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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  $\alpha$ -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  $\pi$ - $\pi$  interactions (See Figure 1).<sup>1</sup> In order to combine a binding site with a chiral catalytic group we recently synthesized a series of receptors functionalized with chiral  $\beta$ -amino alcohols.<sup>2</sup> 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  $\beta$ -amino alcohol contaning chiral receptors as enantioselective supramolecular catalysts for the Baylis-Hillman reaction (Scheme 1) because this reaction is catalyzed by tertiary amines.<sup>3,4</sup> In addition a rate enhancement is observed when an amine is used that contains a hydroxyl function in the  $\beta$ -position (*e.g.* 3-hydroxy-quinuclidine).<sup>5</sup> The tertiary amines of some of the receptors (e.g. **1a** and **1e**) have branches at their  $\alpha$ -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



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.<sup>6</sup> 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.<sup>7</sup> Isaacs reported e.e. values varying from 0-17 % using various

chiral amines as catalyts.<sup>8</sup> The best results obtained sofar with chiral amines were recently reported by Hirama et al.<sup>9</sup> 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.<sup>10,11</sup> 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.<sup>6</sup> Acrylonitrile and benzaldehyde were chosen as the reactants. The possibility of  $\pi$ - $\pi$  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.





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





**Figure 2.** Mechanism of the Baylis-Hillman reaction as proposed by Hill and Isaacs.<sup>10</sup>

### **Results and discussion.**

#### Model compounds.

In preliminary experiments using acrylonitrile, benzaldehyde, and 1a in THF under high pressure<sup>12</sup> 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



Yield%	8528000990098288
T/°C	222222222222222222222222222222222222222
ų	21433088823166111 2143308823366116 21433088233669116
Pressure /Kbar	2424444222222222222
Solvent	Meco:
Conc. of catalyst <sup>b</sup> /mol%	010 0.11 13.8 0.0 0.0 0 0.0 0 0 0 0 0 0 0 0 0 0 0 0
Catalyst	<b>昭昭昭昭昭昭</b> 5995555550000409700 NNNNNNN
Benzaldehyde/M	6.2 3.5 0.0 0.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0
Acrylonitrile/M	20080000000000000000000000000000000000
Entry	-964200890111114591

Table I- Baylis-Hillman Reaction of Benzaldehyde with Acrylonitrile under High Pressure in the Presence of Model Compounds.<sup>a</sup>

<sup>a</sup> Product is 2-(1-hydroxy-1-phenylmethyl)acrylonitrile. In some cases (entries 3 and 8-17) a small amount of 5-*iert*-butyl-4-hydroxy-2-methylphenyl sulfide was added to the reaction mixture. b Based on benzaldehyde.

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Table II-	Baylis-Hillman Reaction	on of Benzaldehyde with	Acrylonitril	e under High	Pressure in the Pres	ence of Rece	ptors 1. <sup>a</sup>		
Entry	Acrylonitrile/M	Benzaldehyde/M	Receptor	Catalyst/ Mol%b	Solvent Pre	ssure Cbar	г Ч	ç Q	rield/%
-	76	13	41	9	тнг	15	74	00	6
- (						25			> c
7	7.0	1.0	TC	D	1 HL	71	0	50	>
en.	0.16	0.1	1d	15	THF	14	80	20	0
4	0.16	0.1	ld	15	CDCJ	14	66	20	45
ŝ	0.16	0.1	1d	15	CDC,	15	19	20	95
9	0.16	0.1	le	16	CDCI3	15	19	50	Ŷ
<sup>a</sup> Product is	2-(1-hydroxy-1-phenylmethy	d)acrylonitrile. In all cases a sr	nall amount of 5	6- <i>tert</i> -butyl-4-hy	droxy-2-methylphenylsulfi	de was added t	o the reaction	mixture.	
<sup>b</sup> Based on 1	senzaldehyde.								
Table III 1. <sup>a</sup>	- Baylis-Hillman React	tion of 3,5-Dihydroxyber	ızaldehyde w	vith Acryloni	trile under High Pres	sure in the F	resence of	Triethyl	amine or
Entry	Acrylonitrile/M	3,5-Di-hydroxy- benzaldehyde/M	Catalyst	Mol% <sup>b</sup>	Solvent (v/v)	Pressure /Kbar	Ł	TPC	Yield/%
-	0.15	0.07	Et.N	15	MeCN/CHCl <sub>2</sub> (1.1)	14	99	00	c
• ~	0.15	0.07	EtaN	20	MeCN/CHCla(2:3)	15	9 E	36	> <b>'</b> Ç
l m	0.15	0.07	EtaN	26	THF/CHCl <sub>3</sub> (1:1)	16	69	50	6
4	0.15	0.07	EtaN	19	THF/CHCl3 (1:1)	15	19	50	75
ŝ	0.15	0.07	Id	15	THF/CHCI3 (1:1)	15	17	50	0
9	0.15	0.07	1d	15	MeCN/CHCl <sub>3</sub> (1:1)	15	17	50	0
7	0.15	0.07	1d	16	CHCl <sub>3</sub> /2-pro-	15	19	50	30
			,		panol(10:1)				
œ	0.15	0.07	le	16	CHCl <sub>3</sub> /2-pro- panol(10:1)	15	19	50	0
<sup>a</sup> Product is b Based on a	2-(a-hydroxy(3,'5'-dihydroxy Ildehyde.	/)benzyl)acrylonitrile. In all cas	ses a smail amou	int of <i>5-tert-</i> buty	-l-4-hydroxy-2-methylphen	ıyl-sulfide was a	added to the	eaction mi	kture.

The performance of tertiary amines as catalysts

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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<sup>13</sup> 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  $\alpha$ -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  $\alpha$ -branches prevent attack of the lone pair of the amine on the double bond of acrylonitrile. Furthermore  $\alpha$ -branching probably forces tertiary amines in a more sp<sup>2</sup> 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<sup>3</sup> 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<sup>14</sup> 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<sub>3</sub>. 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 <sup>1</sup>H-NMR using a shift reagent. The e.e. turned out to be less than 5%. For receptor 1e, which has branches at the  $\alpha$ -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.<sup>15</sup> As this aldehyde is virtually insoluble in chloroform we had to use mixtures of solvents. In preliminary experiments with Et<sub>3</sub>N 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<sub>3</sub> 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  $\alpha$ -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  $\alpha$ -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<sup>16</sup> enantioselectivity may be induced by donor-acceptor interactions of the reactants with the chiral ligand.

### **Experimental** section

**General.** <sup>1</sup>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 F254 plates. n-Hexane was distilled prior to use. Benzaldehyde was purified as described in the literature.<sup>17</sup> The synthesis and the procedure for drying of the receptors is described in an other paper.<sup>2</sup> THF was distilled from sodium ketyl prior to use. CDCl<sub>3</sub> and MeCN were dried over 4 Å molecular sieves. CHCl<sub>3</sub> for the catalytic experiments was purified according to a literature procedure.<sup>17</sup> 3,5-Dihydroxybenzaldehyde was a commercial product and purified over a short column of silica gel (eluent, 2% MeOH/CHCl<sub>3</sub>, 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.<sup>18</sup> 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-1butanol, 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<sub>3</sub>, 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.<sup>19</sup> R<sub>f</sub>=0.46 (silica, eluent 10% MeOH/CHCl<sub>3</sub>, v/v),  $[\alpha]^D_{20}$ =-86,9°(c=1.0, CHCl<sub>3</sub>); <sup>1</sup>H-NMR(90 MHz, CDCl<sub>3</sub>):  $\delta$  3.53 (d, 1H, CHHOH, J=10.0 Hz), 3.47 (d, 1H, CHHOH, J=10.0 Hz), 3.13 (t, 1H, OH, J=10.0 Hz), 2.46 (m, 5H, NCH and NCH<sub>2</sub>), 1.92 (m, 6H, CH<sub>2</sub>), 0.84 (t, 9H, CH<sub>3</sub>, 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<sub>2</sub>CO<sub>3</sub>, 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<sub>2</sub>CO<sub>3</sub> 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); <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 90 MHz):  $\delta$  3.89-3.42 (m, 2H, C(OH)*H* and OH), 2.69-1.98 (m, 6H, NCH<sub>2</sub>), 1.49 (m, 4H, CH<sub>2</sub>), 1.04 (d, 3H, C(OH)*CH*<sub>3</sub>, J=6.0 Hz), 0.82 (t, 3H, CH<sub>3</sub>, J=7.0 Hz); HRMS (EI) m/e: 159.1624 (calc. for C<sub>9</sub>H<sub>21</sub>NO(M<sup>+</sup>): 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<sub>3</sub>, v/v). Yield 45% of 6 as a colorless oil:  $R_{f^{\pm}}$  0.2 (silica gel, eluent 1% MeOH/CHCl<sub>3</sub>, v/v); <sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>):  $\delta$  7.27 (m, 5H, Ph), 3.83 (q, 1H, CHCH<sub>3</sub>N, J=7.2 Hz), 2.30 (m, 4H, NCH<sub>2</sub>),1.33 (m, 7H, CH<sub>2</sub> and NCCH<sub>3</sub>), 0.87 (t, 6H, CH<sub>3</sub>, J=6.3 Hz); HRMS (EI) m/e: 205.1831 (calc. for C<sub>14</sub>H<sub>23</sub>N(M<sup>+</sup>): 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 disopropylether). Yield 77% of 7 as a colorless oil. Spectroscopic data were in accordance with previously reported values.<sup>20</sup> 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 <sup>1</sup>H-NMR spectra of the samples. Conversions were determined by GC analyses of the reaction mixture. For less concentrated samples conversions were determined by OGC. 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 <sup>1</sup>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.<sup>22</sup>

**2-(1-Hydroxy-1-(3',5'-dihydroxybenzyl)acrylonitrile**. <sup>1</sup>H-NMR (signals from the crude reaction mixture, 90 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD (3:1, v/v)):  $\delta$  6.41 (m, 2H, ArH), 6.33 (m, 1H, ArH), 6.1 and 6.0 (2x s, 2H, CH<sub>2</sub>=C(CN)), 5.13 (br s, 1H CH(OH)).

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