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Effect of Branching in Alkylgroups of Tertiary Amines on Their Performance as Catalysts in the High Pressure Promoted Baylis-Hillman Reaction

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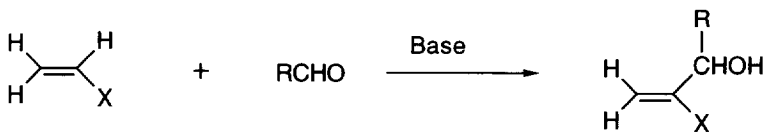
Abstract: Receptors **1** were tested as catalysts for the high pressure promoted Baylis-Hillman reaction. Surprisingly most of the compounds were found to be catalytically inactive. With model compounds (simple acyclic tertiary amines) it could be shown that tertiary amines with branches at their α-carbon atoms show a remarkable decreased activity. It is proposed that the branches prevent attack of the lone pair of the amine on the double bond of the alkene. This explains why only receptors without this feature are catalytically active. Copyright © 1996 Elsevier Science Ltd

Introduction

The development of synthetic receptors that catalyze enantioselective transformations of neutral guests is still at its infancy. In our current research program we focus on synthetic receptors of type **1**. Previously we have shown that these compounds (e.g. **1b**) are able to bind dihydroxy-substituted aromatic guests by means of hydrogen bonding as well as π-π interactions (See Figure 1).[1] In order to combine a binding site with a chiral catalytic group we recently synthesized a series of receptors functionalized with chiral β-amino alcohols.[2] These chiral receptors were tested as enantioselective supramolecular catalysts for a Michael addition reaction and a hydrocyanation reaction for reactants that are bound in the cavity of **1**. It seemed also of interest to test these β-amino alcohol contaning chiral receptors as enantioselective supramolecular catalysts for the Baylis-Hillman reaction (Scheme 1) because this reaction is catalyzed by tertiary amines.[3,4] In addition a rate enhancement is observed when an amine is used that contains a hydroxyl function in the β-position (*e.g.* 3-hydroxy-quinuclidine).[5] The tertiary amines of some of the receptors (e.g. **1a** and **1e**) have branches at their α-carbon atoms. We reasoned that this would be favourable since it brings the chiral auxiliary as close as possible to the tertiary amine.

Scheme 1



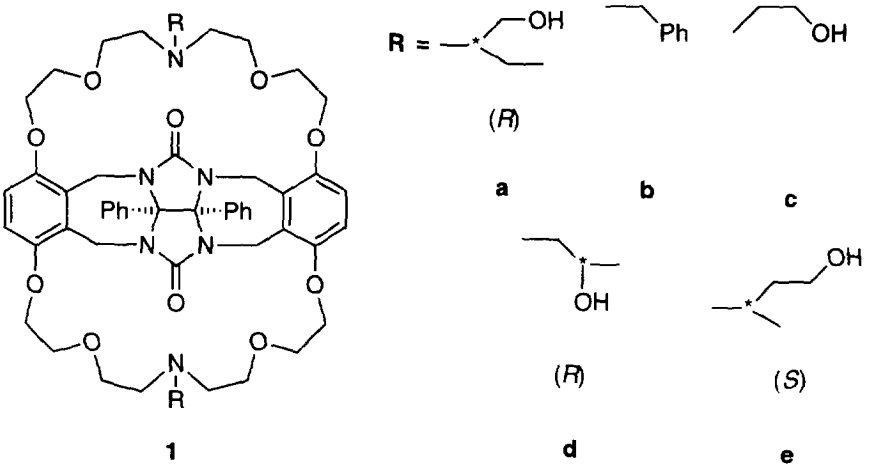
X = CHO, CO_2R, COR, CN.

Several papers have been published in which chiral amines are used as catalysts for the Baylis-Hillman reaction. Alkaloids of the quinine family were tested by Drewes.[6] He obtained a maximum of 12 % e.e. for the reaction between acetaldehyde and methyl acrylate catalyzed by quinidine. In our own group several alkaloids were tested as catalysts for the hydroxyalkylation of acetonitrile with benzaldehyde. An e.e. value of 15% was found when brucine or strychnine was used.[7] Isaacs reported e.e. values varying from 0-17 % using various

chiral amines as catalyts.[8] The best results obtained sofar with chiral amines were recently reported by Hirama et al.[9] With chiral 2,3-disubstituted 1,4-diazabicylo[2.2.2]octanes as catalyst an e.e. of 47% was found.

The Baylis Hillman reaction proceeds *via* dipolar intermediates (Figure 2) and is accelerated by pressure. When the reaction is carried out under high pressure 5-10 mol % triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) are generally added as catalysts.[10,11] As solvents reduce the reaction rate, neat conditions are generally applied. However, to allow for structural variation of the aldehyde (which includes the use of solid ones) we decided to test our catalysts in the presence of a solvent, *i.e.* diethyl ether and THF.[6] Acrylonitrile and benzaldehyde were chosen as the reactants. The possibility of π-π stacking interactions between our chiral receptors and benzaldehyde was the basis for the choice of this aldehyde. Also 3,5-dihydroxybenzaldehyde, which forms a 1:1 complex with our receptors, was tested as a reactant.

Chart 1



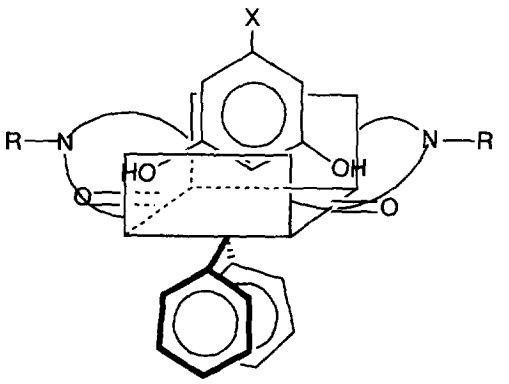


Figure 1. Schematic representation of the host-guest complex.

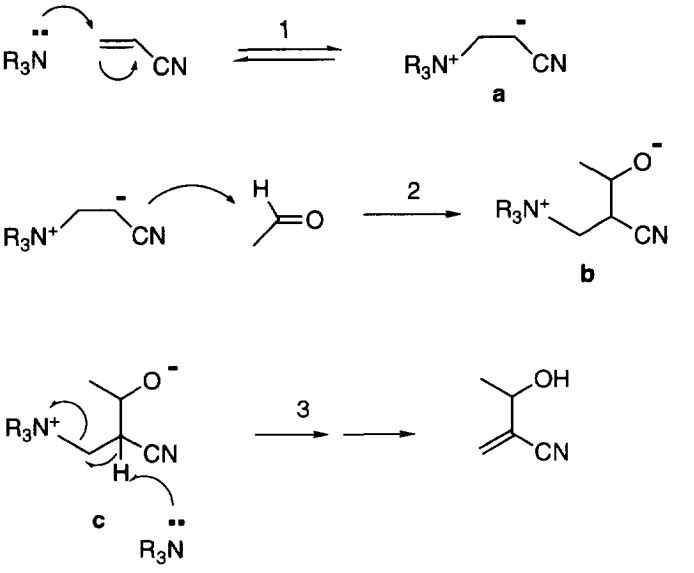


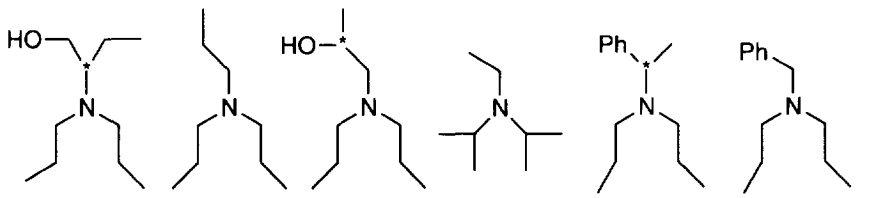
Figure 2. Mechanism of the Baylis-Hillman reaction as proposed by Hill and Isaacs.[10]

Results and discussion.

Model compounds.

In preliminary experiments using acrylonitrile, benzaldehyde, and **1a** in THF under high pressure[12] surprisingly no product formation was observed. Also under neat conditions the receptor turned out to be catalytically inactive. To elucidate whether this result was caused by structural features of **1a** or was due to the reaction conditions, we decided to perform detailed experiments with model compounds of our receptors.

Chart 2



(*R*) (*R* and *S*) (*R*)

2 **3** **4** **5** **6** **7**

Table I- Baylis-Hillman Reaction of Benzaldehyde with Acrylonitrile under High Pressure in the Presence of Model Compounds.[a]

Entry	Acrylonitrile/M	Benzaldehyde/M	Catalyst	Conc. of catalyst[b] /mol%	Solvent	Pressure /Kbar	t/h	T/°C	Yield/%
1	6.2	6.2	Et_3N	10	-	15	11	20	82
2	6.5	6.5	Et_3N	0.9	-	14	11	20	14
3	7.9	3.0	Et_3N	1.6	-	12	23	50	95
4	2.0	1.0	Et_3N	18	THF	14	16	20	96
5	1.0	1.0	Et_3N	13	THF	14	16	20	93
6	3.0	3.0	Et_3N	10	THF	14	11	20	95
7	2.0	1.0	Et_3N	5	THF	14	16	20	97
8	1.9	1.0	**2**	5	THF	15	16	20	0
9	2.0	1.0	**2**	5	THF	12	23	50	0
10	2.0	1.0	**2**	10	THF	15	89	20	0
11	2.0	1.0	**3**	5	THF	12	18	50	97
12	2.8	1.4	**4**	7	THF	15	16	20	95
13	2.0	1.0	**5**	5	THF	15	89	20	0
14	2.6	1.4	**6**	6	THF	16	70	20	0
15	2.8	1.4	**7**	6	THF	15	23	20	95
16	2.0	1.0	**2**	5	$CHCl_3$	15	14	20	12
17	2.0	1.0	**2**	5	MeCN	15	21	20	20

[a] Product is 2-(1-hydroxy-1-phenylmethyl)acrylonitrile. In some cases (entries 3 and 8-17) a small amount of 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide was added to the reaction mixture.

[b] Based on benzaldehyde.

Table II- Baylis-Hillman Reaction of Benzaldehyde with Acrylonitrile under High Pressure in the Presence of Receptors **1**.[a]

Entry	Acrylonitrile/M	Benzaldehyde/M	Receptor	Catalyst/ Mol%[b]	Solvent	Pressure /Kbar	t/h	T/°C	Yield/%
1	2.6	1.3	**1b**	6	THF	15	24	20	0
2	2.0	1.0	**1c**	6	THF	12	16	20	0
3	0.16	0.1	**1d**	15	THF	14	66	20	0
4	0.16	0.1	**1d**	15	$CDCl_3$	14	66	20	45
5	0.16	0.1	**1d**	15	$CDCl_3$	15	19	50	95
6	0.16	0.1	**1e**	16	$CDCl_3$	15	19	50	<5

[a] Product is 2-(1-hydroxy-1-phenylmethyl)acrylonitrile. In all cases a small amount of 5-*tert*-butyl-4-hydroxy-2-methylphenylsulfide was added to the reaction mixture.
[b] Based on benzaldehyde.

Table III- Baylis-Hillman Reaction of 3,5-Dihydroxybenzaldehyde with Acrylonitrile under High Pressure in the Presence of Triethylamine or **1**.[a]

Entry	Acrylonitrile/M	3,5-Di-hydroxy-benzaldehyde/M	Catalyst	Mol%[b]	Solvent (v/v)	Pressure /Kbar	t/h	T/°C	Yield/%
1	0.15	0.07	Et_3N	15	MeCN/$CHCl_3$(1:1)	14	66	20	0
2	0.15	0.07	Et_3N	20	MeCN/$CHCl_3$(2:3)	15	19	50	<5
3	0.15	0.07	Et_3N	26	THF/$CHCl_3$ (1:1)	16	69	20	9
4	0.15	0.07	Et_3N	19	THF/$CHCl_3$ (1:1)	15	19	50	75
5	0.15	0.07	**1d**	15	THF/$CHCl_3$ (1:1)	15	17	50	0
6	0.15	0.07	**1d**	15	MeCN/$CHCl_3$(1:1)	15	17	50	0
7	0.15	0.07	**1d**	16	$CHCl_3$/2-pro-panol(10:1)	15	19	50	30
8	0.15	0.07	**1e**	16	$CHCl_3$/2-pro-panol(10:1)	15	19	50	0

[a] Product is 2-(a-hydroxy(3,'5'-dihydroxy)benzyl)acrylonitrile. In all cases a small amount of 5-*tert*-butyl-4-hydroxy-2-methylphenyl-sulfide was added to the reaction mixture.
[b] Based on aldehyde.

The effect of the catalyst concentration and the solvent on the reaction between acrylonitrile and benzaldehyde was determined for triethylamine. Under neat conditions, lowering of the amount of catalyst gave rise to polymerization of the acrylonitrile (see Table I, entries 1 and 2). Addition of a radical inhibitor could prevent this polymerization reaction (entry 3). In THF good conversions were obtained even when the catalyst concentration was lowered to 5 mol% (entries 4-7). In a second series of experiments we tested **2**, which is a model compound for **1a**, as a catalyst. Surprisingly, **2** did not catalyze the reaction (entry 8). Use of higher temperatures (entry 9) or longer reaction times (entry 10) had no effect. Elongation of the side chains of the tertiary amine (compound **3**) was found to have little effect on its catalytic activity (entry 11). We reasoned that the formation of a strong intramolecular hydrogen bond[13] under high pressure might be the reason for the lack of activity of **2**. The results obtained with **4** however show that this explanation is less likely (entry 12). Subsequently, we tested compound **5** as a catalyst (entry 13). It turned out to be completely unreactive.

Apparently, branches at the α-carbon atom decrease the catalytic activity of the tertiary amine. This was further confirmed when **6** and **7** were measured (entries 14 and 15). We propose that α-branches prevent attack of the lone pair of the amine on the double bond of acrylonitrile. Furthermore α-branching probably forces tertiary amines in a more sp^2 type of configuration which results in a reduced nucleophilicity of the free electron pair. This is in line with the observed effectiveness of bicyclic amines (e.g. DABCO) for which the amine has a fixed sp^3 configuration.

In more polar solvents however a slow conversion was also found in the presence of catalysts with branches (entries 16 and 17). This solvent effect is in agreement with results of Bode and Kaye[14] who have shown that the rate of the Baylis-Hillman reaction at ambient pressure is enhanced in more polar reaction mixtures.

Reaction in the presence of receptors.

The lack of catalytic activity observed for **1a** in the initial experiments is in line with the results obtained with model compound **2**. To our surprise we found that also receptors **1b**, **1c**, and **1d** did not catalyze the Baylis-Hillman reaction (Table II, entries 1, 2, and 3). Inspection of space filling (Corey-Pauling-Koltun, CPK) models of receptors **1b** and **1d** and model compounds **7** and **4** revealed that for both type of compounds the lone pair of the nitrogen atom is equally available for catalysis. The difference in catalytic activity could be caused by a decreased solubility of the receptors under high pressure conditions. However, as the reactions were performed at low catalyst concentrations and the reaction mixtures were found to be homogeneous when depressurized quickly, such an explanation is less likely. As we had found that the reaction is promoted by more polar solvents we repeated the experiment with **1d** in $CDCl_3$. In this solvent after 66 hours 45% conversion was reached (Table II, entry 4). Raising the temperature to 50 °C increased the conversion even to 95% (Table II, entry 5). After workup the e.e. value of the product was determined by ^{1}H-NMR using a shift reagent. The e.e. turned out to be less than 5%. For receptor **1e**, which has branches at the α-carbon, only a trace of product was formed even at 15 KBar and 50 °C (Table II, entry 6).

Subsequently, we tested 3,5-dihydroxybenzaldehyde, which forms 1:1 complexes with receptors **1**, as the reagent.[15] As this aldehyde is virtually insoluble in chloroform we had to use mixtures of solvents. In preliminary experiments with Et_3N as the catalyst (Table III, entries 1-4) 3,5-dihydroxybenzaldehyde appeared to be less reactive than benzaldehyde. Formation of the Baylis-Hillman product could only be observed at elevated temperatures. The reason for this low reactivity at low temperature is probably a trivial one: after quickly depressurizing the reaction mixture, it was found that the aldehyde had partly precipitated. At 50 °C this compound remains in solution and reacts faster.

Finally, we studied the reaction of 3,5-dihydroxybenzaldehyde and acrylonitrile in the presence of **1d**. Again the receptor catalyst turned out to be less active than triethylamine (Table III, entries 5 and 6). Product formation was only observed when a mixture of 2-propanol and $CHCl_3$ was used as the solvent (Table III, entry 7). The fact that **1d** is only active when an extra hydrogen bond donor (e.g. 2-propanol) is added, may indicate that the hydroxyl function of **1d** is not available for catalysis under the employed reaction conditions. Because of the low conversion no e.e. value was determined. In line with the results obtained for benzaldehyde we found that the receptors with branches at the α-carbon atom were unreactive, even at 15 KBar and 50 °C (Table III, entry 8).

Conclusions

In THF as a solvent triethylamine catalyzes the Baylis-Hillman reaction under high pressure at concentrations of approximately 5 mol% . Under similar conditions simple acyclic tertiary amines with branches at their α-carbon atoms show a remarkable decreased activity. This means that most of the receptors prepared in the course of our studies are not suitable as catalysts for the Baylis-Hillman reaction, since all (except **1d**) possess this feature.

In future work we will concentrate on receptor molecules having chiral centers that are further removed from the nitrogen. In such an approach[16] enantioselectivity may be induced by donor-acceptor interactions of the reactants with the chiral ligand.

Experimental section

General. ^{1}H-NMR spectra were recorded on a Bruker AM 400 or a Bruker WH-90 spectrometer. spectrophotometer. Optical rotations were measured on a Perkin Elmer 241 Polarimeter. For column chromatography Merck silica gel 60 and 60H were used and for TLC pre-coated silica gel F_{254} plates. n-Hexane was distilled prior to use. Benzaldehyde was purified as described in the literature.[17] The synthesis and the procedure for drying of the receptors is described in an other paper.[2] THF was distilled from sodium ketyl prior to use. $CDCl_3$ and MeCN were dried over 4 Å molecular sieves. $CHCl_3$ for the catalytic experiments was purified according to a literature procedure.[17] 3,5-Dihydroxybenzaldehyde was a commercial product and purified over a short column of silica gel (eluent, 2% MeOH/$CHCl_3$, v:v) prior to use. All other compounds were commercial products and used as received. For the high pressure experiments, reaction vessels with teflon ampoules were used which are equipped with a steel screw. The apparatus used to perform the high pressure experiments has been described previously.[18] GLC analysis was performed on a Hewlett-Packard 5890A gas chromatograph equipped with a capillary column HP-1 using the following temperature program: 100°C(5 min.)/100°C-150°C(5°C/min)/150°C(5 min). Nitrogen(1 ml/min) was used as a carrier gas.

(*R*)-(-)-*N,N*-Dipropyl-2-amino-butanol (2). A mixture of 3.5 g (39 mmol) of (*R*)-(-)-2-amino-1-butanol, 14 g of K_2CO_3, and 14 g (82 mmol) of n-propyl iodide in 150 ml of THF was refluxed with stirring under nitrogen for 68 hrs.. After filtration of the K_2CO_3 the solvent was evaporated, and the product was purified over silica gel (eluent 3% MeOH/$CHCl_3$, v/v). Yield 48% of **2** as a colorless oil. This compound has been described previously. Boiling point and analytical data were reported in the literature.[19] R_f=0.46 (silica, eluent 10% MeOH/$CHCl_3$, v/v), $[\alpha]^D_{20}$=-86,9°(c=1.0, $CHCl_3$); ^{1}H-NMR(90 MHz, $CDCl_3$): δ 3.53 (d, 1H, C*H*HOH, J=10.0 Hz), 3.47 (d, 1H, CH*H*OH, J=10.0 Hz), 3.13 (t, 1H, OH, J=10.0 Hz), 2.46 (m, 5H, NCH and NCH_2), 1.92 (m, 6H, CH_2), 0.84 (t, 9H, CH_3, J=14.0 Hz).

(±)-*N,N*-Dipropyl-1-amino-2-propanol (4). A mixture of 3 g (40 mmol) of (±)-1-amino-2-propanol, 10 g of K_2CO_3, and 13.5 g (79 mmol) of propyl iodide, in 30 ml of acetonitrile was refluxed with stirring under nitrogen for 14 hrs.. After filtration of the K_2CO_3 the solvent was evaporated, and the product was purified over a short silica gel column using THF as eluent. Yield 40% of **4** as a colorless oil: R_f = 0.77 (silica gel, eluent THF); ^{1}H-NMR($CDCl_3$, 90 MHz): δ 3.89-3.42 (m, 2H, C(OH)*H* and OH), 2.69-1.98 (m, 6H, NCH_2), 1.49 (m, 4H, CH_2), 1.04 (d, 3H, C(OH)C*H*$_3$, J=6.0 Hz), 0.82 (t, 3H, CH_3, J=7.0 Hz); HRMS (EI) m/e: 159.1624 (calc. for $C_9H_{21}NO(M^+)$: 159.1623).

(*R*)-(+)-*N,N*-Dipropyl-1-phenylethylamine (6). This compound was synthesized from (*R*)-(+)-*N,N*-dipropyl-1-phenylethylamine (4 g, 33 mmol) and propyl iodide (11 g, 65 mmol) as described for **4**. The product was purified over a silica gel column (eluent 1% MeOH in $CHCl_3$, v/v). Yield 45% of **6** as a colorless oil: R_f= 0.2 (silica gel, eluent 1% MeOH/$CHCl_3$, v/v); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.27 (m, 5H, Ph), 3.83 (q, 1H, C*H*CH_3N, J=7.2 Hz), 2.30 (m, 4H, NCH_2),1.33 (m, 7H, CH_2 and $NCCH_3$), 0.87 (t, 6H, CH_3, J=6.3 Hz); HRMS (EI) m/e: 205.1831 (calc. for $C_{14}H_{23}N(M^+)$: 205.1830).

***N,N*-Dipropylbenzylamine (7)** This compound was synthesized from benzylamine (4 g, 37 mmol) and propyl iodide (15 g, 88 mmol) as described for **4**. The product was purified over a short silica gel column (eluent diisopropylether). Yield 77% of **7** as a colorless oil. Spectroscopic data were in accordance with previously reported values.[20] HRMS (EI) m/e: 191.1675 (calc. for $C_{13}H_{21}N(M^+)$: 191.1674).

General procedure for the Baylis-Hillman reaction. Benzaldehyde (212 mg, 2 mmol), acrylonitrile (212 mg, 4 mmol), the amine catalyst (100 mg of a 10 mol % solution in THF) and THF (1.27 g) were weighted into a flask. To this mixture a small amount of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide was added. A Teflon reaction vessel (0.7 or 1.5 ml) was filled with the reaction mixture and sealed with a screw. The conversions were determined as follows: for concentrated samples (little or no solvent), the reaction mixture was transferred quantitatively into a NMR tube after pressure release. Conversions were determined by comparing the integrals of the aldehyde peak and the vinyl protons of the allyl alcohol in the ^{1}H-NMR spectra of the samples. Conversions were also checked by GC analyses of the reaction mixture. For less concentrated samples conversions were determined by GC. Then the reaction mixture was concentrated and checked by NMR. The yields determined by both methods were in good agreement. For 3,5-dihydroxybenzaldehyde the conversion was checked by ^{1}H-NMR after evaporation of the volatile products.

Acrylonitrile can polymerize with strong evolution of heat under high pressure conditions [21], especially when concentrations are to high (> 20 volume %). Therefore most experiments were performed at less then 20 volume %. Furthermore the reactions were performed in small reaction vessels (0.7 or 1.5 ml). Care should be taken when repeating the experiments with high acrylonitrile concentration on a larger scale.

2-(1-Hydroxy-1-phenylmethyl)acrylonitrile. After the reaction the solvent was evaporated and the product was purified over a silica gel column (eluent EtOAc/n-hexane, 1:2, v/v). The analytical data of this compound were the same as those reported in the literature.[22]

2-(1-Hydroxy-1-(3',5'-dihydroxybenzyl)acrylonitrile. ^{1}H-NMR (signals from the crude reaction mixture, 90 MHz, $CDCl_3/CD_3OD$ (3:1, v/v)): δ 6.41 (m, 2H, ArH), 6.33 (m, 1H, ArH), 6.1 and 6.0 (2x s, 2H, CH_2=C(CN)), 5.13 (br s, 1H C*H*(OH)).

References and notes.

1 Schuurman, R.J.W.; Ph.D.Thesis, Nijmegen, 1994. Sijbesma, R.P.; Nolte, R.J.M. *J.Org.Chem.* **1991**, *56*, 3122.

2 Schuurman, R.J.W.; Grimbergen, R.P.F.; Scheeren, J.W. and Nolte, R.J.M. accepted for publication in *Recl.Trav.Chim.Pays-Bas.* All compounds were fully characterized.

3 Drewes, S.E., Roos, G.H.P., *Tetrahedron,* **1988**, *44,* 4653.

4 Baylis, A.B.; Hillman, M.E.D., German Patent 2155113, 1972. *Chem.Abrstr.* **1972**, *77,* 34174q.

5 Ameer, F.; Drewes, S.E.; Freese, S.; Kaye, P.T., *Synthetic.Comm.*, **1988**, *18*, 495.

6 Drewes, S.E.; Roos, G.H.P. *Tetrahedron* **1988**, *44* , 4653.

7 van Rozendaal, E; *Thesis*, **1994**, Nijmegen.

8 Gilbert, A; Heritage, T.W.; Isaacs, N.S. *Tetrahedron : Asymmetry* **1991**, *2* , 969.

9 Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.

10 Hill, J.S.; Isaacs, N.S.; *J.Chem.Research(S)* **1988**, 330.

11 Isaacs, N.S.; Hill, J.S.; Netherlands Patent NL 8500804,1985.

12 Some of the experiments presented in Tables I and II were also performed at 1 bar. For model compounds **3**, **5** and **6**, and receptors **1d** and **1e** even after 500 hrs no product could be detected. (reaction conditions: acrylonitrile, 0.16 M; benzaldehyde, 0.1 M; amine catalyst 10-15 Mol%, solvent $CHCl_3$)

13 Hydrogen bond formation leads to a volume decrease of *ca.* 4 cm^3/ mole, see: le Noble, W.J. in *High Pressure Chemistry and Biochemistry*, D. Reidel Publishing Company, Dordrecht, 1987, 284.

14 Bode, M.L.; Kaye, P.T. *Tetrahedron Lett.* **1991**, *32*, 5611.

15 The formation of 1:1 complexes between 3,5-dihydroxybenzaldehyde and receptors **1** follows from the following experiments: when a solution of one the receptors in $CDCl_3$, to which was added an excess of 3,5-dihydroxybenzaldehyde, was filtered, approx. 1 equiv. of the aldehyde was left, indicating the formation of 1:1 complexes. More details will be published elswhere.

16 For an example of such an approach see: Seerden, J.P.; Scheeren, J.W. *Tetrahedron Lett.* **1993**, *34*, 2669 and references cited therein.

17 Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of laboratory chemicals*, Pergamon Press, Oxford, 1966, 110.

18 Aben, R.W.M.; Scheeren, J.W. *J.Org.Chem.* **1987**, *52*, 365.

19 Prelog, V.; Rajner, E.; Stern, P. *Helv.Chim.Acta* **1943**, *26*, 1176.

20 Deno, N.C.; Fruit, Jr, R.E. *J.Am.Chem.Soc.* **1968**, *90*, 3502.

21 Scheeren, J.W. in *High pressure chemical synthesis* Jurczak, J.; Baranowski, B.; Eds.; 1989, Elsevier, Amsterdam, 207.

22 Imagawa,T.; Uemura, K.; Nagai, Z.; Kawanisi, H. *Synthetic.Comm.* **1984**, *14*, 1267.

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