



## Enantioselective Conjugate Addition of Diethylzinc to Chalcones Catalysed by Chiral Ni(II) Aminoalcohol Complexes

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**Abstract:** Conjugate addition of diethylzinc to chalcones is catalysed by complexes prepared *in situ* from Ni(acac)<sub>2</sub> and *cis-exo-N,N*-dialkyl-3-aminoisoborneols or (+)-*cis-endo-N,N*-dimethyl-3-aminoborneol ((+)-DAB) (**13b**). The products are obtained with enantioselectivities up to 84 %. When scalemic (-)-*cis-exo-N,N*-dimethyl-3-aminoisoborneol ((-)-DAIB) (**3c**) was employed in the reaction a positive nonlinear relationship was found. Several factors which govern catalyst activity and enantioselectivity have been investigated.

### INTRODUCTION

A major synthetic challenge is the development of methodology for catalytic enantioselective C-C bond formation. Among these, the catalytic enantioselective addition of organometallic reagents to aldehydes has been studied extensively.<sup>1</sup> Reports on chiral catalysts for conjugate addition reactions of organometallic reagents are rare.<sup>2</sup> Excellent selectivities have been reached in the synthesis of  $\beta$ -substituted ketones using stoichiometric or excess amounts of chiral organocopper reagents.<sup>3</sup> Catalytic enantioselective additions of Grignard reagents to cyclohexenone have been demonstrated with chiral zinc(II)<sup>4</sup> and copper(I) complexes.<sup>5,6,7</sup>

Based on earlier work of Green *et al.*<sup>8</sup>, Soai and co-workers developed an enantioselective modification of the nickel catalysed alkyl transfer from diorganozinc reagents to enones.<sup>9</sup> With *N,N*-dialkylnorephedrine as chiral ligand and 2,2'-bipyridine as additional achiral ligand, the products could be obtained with enantioselectivities up to 90 %. Similar results were obtained by Bolm and co-workers using C<sub>2</sub>-symmetric bipyridines or substituted chiral pyridines as ligands in the same reaction.<sup>10</sup> We found that comparable enantioselectivities could be reached with *cis-exo-N,N*-dimethyl-3-aminoisoborneol as chiral ligand.<sup>11</sup> Recently, others have shown that a chiral tricarbonyl(1,2-disubstituted arene)chromium complex,<sup>12</sup> chiral *t*-butylaminocarbonylpyrrolidine acetylacetonate Ni(II) hexafluorophosphate and their corresponding complexes supported on inorganic matrices<sup>13</sup> are enantioselective as well, in the nickel catalysed conjugate addition of diethylzinc to chalcone. While these efforts represent a significant advance in this field, there is yet no general solution to the problem of achieving efficient catalytic enantioselective conjugate addition.

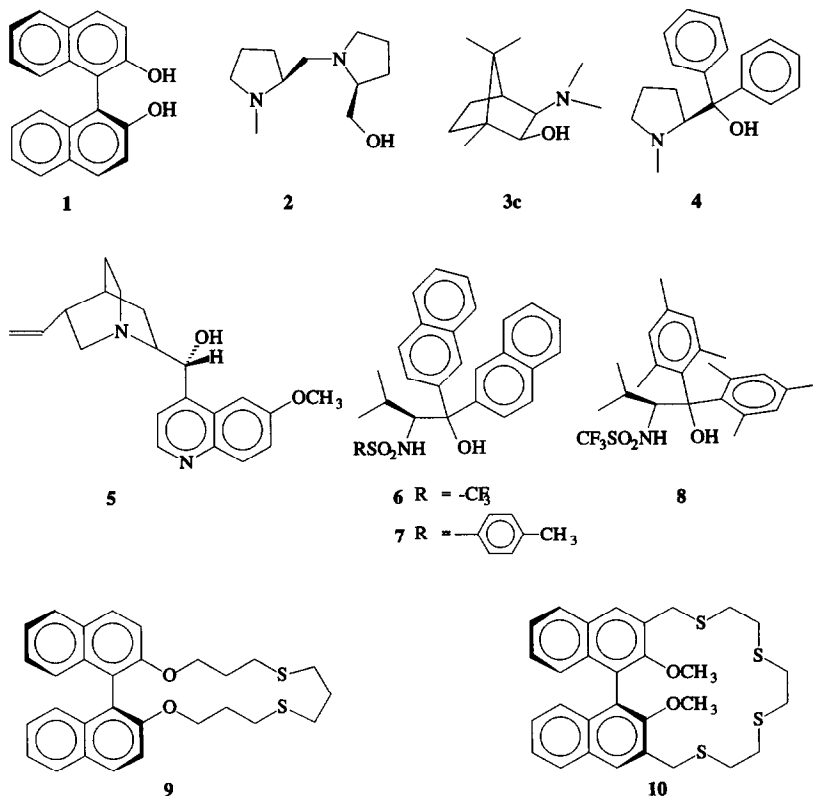
In this article we describe details of our investigation on the nickel/aminoalcohol catalysed

conjugate addition of diethylzinc to chalcones. This study was initiated by the challenging goal of developing an efficient catalyst for the enantioselective conjugate addition of organometallic reagents. Several years ago, we investigated the conjugate addition of Grignard reagents using an organozincate with either a chiral diamine or a chiral alkoxide ligand.<sup>14</sup> With these chiral zinc(II) complexes we were able to catalyse the enantioselective 1,4-addition to enones.<sup>4,14b</sup> Mainly due to competitive uncatalysed conversion of enones by Grignard reagents, the enantioselectivity did not exceed 33 %. Therefore, we decided to study the nickel catalysed conjugate addition of less reactive dialkylzinc to enones. Our initial approach was to screen a number of ligands in order to find a catalyst capable of reaching a high degree of enantioselectivity.

## RESULTS AND DISCUSSION

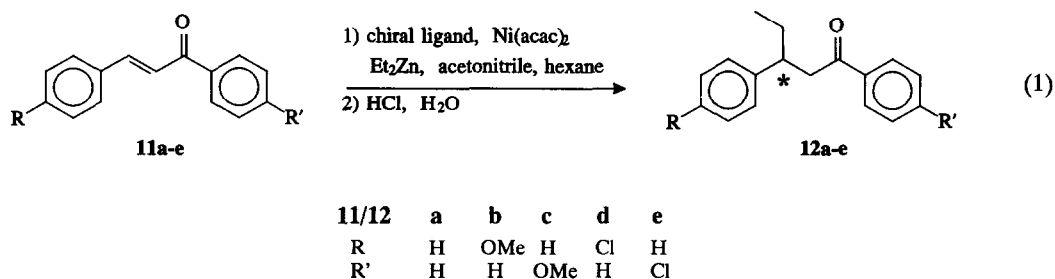
### *Initial experiments*

In order to find a good ligand which could be modified systematically to optimise the enantioselectivity, we examined ten chiral ligands (see Fig. 1). Compounds **1**, **2**, **3c**, **4** and **5**, also used successfully in the 1,2-addition of dialkylzinc to benzaldehyde,<sup>1</sup> were either obtained commercially or synthesised using published procedures. Compounds **6-8** and **9** and **10** were synthesised in this laboratory from *L*-Valine<sup>15</sup> and bis- $\beta$ -naphthol<sup>16</sup> respectively. Compounds **1-10** were used as chiral ligand in the



**Fig. 1.** Structures of the chiral ligands **1-10**.

nickel catalysed conjugate addition of diethylzinc to chalcone (**11a**, eq. 1). Reactions were run on a 1mmol scale. In general a solution of 7 mol % Ni(acac)<sub>2</sub> and 16 mol % chiral ligand in 2 ml acetonitrile was heated to reflux for 1 hour, then substrate was added at room temperature followed by 1.5 ml diethylzinc in hexane (1 M) at -30°C. The product 1,3-diphenylpentanone was isolated by standard techniques and the enantiomeric excess determined by HPLC (see experimental). The results of these reactions are shown in Table 1. Good chemical yields of **12a** were obtained in most cases.



**Table 1.** Enantioselective conjugate addition of diethylzinc to chalcone **11a** (eq. 1).<sup>a</sup>

entry	ligand	yield, <sup>b</sup> %	ee, <sup>c</sup> %	abs. conf. <sup>d</sup>
1	<b>1</b>	87	0	-
2	<b>2</b>	92	8	<i>R</i>
3	<b>3c</b>	94	59	<i>R</i>
4	<b>4</b>	94	25	<i>R</i>
5	<b>5</b>	89	5	<i>S</i>
6	<b>6</b>	96	2	<i>R</i>
7	<b>7</b>	98	2	<i>R</i>
8	<b>8</b>	97	6	<i>R</i>
9	<b>9</b>	63	2	<i>R</i>
10	<b>10</b>	76	3	<i>R</i>

a. Reactions at -30°C in 2 ml acetonitrile and 1.5 ml hexane using an *in situ* prepared catalyst from 7 mol % Ni(acac)<sub>2</sub> and 16 mol % chiral ligand (see text and experimental). Reaction time 16 hours. b. Isolated yield of crude product. Conversion > 95 % (based on GC analysis). c. Determined by HPLC analysis: Daicel, Chiralcel OD; 0.25 % *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm). d. Comparison of retention times with known data gave the absolute configuration of **12a**.<sup>10c</sup>

The yields using thia crown ether ligands **9** or **10** were slightly lower, possibly due to shielding of the nickel catalyst by one or two crown ethers. Significant enantiomeric excesses were only obtained for (-)-*cis-exo-N,N*-dimethyl-3-aminoisoborneol ((-)-DAIB) (**3c**)<sup>17,18,19,20,21</sup> and (+)-diphenyl(1-methylpyrrolidin-2-yl)-methanol ((+)-DPMPM) (**4**).<sup>22,23</sup> It is noted that both ligands are β-aminoalcohols. Bis-β-naphthol (**1**), (2*S*,2'*S*)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]-pyrrolidine (**2**), quinine (**5**), β-hydroxysulfonamides **6-8** and mixed crown ethers **9** and **10** gave low enantioselectivities, indicating that very specific ligand properties are required for enantioselective catalysis.

*Variation of the catalyst composition*

Since (-)-DAIB gave the highest ee in the nickel catalysed conjugate addition we selected this ligand for further studies. First we examined the effect of additional achiral amine ligands which showed to be essential to obtain high ee's in a related system.<sup>9c</sup> With piperidine or 2,2'-bipyridine (1 eq. with respect to nickel) the ee raised to 70 % and 85 % respectively in the addition of diethylzinc to chalcone (eq. 1).<sup>11</sup> It should be emphasised that after careful examination of the chiral ligand employed it appeared that slightly polluted (-)-DAIB was used.<sup>17</sup> After exhaustive purification isomerically pure (-)-DAIB was obtained (see experimental). When we employed pure (-)-DAIB<sup>24</sup> the ee of **12a** raised from 59 to 65 % but the promoting effect on the enantioselectivity of additional achiral ligands disappeared (Table 2, entries 1-4). A slight colour change from green to brown was observed when 2,2'-bipyridine was added, but no significant change in yield or ee occurred. Probably (+)-*cis-endo-N,N*-dimethyl-3-aminoborneol ((+)-DAB) (**13b**, Fig. 2) or another stereoisomer in combination with (-)-DAIB and 2,2'-bipyridine was responsible for the substantial improvement of the enantioselectivity.<sup>25</sup> The use of a weighed combination of 15 mol % (-)-DAIB and 2 mol % (+)-DAB with 7 mol % of 2,2'-bipyridine however, resulted in **12a** with only 55 % ee (entry 5), indicating that the highest enantioselective 1,4-addition could not be reproduced with this mixed ligand system.

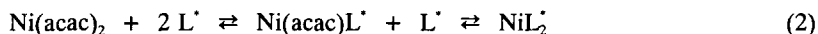
**Table 2.** Effect of catalyst composition on the enantiomeric excess of **12a** (eq. 1).<sup>a</sup>

entry	ligand, mol %	nickel salt, mol %	add. ligand, mol %	yield, <sup>b</sup> %	ee, <sup>b</sup> %	abs. conf. <sup>b</sup>
1	<b>3c</b> , 16	Ni(acac) <sub>2</sub> , 7	-	81	65	<i>R</i>
2	<b>3c</b> , 16	Ni(acac) <sub>2</sub> , 7	2,2'-bipyridine, 7	82	64	<i>R</i>
3	<b>3c</b> , 16	Ni(acac) <sub>2</sub> , 7	2,2'-bipyridine, 12	86	63	<i>R</i>
4	<b>3c</b> , 20	Ni(acac) <sub>2</sub> , 7	2,2'-bipyridine, 7	90	69	<i>R</i>
5	<b>3c</b> , 15, <b>13b</b> , 2	Ni(acac) <sub>2</sub> , 7	2,2'-bipyridine, 7	74	55	<i>R</i>
6	<b>3c</b> , 16	Ni(acac) <sub>2</sub> , 8	-	82	55	<i>R</i>
7	<b>3c</b> , 16	Ni(acac) <sub>2</sub> , 3	-	79	70	<i>R</i>
8	<b>3c</b> , 16	Ni(acac) <sub>2</sub> , 1	-	69	72	<i>R</i>
9	<b>3c</b> , 2	Ni(acac) <sub>2</sub> , 0.4	-	69	31	<i>R</i>
10	<b>3c</b> , 0.2	Ni(acac) <sub>2</sub> , 0.04	-	71	6	<i>R</i>
11 <sup>c</sup>	<b>3c</b> , 10	-	-	nd <sup>d</sup>	6	<i>S</i>
12 <sup>c</sup>	<b>3c</b> , 20	-	-	nd <sup>d</sup>	15	<i>S</i>
13 <sup>c</sup>	<b>3c</b> , 50	-	-	nd <sup>d</sup>	21	<i>S</i>
14 <sup>e</sup>	<b>3c</b> , 20	-	-	nd <sup>d</sup>	16	<i>S</i>
15	<b>3c</b> , 16	NiBr <sub>2</sub> , 7	-	80	39	<i>R</i>
16	<b>3c</b> , 16	NiBr <sub>2</sub> , 7	2,2'-bipyridine, 7	74	54	<i>R</i>
17	<b>3c</b> , 8, <b>13b</b> , 8	Ni(acac) <sub>2</sub> , 7	2,2'-bipyridine, 7	74	13	<i>S</i>

a. Reaction conditions see Table 1 unless stated otherwise. b. See Table 1. c. 0.5 mmol chalcone (**11a**). Reaction time 4 days at room temperature, in 3.5 ml hexane. d. nd: crude yield was not determined, conversion > 95 % (based on GC analysis). e. 0.5 mmol chalcone (**11a**). Reaction time 6 days at room temperature, in 2 ml acetonitrile and 1.5 ml hexane.

The ee of **12a** showed to be dependent on the ligand-to-nickel ratio and the concentration. With more Ni(acac)<sub>2</sub> and the same amount of chiral ligand the ee was lowered to 55 % (entry 6). By decreasing the amount of Ni(acac)<sub>2</sub> to 3 or 1 mol% the enantiomeric excess increased to 70 and 72 % respectively (entries 7 and 8). By decreasing the concentration of chiral ligand and Ni(acac)<sub>2</sub> the ee of **12a** dropped dramatically (entries 9 and 10). In order to obtain **12a** with a considerable ee, an

appropriate ligand-to-nickel ratio and chiral ligand concentration is required. We also demonstrated (*vide infra*) that the enantioselective catalyst presumably is a diastereomeric mononuclear nickel complex (see Fig. 3, **15a**). With a low concentration of chiral ligand the concentration of enantioselective catalyst ( $[\text{NiL}_2^*]$ ) is small. The asymmetric induction could well depend on the equilibrium between chiral nickel complexes ( $\text{NiL}_2^*$ ) and catalytically active nickel species ( $\text{Ni}(\text{acac})_2$ ,  $\text{Ni}(\text{acac})\text{L}^*$ ) which produce racemic material (see eq. 2).



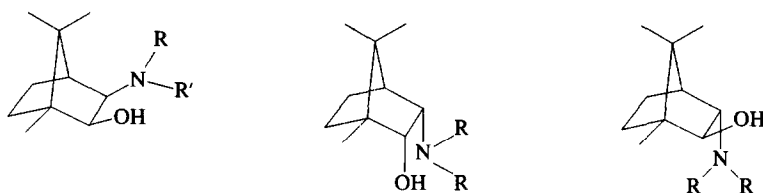
Without the nickel salt, but in the presence of 10, 20 or 50 mol % of **3c** complete conversion is only achieved after 4 days (in hexane) or 6 days (in acetonitrile/hexane) at room temperature. The *S*-enantiomer was formed in a slight excess ( $ee \leq 21\%$ , entries 11-14).

The use of  $\text{NiBr}_2$  instead of  $\text{Ni}(\text{acac})_2$  resulted in a relatively slow conversion of **11a** (90 % after 16 hours) and a moderate  $ee$  of **12a** (entry 15). With 7 mol % of 2,2'-bipyridine the  $ee$  of **12a** increased to 54 % (entry 16). The slow conversion and relatively small  $ee$ 's probably are a consequence of the poor solubility of  $\text{NiBr}_2$  in acetonitrile. An attempt to create a catalyst consisting of nickel, (-)-DAIB and stereoisomer (+)-DAB failed. With 8 mol % of (-)-DAIB and 8 mol % of (+)-DAB the *S*-enantiomer of **12a** was isolated with 13 %  $ee$  (entry 17).

#### Variation of the ligand structure

In an attempt to improve the enantioselectivity in the conjugate addition we turned our attention to the ligand structure. Since many asymmetric reactions require steric bulk in order to reach high enantioselectivities, we synthesised, according to standard *N*-alkylating procedures, *N*-mono- and *N*-di-alkylated aminoisoborneols **3b-f** (see Fig. 2). The alkylation of *cis-exo*-3-aminoisoborneol (**3a**), derived of (+)-camphor,<sup>18</sup> with excess of methyl iodide, 1,3-dibromopropane or 1,4-dibromobutane gave ligands **3c-e**. The enantiomeric purity was determined by  $^{31}\text{P}$  NMR. Derivatisation of racemic **3c** or **3d** with chiral trivalent diazaphospholidines in  $\text{C}_6\text{D}_6$  gave two base line separated absorptions in the decoupled  $^{31}\text{P}$  NMR spectrum. With enantiomerically pure **3c** or **3d** only one signal was found.<sup>24</sup>

In an attempt to synthesise *N,N*-diethyl-3-aminoisoborneol following the same procedure as described above we could only isolate the mono alkylated ligand **3f**. *N*-methyl-3-aminoisoborneol



<b>3a</b>	R = R' = H		
<b>3b</b>	R = CH <sub>3</sub> , R' = H		
<b>3c</b>	R = R' = CH <sub>3</sub>	<b>13a</b>	R = H
<b>3d</b>	R, R' = (-CH <sub>2</sub> ) <sub>3</sub>	<b>13b</b>	R = CH <sub>3</sub>
<b>3e</b>	R, R' = (-CH <sub>2</sub> ) <sub>4</sub>		
<b>3f</b>	R = C <sub>2</sub> H <sub>5</sub> , R' = H	<b>14a</b>	R = H
		<b>14b</b>	R = CH <sub>3</sub>

Fig. 2. Structures of ligands **3a-f**, **13a,b** and **14a,b**.

**Table 3.** Effect of ligand structure on ee of **12a**<sup>a</sup>

entry	ligand, 16 mol %	yield, <sup>b</sup> %	ee, <sup>b</sup> %	abs. conf. <sup>b</sup>
1	<b>3a</b>	nd <sup>c</sup>	0	-
2	<b>3b</b>	85	4	<i>R</i>
3	<b>3c</b>	81	65	<i>R</i>
4	<b>3d</b>	78	33	<i>R</i>
5	<b>3e</b>	nd <sup>c</sup>	35	<i>R</i>
6	<b>3f</b>	84	7	<i>R</i>
7	<b>13b</b>	82	79	<i>S</i>
8	<b>14b</b>	82	4	<i>R</i>
9 <sup>d</sup>	<b>13b</b>	87	82	<i>S</i>
10 <sup>e</sup>	<b>13b</b>	74	84	<i>S</i>

a. Reaction conditions see Table 1 unless stated otherwise. b. See Table 1. c. See Table 2. d. With 7 mol % 2,2'-bipyridine. e. With 1 mol % Ni(acac)<sub>2</sub>.

((+)-MAIB) (**3b**) was prepared from **3a** according to a literature procedure.<sup>26</sup> The results of the catalytic 1,4-addition using various amino(iso-)borneols as chiral ligand are summarised in Table 3. Unfortunately we found that the other *N,N*-dialkylated aminoisoborneols are less enantioselective than **3c** (entries 4 and 5). Probably azetidiny- and pyrrolidinyl-isoborneol are not flexible enough to create an enantioselective nickel catalyst. The *N,N*-dialkylgroup, especially *N,N*-dimethyl, was found to be essential to reach high enantioselectivity because isoborneol **3a** and *N*-monoalkyl isoborneols **3b** and **3f** gave **12a** with small ee's (entries 1,2 and 6). *trans-N,N*-Dimethyl-3-aminoisoborneol (**14b**), prepared from *trans*-3-aminoisoborneol (**14a**),<sup>18</sup> gave an almost racemic product indicating the necessity of *cis*-configuration of the alcohol and the tertiary amine moieties (entry 8). With pure (+)-DAB, derived from *cis-endo*-3-aminoborneol (**13a**)<sup>27</sup> in the same way as described for (-)-DAIB, **12a** was obtained with 79 % ee (entry 7). The enantioselectivity could be slightly enhanced by using an additional achiral ligand or by decreasing the amount of Ni(acac)<sub>2</sub> to 1 mol % (entries 9 and 10).

#### *Variation of substrate, solvent, temperature and reagent*

With (-)-DAIB (**3c**) as chiral ligand we varied the substrate, solvent and reaction temperature. Substituted chalcones **11b-e** were alkylated with good conversion using the standard reaction conditions (eq. 1). Methoxy and chloro substituents at either of the aromatic rings were tolerated and ee's in the range of 51 to 61 % were achieved (Table 4, entries 1-4). To ensure the correct assignment of the HPLC signals, racemic products were analogously synthesised by nickel catalysis and analysed by the same method.<sup>10c</sup> No addition occurred when 3-nitrochalcone was used (entry 5).

Studies of the reaction conditions have shown that acetonitrile or propionitrile as solvent is essential to reach high enantioselectivity.<sup>9,10</sup> With butyronitrile instead of acetonitrile the same degree of asymmetric induction in the conjugate addition was found (entry 6). Decreasing the reaction temperature did enhance the enantioselectivity (entry 7-9), especially for butyronitrile. When we employed 16 mol % of (+)-DAB (**13b**) in propionitrile at -50°C the *S*-enantiomer of **12a** could be obtained with 84 % ee (entry 10).

No major change in enantioselectivity was observed when dimethylzinc in toluene instead of diethylzinc in hexane was used in the conjugate addition to chalcone (entry 11).

**Table 4.** Enantioselective alkylation of chalcones using **3c**. Variation of solvent and temperature.<sup>a</sup>

entry	substrate	solvent	temp. °C	yield, <sup>b</sup> %	ee, <sup>b</sup> %	abs. conf. <sup>b</sup>
1	4-methoxychalcone ( <b>11b</b> )	acetonitrile	-30	nd <sup>c</sup>	57	<i>R</i>
2	4'-methoxychalcone ( <b>11c</b> )	acetonitrile	-30	nd <sup>c</sup>	51	<i>R</i>
3	4-chlorochalcone ( <b>11d</b> )	acetonitrile	-30	nd <sup>c</sup>	61 <sup>d</sup>	<i>R</i>
4	4'-chlorochalcone ( <b>11e</b> )	acetonitrile	-30	nd <sup>c</sup>	59	<i>R</i>
5	3-nitrochalcone ( <b>11f</b> )	acetonitrile	-30	< 10	-	-
6	<b>11a</b>	butyronitrile	-30	nd <sup>c</sup>	69	<i>R</i>
7	<b>11a</b>	butyronitrile	-50	84	81	<i>R</i>
8	<b>11a</b>	propionitrile	-50	77	72	<i>R</i>
9	<b>11a</b>	isobutyronitrile	-50	79	72	<i>R</i>
10 <sup>e</sup>	<b>11a</b>	propionitrile	-50	82	84	<i>S</i>
11 <sup>f</sup>	<b>11a</b>	acetonitrile	-30	nd <sup>c</sup>	59	<i>R</i>

a. Reaction conditions see Table 1 unless stated otherwise. b. See Table 1. c. See Table 2. d. HPLC signals not base line separated. e. With 16 mol % of **13b**. f. With 0.75 ml of dimethylzinc in toluene (2 M).

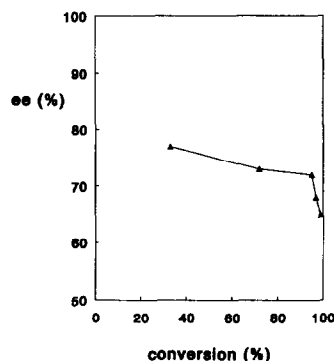
#### Variation of reaction time

In order to gain insight into other factors which influence the reaction, the dependence of the ee of **12a** on reaction time and conversion of **11a** was studied. At various intervals samples of the reaction mixture, using the conditions of entry 1 in Table 2, were taken and the conversion was determined by GC analysis. Table 5 shows a conversion of 97 % of **11a** after 90 minutes. The enantiomeric excess, determined by HPLC analysis, significantly *decreased* with time.<sup>28</sup> Whereas the product isolated after 10 minutes had an ee of 77 %, it had only 68 % ee after 90 minutes. Thus, at higher conversion of **11a**, product **12a** with a lower ee was obtained. This remarkable time dependency might be explained by a mechanism proposed by Bolm.<sup>10c</sup> The organozinc reagent is used to reduce nickel(II) to nickel(I) and nickel(0). Nickel(I) is most likely responsible for an efficient catalysis by electron transfer.<sup>29</sup> In combination with ligand **3c** the nickel(I) species is highly enantioselective. After a certain time the selective catalyst is transformed into species which are still active, but produce racemic material. As a result, the overall ee of the product will decrease with time.

**Table 5.** Effect of reaction time on ee of product **12a**.<sup>a</sup>

entry	reaction time (min)	conversion, <sup>b</sup> %	ee, <sup>c</sup> %
1	10	33	77
2	30	72	73
3	50	95	72
4	90	97	68
5	1260	> 99	65

a. Reaction conditions see Table 1. b. conversion based on GC analysis  
c. See Table 1.



#### Asymmetric amplification

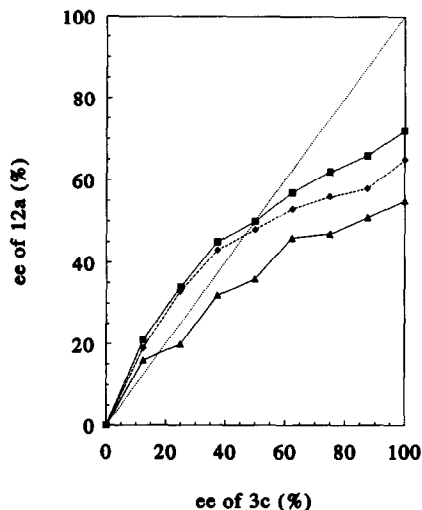
In order to gain more insight in the nature of the catalytically active species, the relationship between the ee of ligand **3c** and product **12a** was determined. Scalemic **3c**<sup>30</sup> with defined ee was employed in the nickel catalysed conjugate addition of diethylzinc to chalcone **11a**. A *positive nonlinear*

relationship was found. The use of **3c** with low ee resulted in the formation of **12a** with higher ee than expected on the basis of a linear relationship. Next, we examined the influence of the ligand-to-nickel ratio on the phenomenon. While the amount of **3c** was kept constant (16 mol %), 1, 7 and 8 mol % Ni(acac)<sub>2</sub> was used as catalyst (see Table 6). A decrease in the amount of Ni(acac)<sub>2</sub> raised the asymmetric amplification factor.

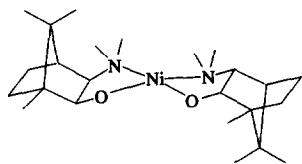
Table 6. Effect of ee of **3c** on ee of **12a**.<sup>a</sup>

ee of <b>3c</b> <sup>b</sup>	ee of <b>12a</b> with mol % of Ni(acac) <sub>2</sub> <sup>c</sup>		
	8 (▲)	7 (◆)	1 (■)
12.5	16	19	21
25	20	33	34
37.5	32	43	45
50	36	48	50
62.5	46	53	57
75	47	56	62
87.5	51	58	66
100	55	65	72

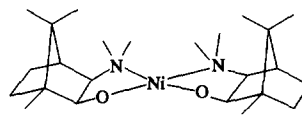
a. Reaction conditions see Table 1. b. Enantiomerically pure (-)-DAIB mixed with racemic DAIB. c. See Table 1.



Nonlinear relationships between ee of chiral auxiliaries and products in asymmetric catalysis were described by Kagan and Agami *et al.*<sup>31</sup> Extensive investigations of non-linear effects were carried out in the enantioselective alkylation of aldehydes.<sup>1a,32</sup> These phenomena have been interpreted in terms of differences in the chemical behaviour of *diastereomeric* dinuclear complexes.<sup>33</sup> The asymmetric amplification in our system can also be explained by the difference in chemical properties of diastereomeric complexes. In the conjugate addition of diethylzinc to chalcone, Sánchez and co-workers used fully characterised nickel complexes where an acetylacetonate anion has been replaced by one equivalent of *N*-alkylaminocarbonylpyrrolidine.<sup>13,34</sup> It is reasonable to assume that two equivalents of scalemic DAIB replace both acetylacetonate anions from Ni(acac)<sub>2</sub> forming diastereomeric *mononuclear* nickel complexes **15a** and **15b** (Fig. 3). Predominant reaction of diethylzinc with



**15a** (2*S*, 3*R*)-DAIB, (2*S*, 3*R*)-DAIB



**15b** (2*S*, 3*R*)-DAIB, (3*S*, 2*R*)-DAIB

Figure 3. Possible diastereomeric nickel complexes (only *cis*-complexes are shown).



the less stable optically active complex **15a** would lead to the formation of a homochiral catalytically active species. The minor enantiomer of the ligand is trapped in the more stable *meso* complex **15b**, and becomes less available for catalyst formation.

#### Concluding remarks

It has been demonstrated that the conjugate addition of diethylzinc to chalcone is effectively catalysed by chiral Ni(II) complexes derived of *cis-exo*- and *cis-endo-N,N*-dimethyl-3-amino(*iso*-)borneols with enantioselectivities up to 84 %. Though the true nature of the catalyst system is still unknown a model is presented based on observed nonlinear effects and this constitutes a starting point for further investigation. There are no unifying views on the ligand structure-enantioselectivity relationship yet.<sup>35</sup> Further investigations will concentrate on the use of other ligands and metals as well as the mechanism and catalyst structure involved in the nickel catalysed 1,4-addition. Studies of alkyl bridged (-)-DAIB moieties, resulting in  $C_2$ -symmetric  $N_2O_2$ -donor ligands, are in progress.

## EXPERIMENTAL

**General** All reaction mixtures were stirred magnetically and a normal atmosphere was used unless stated otherwise. Dichloromethane ( $CH_2Cl_2$ ), ether, and hexane were distilled from  $P_2O_5$  and stored over 4 Å molsieves. Methanol and ethanol were distilled from Mg and stored over 3 Å molsieves. All nitriles and 2-propanol (p.a.) were purchased from Janssen and Merck respectively and were used without further purification.  $^1H$  and  $^{13}C$  NMR spectra were recorded on a Varian Gemini 200 (at 200 and 50 MHz respectively); solvent  $CDCl_3$  unless stated otherwise. The chemical shifts are denoted in  $\delta$  units (ppm) relative to TMS ( $\delta = 0.00$ ) for protons or  $CDCl_3$  ( $\delta = 76.91$ ) for carbon atoms. Splitting patterns for  $^1H$ : s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and for  $^{13}C$  determined with the APT pulse sequence: q (quartet,  $CH_3$ ), t (triplet,  $CH_2$ ), d (doublet, CH), s (singlet, C). Optical rotations: Perkin-Elmer 241 MC (at room temperature). High Resolution Mass Spectra (HRMS): AEI MS-902 spectrometer. Gas liquid chromatograph (GC): Hewlett Packard 5890 II, column: HP-1. HPLC: Waters, Model 480 LC, column: Chiralcel OD, 4.6 x 250 mm.

The following compounds were commercially available and used without further purification: (*S*)-(-)-1,1'-bi-2-naphthol (**1**; Janssen), (2*S*,2'*S*)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (**2**; Merck), quinine (**5**; Janssen), 1,3-diphenylpropanone (chalcone, **11a**; Janssen), all substituted chalcones (**11b-f**; Lancaster), nickel(II)acetylacetonate (anhydr.; Aldrich),  $NiBr_2$  (anhydr.; Janssen), diethylzinc (1 M in hexane; Aldrich, 15 wt % in hexane; Janssen), dimethylzinc (2 M in toluene; Aldrich), 2,2'-bipyridine (Merck), MeI (Merck) and 1,*n*-dibromoalkanes (Janssen).

**Preparation of compounds** *Cis-exo*-3-aminoisborneol (**3a**),<sup>18</sup> *cis-exo-N*-monomethyl-3-aminoisborneol ((+)-MAIB) (**3b**),<sup>26</sup> (+)-diphenyl(1-methylpyrrolidin-2-yl)-methanol ((+)-DPMPM) (**4**),<sup>22</sup>  $\beta$ -hydroxysulfonamides **6-8**,<sup>15</sup> mixed crown ethers **9** and **10**,<sup>16</sup> *cis-endo*-3-aminoborneol (**13a**)<sup>27</sup> and *trans*-3-*endo*-aminoisborneol (**14a**)<sup>18</sup> were prepared according to published procedures.

(-)-*Cis-exo-N,N*-dimethyl-3-aminoisborneol (**DAIB**) (**3c**) Aminoalcohol **3a** (4.00 g, 23.6 mmol), MeI (7.25 g, 51.0 mmol), NaOH (3.0 g, 75 mmol) and 1 ml  $H_2O$  were successively added to 30 ml ether. The mixture was stirred for 16 hours and an additional 2.00 g (14.0 mmol) of MeI was added. After another 24 hours the mixture was poured into 50 ml  $H_2O$ . The two layers were separated and

the water phase was extracted with ether (2 x 30 ml). The combined organic layers were dried with brine (50 ml) and Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave 3.69 g of **3c** as an oil. Purification by bulb to bulb distillation (80-90°C, 0.4 mmHg), column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/methanol (4:1)) and another bulb to bulb distillation (75°C, 0.05 mmHg) provided pure **3c** as a colourless oil (2.10 g, 10.6 mmol, 45%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -14.5° (c 0.93, C<sub>2</sub>H<sub>5</sub>OH) [Lit.<sup>21</sup> [ $\alpha$ ]<sub>D</sub><sup>28</sup> -14.7° (c 4.58, C<sub>2</sub>H<sub>5</sub>OH)] <sup>1</sup>H NMR  $\delta$  0.75 (s, 3H), 0.84-0.99 (m, 2H), 0.94 (s, 3H), 1.04 (s, 3H), 1.30-1.45 (m, 1H), 1.61-1.75 (m, 1H), 1.93 (d, *J* = 4.7 Hz, 1H), 2.20 (d, *J* = 7.1 Hz, 1H), 2.26 (s, 6H), 3.40 (d, *J* = 7.1 Hz, 1H), 4.1-4.4 (bs, 1H). <sup>13</sup>C NMR  $\delta$  11.46 (q), 20.76 (q), 22.06 (q), 27.86 (t), 32.24 (t), 46.30 (s), 47.03 (d), 49.06 (s), 74.13 (d), 78.73 (d), N-CH<sub>3</sub> was not observed due to unknown reason. HRMS calculated for C<sub>12</sub>H<sub>23</sub>NO: 197.178, found 197.177. Racemic DAIB was obtained in a similar manner. (-)-DAIB was enantiomerically pure, as confirmed by <sup>31</sup>P NMR with a chiral derivatising agent.<sup>24</sup>

**General procedure for the *N,N*-dialkylation of primary aminoalcohol **3a**** A mixture of 10 mmol of **3a**, 11 mmol of 1,*n*-dibromoalkane and 25 mmol of K<sub>2</sub>CO<sub>3</sub> in 30 ml ethanol was stirred and refluxed for 16 hours. The mixture was poured into 100 ml H<sub>2</sub>O and extracted with ether (3 x 30 ml). The combined organic layers were dried with brine (50 ml) and Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave a crude oil. Purification by bulb to bulb distillation followed by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/methanol (4:1)) afforded the pure aminoalcohols. The properties of the compounds are as follows:

(-)-*Cis-exo-3-(1-azetidiny)isoborneol (3d)* [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 9.2° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>) <sup>1</sup>H NMR  $\delta$  0.68 (s, 3H), 0.85 (s, 3H), 0.88-0.93 (m, 2H), 0.99 (s, 3H), 1.30-1.45 (m, 1H), 1.53-1.72 (m, 1H), 1.64 (bs, 1H), 2.00-2.15 (quintet, *J* = 7.1 Hz, 2H), 2.55 (d, *J* = 7.1 Hz, 1H), 3.17-3.54 (m, 4H), 3.35 (d, *J* = 7.1 Hz, 1H). <sup>13</sup>C NMR  $\delta$  11.08 (q), 17.33 (t), 20.28 (q), 21.80 (q), 26.88 (t), 32.46 (t), 46.02 (s), 46.68 (d), 49.13 (s), 55.63 (t), 74.89 (d), 78.67 (d). HRMS calculated for C<sub>13</sub>H<sub>23</sub>NO: 209.178, found 209.178

(+)-*Cis-exo-3-(1-pyrrolidiny)isoborneol (3e)* [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 14.8° (c 0.4, CH<sub>2</sub>Cl<sub>2</sub>) <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  0.83 (s, 3H), 0.95 (s, 3H), 1.02-1.08 (m, 2H), 1.12 (s, 3H), 1.45-1.55 (m, 1H), 1.67-1.95 (m and bs, 5H), 2.02 (d, *J* = 4.7 Hz, 1H), 2.66-3.07 (m, 5H), 3.54 (d, *J* = 7.3 Hz, 1H). <sup>13</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  11.40 (q), 20.92 (q), 21.87 (q), 23.86 (t), 27.91 (t), 32.71 (t), 47.23 (s), 50.31 (s), 56.12 (t), 74.84 (d), 78.87 (d). HRMS calculated for C<sub>14</sub>H<sub>25</sub>NO: 223.194, found 223.194

(+)-*Cis-exo-N-ethyl-3-aminoisoborneol (3f)* A mixture of 10 mmol of **3a**, 25 mmol of ethyl iodide and 25 mmol of K<sub>2</sub>CO<sub>3</sub> in 30 ml ethanol was stirred and refluxed for 5 days. The mixture was poured into 100 ml H<sub>2</sub>O and extracted with ether (3 x 30 ml). The combined organic layers were dried with brine (50 ml) and Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave a crude oil. After bulb to bulb distillation (100°C, 0.1 mmHg), column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/methanol (4:1)) and extraction with 1 N NaOH **3f** could be isolated as a colourless oil (40 %). [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 6.4° (c 0.5, C<sub>2</sub>H<sub>5</sub>OH) <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD)  $\delta$  0.73 (s, 3H), 0.86 (s, 3H), 0.90-1.00 (m, 2H), 0.97 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.33-1.47 (m, 1H), 1.58-1.73 (m, 1H), 1.80 (d, *J* = 4.6 Hz, 1H), 2.68-2.92 (m, 3H), 3.53 (d, *J* = 7.4 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD)  $\delta$  10.93 (q), 13.01 (q), 20.69 (q), 21.48 (q), 26.82 (t), 32.37 (t), 44.14 (t), 46.59 (s), 48.84 (s), 49.25 (d), 64.99 (d), 77.56 (d). HRMS calculated for C<sub>12</sub>H<sub>23</sub>NO: 197.178, found 197.178.

(+)-*Cis-endo-N,N-dimethyl-3-aminoborneol (DAB) (13b)* (+)-DAB was prepared from optically active **13a** by the same procedure as described for (-)-DAIB. [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 35.7° (c 1.0, C<sub>2</sub>H<sub>5</sub>OH) <sup>1</sup>H NMR  $\delta$  0.86 (s, 3H), 0.88 (s, 6H), 1.14-1.24 (m, 1H), 1.43-1.51 (m, 2H), 1.66 (t, *J* = 3.8 Hz, 1H), 1.76-1.89 (m, 1H), 2.20 (s, 6H), 2.40 (dd, *J* = 8.5 Hz, *J* = 3.8 Hz, 1H), 3.05-3.43 (bs, 1H), 3.63 (d, *J* = 8.5 Hz). <sup>13</sup>C NMR  $\delta$  14.41 (q), 18.85 (q), 19.01 (t), 20.03 (q), 26.40 (t), 45.13 (q), 46.89 (s), 48.46 (d), 50.27 (s), 66.07 (d), 73.94 (d).

**(+)-Trans-N,N-dimethyl-3-aminoisoborneol (14b)** This compound was prepared from optically active **14a** by the same procedure as described for (-)-DAIB.  $[\alpha]_D^{20} + 18.2^\circ$  (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>) <sup>1</sup>H NMR δ 0.84 (s, 3H), 0.86 (s, 3H), 1.05 (s, 3H), 1.01-1.14 (m, 1H), 1.45-1.65 (m, 3H), 1.77 (t, *J* = 4.1 Hz, 1H), 2.22 (s, 6H), 2.25-2.32 (m, 1H), 3.29 (d, *J* = 3.0 Hz, 1H). <sup>13</sup>C NMR δ 11.43 (q), 19.24 (t), 19.77 (q), 20.90 (q), 34.45 (t), 44.58 (q), 47.03 (s), 48.21 (d), 49.66 (s), 76.90 (d), 84.85 (d).

**Conjugate addition of diethylzinc to chalcone 11a using in situ prepared chiral nickel complexes.** This procedure is typical for all ligands. A solution of 18 mg (0.07 mmol) of Ni(acac)<sub>2</sub> and 32 mg (0.16 mmol) of **3c** in 2 ml acetonitrile was stirred and refluxed for 1 hour under a nitrogen atmosphere. The solution was cooled to room temperature and 208 mg (1.0 mmol) of 1,3-diphenylpropenone (**11a**) was added. The mixture was cooled to -35°C and 1.5 ml of diethylzinc in hexane (1 M, 1.5 mmol) was added. The colour changed immediately from bright green to dark brownred. Stirring was continued at -30°C for 16 hours. The mixture was poured into 15 ml of 3 M HCl and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried with brine (25 ml) and Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave crude **12a**, which was purified by chromatography with a short column (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>). Yields are shown in Table 1-4. The ee was determined by HPLC analysis; Daicel (Chiralcel OD), 0.25 % *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times (*S*)-**12a** 16.3 min; (*R*)-**12a** 19.0 min. *Rac*-**12a** gave two base line separated signals. <sup>1</sup>H NMR δ 0.85 (t, *J* = 7.3 Hz, 3H), 1.60-1.84 (m, 2H), 3.24-3.33 (m, 3H), 7.18-7.33 (m, 5H), 7.41-7.60 (m, 3H), 7.92-7.96 (m, 2H). <sup>13</sup>C NMR δ 12.12 (q), 29.23 (t), 43.00 (d), 45.60 (t), 126.27 (d), 127.65 (d), 128.05 (d), 128.40 (d), 128.52 (d), 132.90 (d), 137.25 (s), 144.67 (s), 199.19 (s).

**Conjugate addition of diethylzinc to the substituted chalcones 11b-e using Ni(acac)<sub>2</sub> and 3c.** The substituted chalcones (**11b-e**) were alkylated as described in the previous procedure. All spectroscopic data were in good agreement with the literature.<sup>9c</sup> Ee's are given in Table 4, entry 1-4.

**Conjugate addition of diethylzinc to chalcone (11a) using Ni(acac)<sub>2</sub>, 3c and additional achiral ligand.** According to the procedure described above the chiral catalyst was prepared *in situ* in refluxing acetonitrile. The solution was cooled to room temperature and 208 mg (1.0 mmol) of **11a** and 11 mg (0.07 mmol) of 2,2'-bipyridine were added. Further following the same procedure as described above gave **12a** (82 %). Ee values of **12a** are given in Table 2, entries 2-5 and Table 3, entry 9.

**Time dependency of the 1,4-addition.** The same procedure as described above was applied and at various time intervals samples of the solution (0.1 ml) were drawn and quenched with 1 ml of 3 N HCl. After extraction with 1 ml CH<sub>2</sub>Cl<sub>2</sub> the conversion was determined by GC analysis. Retention times (oven temperature 225°C, flow 101.8 ml/min He): 1,3-diphenyl-1-pentanone (**12a**), 7.13 min; 1,3-diphenylpropenone (**11a**), 8.25 min. The ee was determined by HPLC analysis. Time, conversion and ee values are given in Table 5.

**Asymmetric amplification.** The enantiomeric excess of (-)-DAIB was adjusted by mixing appropriate amounts of enantiomerically pure (-)-DAIB and *rac*-DAIB to give 32 mg (0.16 mmol) of scalemic ligand. Ni(acac)<sub>2</sub> (0.08, 0.07 or 0.01 mmol) was added and the same procedure as described above was followed. After 16 hours the conversion (> 95 %) was determined by GC analysis (see previous procedure) and the mixture was worked up. The ee of **12a** was determined by HPLC analysis. Ee values of **3c** and **12a** are given in Table 6.

**Conjugate addition, variation of solvent and temperature.** According to the procedure above the chiral catalyst was prepared *in situ* from Ni(acac)<sub>2</sub> and chiral ligand in 2 ml refluxing butyronitrile,

propionitrile or isobutyronitrile. At room temperature the substrate **11a** and subsequently at  $-55^{\circ}\text{C}$  1.5 ml of diethylzinc (1 M in hexane) were added. After 16 hours (temperature  $-50^{\circ}\text{C}$ ) the conversion ( $> 90\%$ ) was determined by GC analysis (see previous procedure) and the mixture was worked up. The ee of **12a** was determined by HPLC analysis. Ee values of **12a** are given in Table 4, entries 6-10.

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#### REFERENCES AND NOTES

- For reviews see: a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
- For catalytic enantioselective Michael addition, see: a) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. b) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295 and references cited therein.
- a) Tomioka, K.; Koga, K. in *Asymmetric Synthesis*; Morrison, J.D. Ed.; Academic Press: Orlando, 1983, Vol. 2, Chapter 7. b) Schmalz, H.-G. in *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I. Eds.; Pergamon: Oxford, 1991, Vol. 4, Chapter 1.5. c) Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771.
- Jansen, J.F.G.A.; Feringa, B.L. *J. Chem. Soc., Chem. Commun.* **1989**, 741.
- a) Villacorta, G.M.; Rao, C.P.; Lippard, S.J. *J. Am. Chem. Soc.* **1988**, *110*, 3175. b) Ahn, K.-H.; Klassen, R.B.; Lippard, S.J. *Organometallics* **1990**, *9*, 3178.
- Lambert, F.; Knotter, D.M.; Janssen, M.D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetrahedron: Asymmetry* **1991**, *2*, 1097.
- Spescha, M.; Rihs, G. *Helv. Chim. Acta* **1993**, *76*, 1219.
- Green, A.E.; Lansard, J.P.; Luche, J.L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931.
- a) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571. b) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4148. c) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. d) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95 (without nickel or any other transition metal).
- a) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011. b) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701. c) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205.
- Jansen, J.F.G.A.; Feringa, B.L. *Tetrahedron: Asymmetry* **1992**, *3*, 581.
- Uemura, M.; Miyake, R.; Nakayama, K.; Hayashi, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 713.
- Corma, A.; Iglesias, M.; Martín, V.; Rubio, J.; Sánchez, F. *Tetrahedron: Asymmetry* **1992**, *3*, 845.
- a) Jansen, J.F.G.A.; Feringa, B.L. *Tetrahedron Lett.* **1988**, *29*, 3593. b) Jansen, J.F.G.A.; Feringa, B.L. *J. Org. Chem.* **1990**, *55*, 4168.
- Knol, J.; Feringa, B.L. to be published.
- Stock, H.T.; Kellogg, R.M. to be published.
- (-)-DAIB was synthesised according to a published procedure<sup>18</sup> and had the same optical purity,  $[\alpha]_{\text{D}}^{20} -9.77^{\circ}$  (c 0.52,  $\text{C}_2\text{H}_5\text{OH}$ ), as reported by Noyori and co-workers where (-)-DAIB served as an excellent ligand in the enantioselective addition of dialkylzinc to aldehydes.<sup>19</sup> Later we noticed that this batch of (-)-DAIB was polluted with small amounts of (+)-*cis-endo-N,N*-dimethyl-3-aminoborneol ((+)-DAB)(**13b**).<sup>20</sup> Pure (-)-DAIB was obtained by further purification (see experimental)  $[\alpha]_{\text{D}}^{20} -14.5^{\circ}$  (c 0.93,  $\text{C}_2\text{H}_5\text{OH}$ ) [Lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{28} -14.7^{\circ}$  (c 4.58,  $\text{C}_2\text{H}_5\text{OH}$ )].
- Chittenden, R.A.; Cooper, G.H. *J. Chem. Soc. (C)* **1970**, 49.
- Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
- The direct reduction of 3-hydroxyiminobornan-2-one to *cis-exo*-3-aminoisoborncol (**3a**) with  $\text{LiAlH}_4$  is not stereospecific under conditions where the concentration of reactants is low. A considerable amount of *cis-endo*-3-aminoborneol is formed. See: Pauling, H. *Helv. Chim. Acta* **1975**, *58*, 1781 and references cited therein. See also ref. 18.

21. Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19.
22. (+)-DPMPM was synthesised according to a literature procedure<sup>23</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> +55.5° (c 0.98, CHCl<sub>3</sub>) [Lit.<sup>23</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +57.0° (c 1.0, CHCl<sub>3</sub>)].
23. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
24. Confirmed by <sup>1</sup>H and <sup>13</sup>C NMR and HRMS. The enantiomeric purity was determined with <sup>31</sup>P NMR using a chiral trivalent diazaphospholidine derivatising reagent. Hulst, R.; de Vries, N.K.; Zijlstra, R.W.J.; Feringa, B.L. submitted to *J. Org. Chem.*
25. For a discussion on the dramatic effect of adding similar ligands in asymmetric catalysis see: Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804.
26. Daniel, A.; Pavia, A.A. *Bull. Soc. Chim. Fr.* **1971**, 1060.
27. a) Duden, P.; Pritzkow, W. *Ber.* **1899**, *32*, 1538. b) van Tamelen, E.E.; Judd, C.I. *J. Am. Chem. Soc.* **1958**, *80*, 6305, see also ref. 18 and 20
28. Although we cannot exclude a minor effect of sampling on the enantioselectivity it should be noted that less than 5 % of the solution is removed and the concentration of reactants is not affected.
29. For a related mechanism for nickel catalysed conjugate addition of organozirconium to enones: Dayrit, F.M.; Gladkowski, D.E.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 3976.
30. The term scalemic refers to unequal mixtures of enantiomers. Heathcock, C.H.; Finkelstein, B.L.; Jarvi, E.T.; Radcliff, P.A.; Hadley, C.R. *J. Org. Chem.* **1988**, *53*, 1922.
31. Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H.B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.
32. Nonlinear effects: in ene reaction, Terada, M.; Mikami, T.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623, in trimethylsilylcyanations, Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1990**, 1364, in stoichiometric conjugate addition of organocuprates to enones, Ref. 3c and Rossiter, B.R.; Eguchi, M.; Miao, G.; Swingle, N.M.; Hernández, A.E.; Vickers, D.; Fluckiger, E.; Patterson, G.; Reddy, K.V. *Tetrahedron* **1993**, *49*, 965.
33. Wynberg, H.; Feringa, B.L. *Tetrahedron* **1976**, *32*, 2831, see also ref 1a.
34. Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. *J. Organomet. Chem.* **1992**, *431*, 233.
35. For example with *cis-exo-N,N*-dialkyl-3-aminoisoborneol ligands the *N*-alkyl group should be methyl for enantioselective catalysis whereas with *N,N*-dialkylnorephedrine ligands the *N*-butyl substituent is the most enantioselective.<sup>9</sup>

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