3$). IR (KBr): 3080, 3055, 3020 (ArH), 2920, 2870 (CH, CH_2 and CH_3), 1710 (C=O), 1595 (C=C arom.), 1455 (CH_2, CH_3), 1125, 1055 (COC) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 [d, 4H, *o*-Ar*H*C(CH_3), *J* 7.3 Hz], 7.32 [m, 4H, *m*-Ar*H*C(CH_3)], 7.24 [d, 2H, *p*-Ar*H*C(CH_3), *J* 9.2 Hz], 7.13–7.07 (m, 10H, Ph), 6.73 (s, 4H, ArH), 5.65 and 5.61 (2d, 4H, NC*H*HAr, *J* 16.0 Hz), 4.20–3.55 [m, 34H, OCH_2, NCH*H*Ar and NC*H*(CH_3), H_2O], 2.84 [m, 8H, NC*H*(CH_3), CH_2N], 1.42 (d, 6H, CH_3, *J* 6.7 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / e*: 1085 $(M+H)^+$. Anal. calcd. for $C_{64}H_{72}N_6O_{10}\cdot 1.5\ H_2O$: C 69.11, H 6.80, N 7.56; found: C 69.23, H 6.49, N 7.61%.

Compound **2j** Reactants: 4.0 g (4.05 mmol) of **1**, 15 g of NaI, 36 g of K_2CO_3 and 0.94 g (12.9 mmol) of (*S*)-(+)-*sec*-butylamine. The latter compound was added in two portions: 7.2 mmol (refluxing time 4 days) and 5.7 mmol (refluxing time 3 days); yield 1.9 g (44%) of **2j** as a white solid; m.p. 246–249°C; $[\alpha]^{20D}$ +11.5° (*c* 0.9, $CHCl_3$). IR (KBr): 3050, 3020 (ArH), 2950, 2920, 2860 (CH, CH_2 and CH_3), 1710 (C=O), 1595 (C=C arom.), 1455 (CH_2), 1125, 1070 (COC) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): d 7.11–7.03 (m, 10H, ArH), 6.75 (s, 4H, ArH), 5.61 (d, 4H, NC*H*HAr, *J* 16.0 Hz), 4.19–3.65 (m, 28H, OCH_2, NCH*H* Ar), 2.88–2.58 (m, 10H, CH_2N, NC(*H*)$CH_3C_2H_5$), 1.60–1.49 (m, 2H, C*H*HCH_3), 1.33–1.22 (m, 2H, CH*H*CH_3), 0.99 (d, 6H, CH_3, *J* 6.5 Hz), 0.92 (t, 6H, CH_3, *J* 7.3 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / e*: 989 $(M+H)^+$. Anal. calcd. for $C_{56}H_{72}N_6O_{10}\cdot H_2O$: C 66.78, H 7.41, N 8.34; found: C 67.02, H 7.13, N 8.23%.

Compound **2k** Reactants: 4.0 g (4.05 mmol) of **1**, 15 of g NaI, 36 g of K_2CO_3 and 0.83 g (11.1 mmol) of (*R*)-(-)-1-aminopropan-2-ol. The reaction mixture was first refluxed with 6.2 mmol amine for 4 days. Then a second portion of 4.9 mmol amine was added and the reaction mixture was refluxed again for 3 days; yield 1.30 g (33%) of **2k** as a white solid; m.p. 234–236°C; $[\alpha]^{20D}$ −51.0°(*c* 0.5, $CHCl_3$). IR (KBr): 3440 (OH), 3060, 3020 (ArH), 2920, 2860 (CH, CH_2 and CH_3), 1710 (C=O), 1590 (C=C arom.), 1460 (CH_2), 1160, 1070 (COC) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.17–7.05 (m, 10H, ArH), 6.71 (s, 4H, ArH), 5.66 and 5.64 (2d, 4H, NC*H*HAr, *J* 16.1 Hz), 4.20–3.65 [m, 30H, OCH_2, C*H*(OH), NCH*H*Ar], 3.03–2.77 (m, 8H, CH_2N), 2.65 (2d, 2H, NC*H*HCH(OH)CH_3, *J* 12.9 Hz), 2.37 [2d, 2H, NCH*H*CH(OH)CH_3, *J* 12.9 Hz], 2.30–1.50 (br s, 8H, OH, H_2O) 1.13 (d, 6H, CH_3, *J* 6.2 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / z*: 993 $(M+H)^+$. Anal. calcd. for $C_{54}H_{68}N_6O_{12}\cdot H_2O$: C 64.14, H 6.95, N 8.31; found: C 64.36, H 6.77, N 8.20%.

General procedure for the catalytic reactions

The catalyst (0.015 mmol) was dried *in vacuo* (0.5 mmHg) at 100°C for 6 h. in a Schlenk vessel. This vessel was then filled with argon and the solvent (3 ml), benzenethiol (1.81 mmol) and the cyclohex-2-en-1-one (1.56 mmol) were added with a syringe. The reaction mixture was left overnight. The work-up procedure was essentially the same as that of *Hiemstra et al*[12]. The reaction mixture (in cases of poor solubility, diluted with a small amount of CH_2Cl_2) was added dropswise to vigorously stirred *n*-hexane (20 ml). After filtration of the catalyst over Hyflo (without applying vacuum), the *n*-hexane was evaporated *in vacuo*. Then 20 ml of toluene was added and the organic layer was washed twice with 10 ml of aqueous 2N HCl, twice with 10 ml aqueous 2N KOH, and twice with 10 ml of brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. In the case of 3-phenylthiocyclohexanone the spectral data were in agreement with those reported in the literature[19]. For the reaction of 4-hydroxybenzenethiol with cyclohex-2-en-1-one, a different work-up procedure was used. The reaction mixture was taken up in 20 ml of toluene and washed with 10 ml of aqueous 1N HCl (twice), 10 ml of water (twice) and finally with 10 ml of brine. After drying the organic layer over $MgSO_4$, the solvent was evaporated and the product was purified over a silica-gel column using $CHCl_3$ with a few volume % of methanol as the eluent. For analysis, a sample was crystallized by allowing *n*-hexane to diffuse into a mixture of MeOH and $CHCl_3$. 3-(4-Hydroxyphenyl)thiocyclohexanone: m.p. 124°C. IR: (KBr) 3210 (OH), 3020(Ar), 2960, 2940 (CH_2), 1680 (CO), 1605, 1590 (Ar), 1495, 1440, 1410, 1360, 1340, 1320, 820 (Ar), 840 (Ar) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.25 (m, 2H), 6.75 (m, 2H), 3.37 (m, 1H), 2.79 (m, 1H), 2.64–1.44 (m, 7H). EI *m / z*: 222 (M^+). Anal. calcd. for $C_{12}H_{14}O_2S\cdot 0.1\ H_2O$: C 64.31, H 6.39, S 14.31; found: C 64.34, H 6.28, S 14.24%.

Determination of the optical purity

In the case of the reaction of benzenethiol with cyclohex-2-en-1-one, the optical purity was determined by comparing the rotation of the product with the optical rotations and the *ee* values of 3-phenylthiocylohexanone reported in the literature[12]. For the product obtained from the reaction catalyzed by **2c**, the ^{13}C method of *Hiemstra* et al.[20] was followed. The *ee* determined by this method was in good agreement with the optical purity determined by polarimetry.

Kinetic measurements

Cyclohex-2-en-1-one [304 mg (3.16 mmol)], 9.0 g of $CDCl_3$, and 337 mg of (3.06 mmol) benzenethiol were weighed into a flask. To this mixture was added 22.1 mg of trioxane as an internal standard. The receptor (0.01

mmol) was weighed into a second flask to which exactly 2 ml of the above-mentioned mixture was added. Approximately 1 ml of the resulting solution was transferred into an NMR tube. In between the measurements, the tube was placed in a thermostatted bath at 25°C. ^{1}H-NMR (90 MHz) spectra were recorded with a relaxation delay of 4.0 s. The concentration of cyclohex-2-en-1-one was determined by comparing the integral of the ethylenic proton at C3 with the integral of the internal standard. For all measurements, the spectrum of a sample without catalyst was also measured at the beginning and at the end of each measurement. For these samples the conversion was found to be less than 5%.

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15 A detailed study of the conformation of receptors **2a-2k** will be reported in a separate paper.
16 The ^{1}H-NMR spectra of **2b, 2c, 2i**, and **2k** indicated the presence of water molecules. The signals of these molecules coincided with the signals of the hosts. The amount of water calculated from the NMR spectra matched the amount found by elemental analysis. In the ^{1}H-NMR spectrum of **2j** a broad peak at 2.48 ppm was visible. Its integral corresponded to one molecule of water. This is in accordance with the amount of water found in the elemental analysis. For compounds **2e, 2f, 2g**, and **2h**, the presence of water was not apparent from the ^{1}H-NMR spectra. The water signal in these cases was probably broadened, since elemental analysis indicated that water was present in these samples.
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