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A practical *o*-hydroxybenzylamines promoted enantioselective addition of dialkylzincs to aldehydes with asymmetric amplification

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Abstract

The addition of dialkylzincs to aldehydes is accelerated considerably by the presence of a catalytic amount of *o*-hydroxybenzylamine (*R*,*R*)-**2e** to give, after hydrolysis, the corresponding alcohol (*S*)-**9** in good enantiomeric purity. The origins of the enantioselection have been elucidated. A strong positive nonlinear relationship was observed for the reaction enantioselctivity with the use of *o*-hydroxybenzylamine **2e**, which is very accessible through a short stereoselective synthetic route. The enantiomeric purity of the product **9** is much higher than the *d.e.* of the chiral source **2e**, and the rate of the enantioselective catalysis increases considerably with the increase of the *d.e.* of (*R*,*R*)-**2e**.

1. Introduction

In recent years, there has been a great deal of interest in the development of metal catalyzed asymmetric reactions and also in the synthesis of ligands that result in high enantioselectivity in the catalytic asymmetric carbon–carbon bond formation.[1–17] A practical consequence is the discovery of ligand-accelerated catalysis (LAC).[1] Thus, an existing catalyzed process is improved by the addition of a specific ligand, which leads to a faster, 'ligand-accelerated' reaction. In this field, asymmetric addition of diethylzinc to aldehydes using a catalytic amount of chiral catalyst has attracted much attention. It is interesting therefore to develop a much simpler and readily available ligand possessing high catalytic effect that features a deep chiral pocket after complexation with the zinc organometallic reagent in order to realise an efficient catalytic and enantioselective process. Numerous efforts have been made to search for new effective chiral ligands[2–15] and to investigate the reaction mechanism.[16,17] Numerous chiral chelating ligands have been applied in enantioselective additions of organozincs to aldehydes, but ligands obtainable by short synthetic routes are still desirable.

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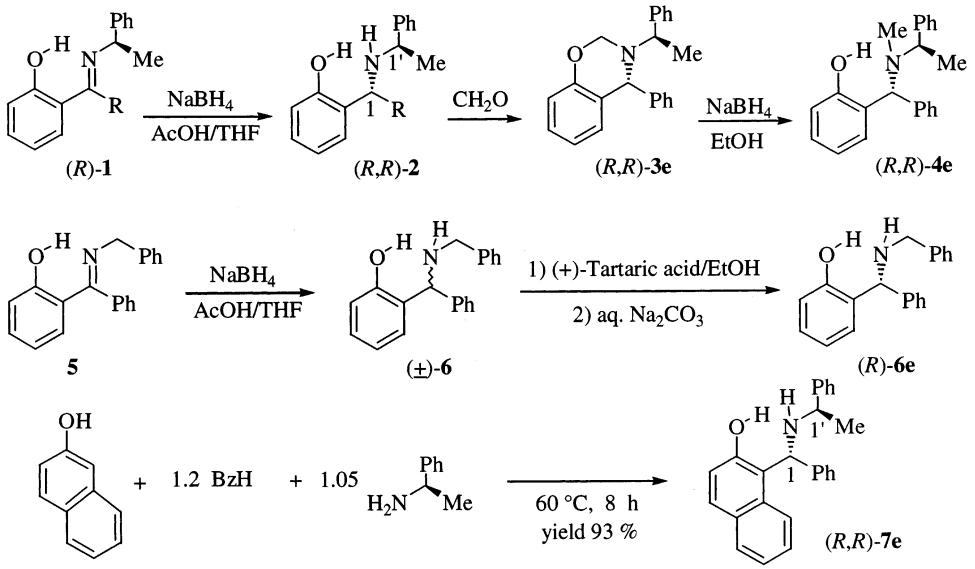
In this paper, following on from previous works,[18,19] I have developed the potentially useful *o*-hydroxybenzylamine ligands **2** to use in the catalytic enantioselective alkylation of aldehydes.

2. Results and discussion

Initial studies were focused on the diethylzinc addition to benzaldehyde, a model reaction, investigating the effect of the different ligands **1**–**4**, **6** and **7** used as precatalysts (see Scheme 1 and Table 1).



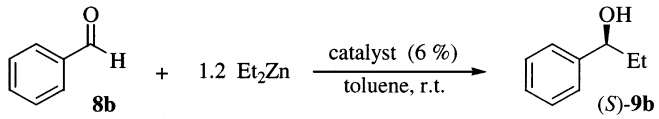
Scheme 1. Synthesis of *o*-hydroxybenzylamines and 2-hydroxy-1-naphthalenemethylamine

The *o*-hydroxybenzylamines **2a**–**e** are the best precatalysts and generally the diastereomer (*R*,*R*)-**2** gives the better performances that the ligand (1*S*,1′*R*)-**2**, enhancing the reactivity of the dialkylzinc and the enantioselectivity towards the aldehydic carbonyl group. In particular the ligand (*R*,*R*)-**2e** gives the best results and only a catalytic amount of this (6%) is enough to perform good enantioselectivity and reactivity (see Fig. 1 and Table 2). The *o*-hydroxybenzylamines (1*S*,1′*R*)-**2c**–**e** are by-products of the reduction of the corresponding imines (*R*)-**1**.

Comparing the *e.e.* values obtained with the use of ligands (1′*R*)-**2f** (16%) and (1*R*)-**6e** (42%) it is possible to conclude that the presence of the stereogenic C-1 is more important than the stereogoenic C-1′ in transferring steric information to the enantioselective alkylation of aldehydes.

It is reported in the literature that generally tertiary amines give better results than secondary ones.[2–15,20–24] The tertiary amine (*R*,*R*)-**4e**, which can be prepared by a problematic selective alkylation of (*R*,*R*)-**2e**,[20–24] or more conveniently through my reported procedure (see Scheme 1), gives no particularly advantageous results (see Table 1, entry 13). With the use of tertiary amines the alkylation reaction is slower and with a lower enantioselectivity (see (*R*,*R*)-**4e** in Fig. 2).[12]

Table 1
Enantioselective addition of diethylzinc to benzaldehyde promoted by enantiopure *o*-hydroxybenzylamines **2a–f** and derivatives



Entry	Catalyst	R	Time (h)	Yield (%)[a]	*e.e.*[b]	Config.[c]
1	(*R*)-**1b**	Et	9	92	18	*S*
2	(*R*,*R*)-**2a**	Me	4	96	55	*S*
3	(*R*,*R*)-**2b**	Et	4	93	57	*S*
4	(*R*,*R*)-**2c**	^{i}Pr	4	92	35	*S*
5	(1*S*,1′*R*)-**2c**	^{i}Pr	15	89	10	*R*
6	(*R*,*R*)-**2d**	^{t}Bu	4	94	62	*S*
7	(1*S*,1′*R*)-**2d**	^{t}Bu	15	88	8	*S*
8	(*R*,*R*)-**2e**	Ph	4	93	89	*S*
9	(1*S*,1′*R*)-**2e**	Ph	12	84	60	*R*
10	(*R*)-**2f**	H	5	92	16	S
11	(*R*,*R*)-**3e**	Ph	44	78	12	*S*
12	(4*S*,1′*R*)-**3e**	Ph	48	73	5	*S*
13	(*R*,*R*)-**4e**	Ph	5	88	71	*S*
14	(*R*)-**6e**	Ph	4	90	42	*S*
15	(*R*,*R*)-**7e**	Ph	4	89	87	*S*

[a] GC yield on the mixture of the two enantiomers.
[b] Determined by capillary chiral GC analysis using the chiral column MEGADEX DMP β.[39]
[c] Configuration determined by the sign of optical rotation.

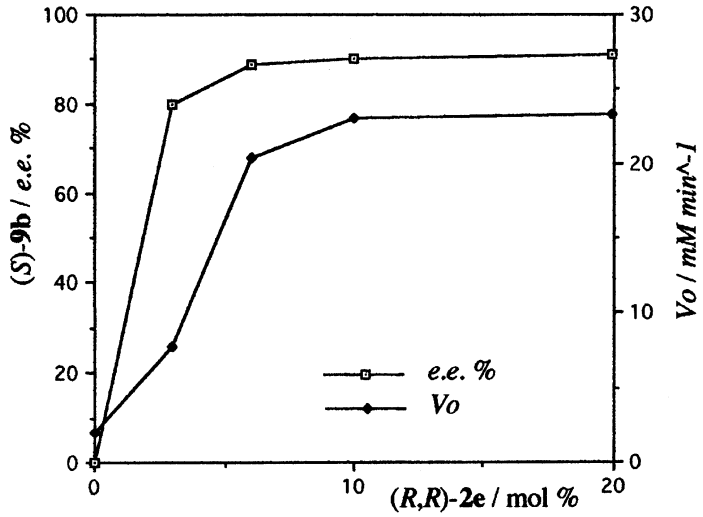


Figure 1. The *e.e.* of product (*S*)-**9b** and the initial rate of the reaction (V_o) as a function of the amount of ligand (*R*,*R*)-**2e** used in the addition of diethylzinc to benzaldehyde. Conditions: [DEZ] = 1.00 M; [BzH] = 0.83 M; toluene; 20°C

Table 2
Optimisation of the enantioselective addition of dialkylzincs to benzaldehyde promoted by *o*-hydroxybenzylamine (*R*,*R*)-**2e**[a]

$$\mathbf{8b} + 1.2\ R_2Zn \xrightarrow{(R,R)\text{-}\mathbf{2e}\ (\text{cat.})} (S)\text{-}\mathbf{9}$$

Entry	R_2Zn		Catalyst (%)	$e.d._{cat.}$	Time (h)/temp. (°C)	Yield (%)[b]	$e.e._{prod.}$[c]
1	Et_2Zn	1.1 M/toluene	0	–	45/20	72	0
2	Et_2Zn	1.1 M/toluene	3	100	15/20	86	80
3	Et_2Zn	1.1 M/toluene	6	100	4/20	93	89
4	Et_2Zn	1.1 M/toluene	10	100	3/20	92	90
5	Et_2Zn	1.1 M/toluene	20	100	3/20	94	91
6	Et_2Zn	1.1 M/toluene	10	68	4/20	90	88
7	Me_2Zn	2.0 M/toluene	10	100	60/20	87	87
8	Bu_2Zn	1.0 M/heptane	10	100	3/20	91	91
9	Et_2Zn	1.0 M/hexane	6	100	2/20	90	87
10	Et_2Zn	1.0 M/hexane	6	100	7/0	88	88
110	Et_2Zn	1.0 M/hexane	6	100	60/−15	84	88

[a] Conditions: [R_2Zn] = 1.00 M; [BzH] = 0.83 M.
[b] GC yield on the mixture of the two enantiomers.
[c] Determined by capillary chiral GC analysis using the chiral column MEGADEX DMP β.[39]

More interesting performances are obtained with the amine (*R*,*R*)-**7e**, which gives results comparable to the amine (*R*,*R*)-**2e** (see Table 1 and Fig. 2). The potentiality of this ligand will be exploited in due course. The ligand (*R*,*R*)-**7e**, structurally similar to the well known Betti

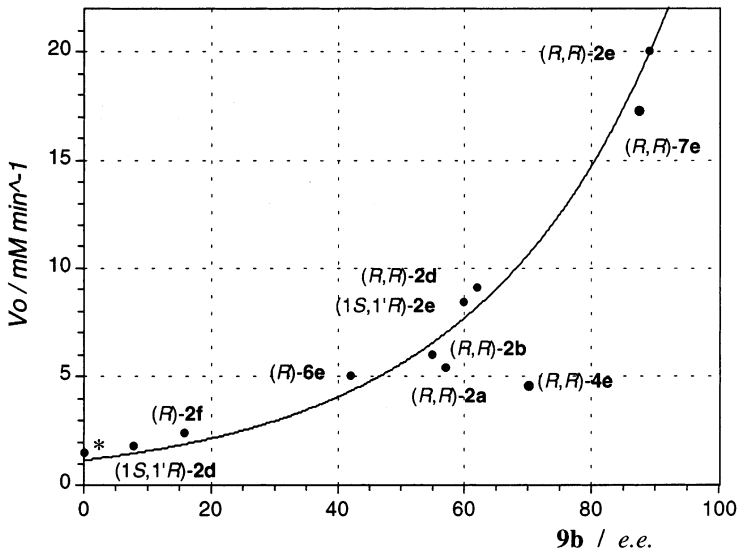


Figure 2. Correlation from the enantioselectivity and the V_o observed for the different ligand precatalyst in the addition of diethylzinc to benzaldehyde. Conditions: [ligand] = 0.050 M; [DEZ] = 1.00 M; [BzH] 0.83 M; toluene; 20°C (* lack of the ligand)

base,[25–27] was prepared through a stereoselective solvent free, very simple and straightforward synthesis optimised as shown in Scheme 1. The forming aminonaphthol (*R*,*R*)-**7e** crystallises spontaneously from the reaction mixture (yield 93%, *d.e.* 99%).

When the initial reaction rates (V_o), observed with the different ligands, are plotted against the enantioselectivity obtained in the reaction of diethylzinc with benzaldehyde, the direct proportionality reported in Fig. 2 is observed. This shows that in the (*R*,*R*)-**2** series, the performance of the catalyst increases approximately with the bulkiness of the R substituent (R = ^{t}Bu, Ph, Et, Me). Presumably, a phenyl group enhances diastereomeric recognition in the transition state due to a larger contact area and multiple interaction sites. The best performances are achieved with (*R*,*R*)-**2e** (R = Ph), the best precatalyst, which is much better than (1*S*,1′*R*)-**2e**. Likewise (*R*,*R*)-**2d** (R = ^{t}Bu) is much better than (1*S*,1′*R*)-**2d**, which shows negligible catalytic ability. Luckily, the more efficient precatalysts (*R*,*R*)-**2a**–**f** are very accessible materials obtained through a short stereoselective synthetic route in high yields as the major diastereomers under the reduction conditions optimised previously.[18] This makes the methodology convenient and of practical use, although *e.e.* values observed in the alkylation reactions are not very high. Lack of the ligand makes the reaction extremely slow (see Table 2 and Fig. 2). In hexane the reactions are faster than in toluene but the same enantioselectivities are observed. There is no enhancement of the enantioselectivity on lowering of reaction temperature, while the reaction time becomes extremely long even at 0°C. It is noteworthy that when the ligand (*R*,*R*)-**2e** with 68% *d.e.* (such as results from the reduction of imidoylphenol (*R*)-**1e**[18]) is used, a product of 88% *e.e.* (Table 2, entry 6; Fig. 4(a), black point) is obtained. This situation is typical for ligands that show asymmetric amplification.[28,29] The alkylation reaction can be performed with dimethyl-, diethyl-, and dibutylzinc with comparable results. With dimethylzinc the methylation reaction proceeds rather slowly (Table 2, compare entry 7 vs. entries 6 and 8).

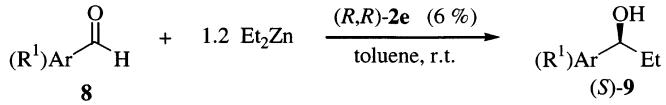
The results for the addition of diethylzinc to several aromatic and aliphatic aldehydes in the presence of (*R*,*R*)-**2e** are summarised in Table 3. All the reactions proceeded smoothly to give the corresponding alcohols (*S*)-**9a**–**u** in good yields. Various substituted aromatic aldehydes gave high enantioselectivity. Generally electron donating substituents in the aldehyde give better *e.e.* values as in **9a**–**e**. This is consistent with a strong coordination of the aldehyde to the zinc atom of the catalyst. The presence of halogen substituents lowered the enantioselectivity as in **9m**,**n**. Branched aliphatic aldehydes (**8o**–**r**) gave high enantioselectivities, better than linear ones, suggesting that the stereoselection is steric in origin. All reactions produced 2–8% of the corresponding benzyl alcohol as a by-product, deriving from the reduction of the aldehydes by dialkylzincs.

The currently accepted mechanism for the β-amino alcohol catalysed addition of dialkylzinc to aldehydes[2,3,16,17] has been reviewed and applied to *o*-hydroxybenzylamines (see Scheme 2). It can be assumed that the active catalytic species is the zincoxazine **10e**, which acts as a bifunctional catalyst that assembles the aldehyde and dialkylzinc, leading to the product forming transition states **15-Ts**. The second equivalent of dialkylzinc facilitates the dissociation of the dimer **11** by the formation of coordinatively unsaturated monomeric **13**. Coordination of the aldehyde to **13** gives the product forming intermediate complex **14**. The latter can be performed by an inverse order of coordination of aldehyde and dialkylzinc to **10**. A subsequent transfer of an alkyl anion from zinc to the coordinated aldehyde gives **16** through the transition state **15-Ts**. This is the turnover limiting and the stereodetermining step. A theoretical scrutiny of the

numerous geometries and relative energies of the possible transition states would greatly help in the understanding of the observed enantioselectivities. In order to estimate the relative energies, at the PM3 semiempirical level,[38] of the possible transition states, dimethylzinc has been considered for simplicity.[17,31–33] The structures *anti-Re*-**15-Ts** and *anti-Si*-**15-Ts** are the two products forming transition states of lowest energy (see Fig. 3). The major transition state *anti-Si*-**15-Ts**, more stable that *anti-Re*-**15-Ts** of 1.32 kcal/mol, leads to alkyl addition of the aldehyde to the *Si* face to afford the alcohol (*S*)-**9**, in agreement with the experimental results.

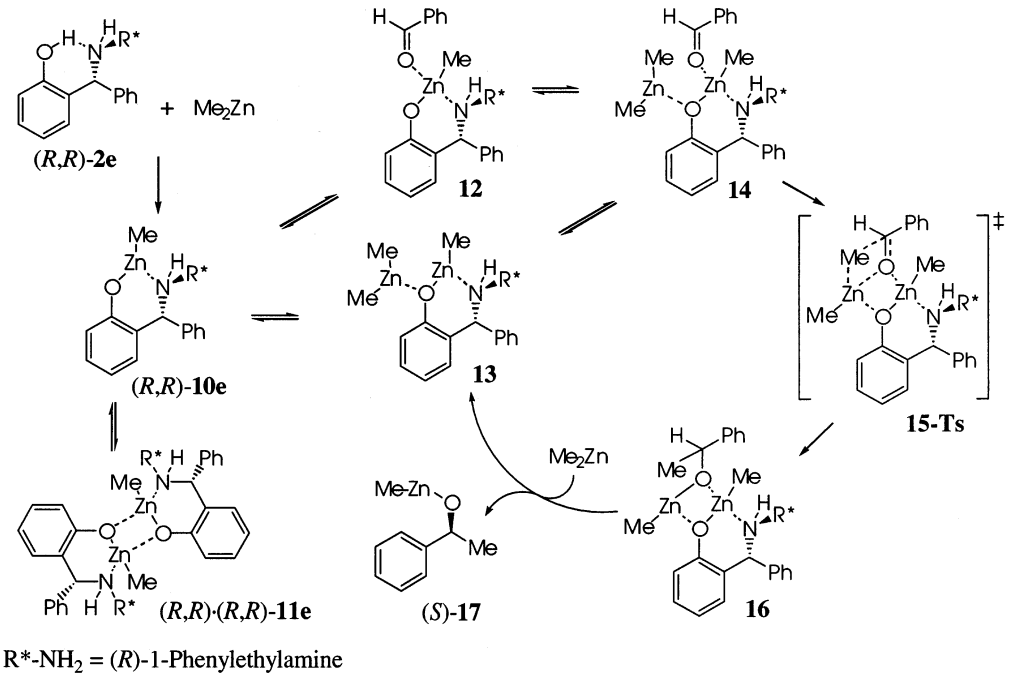
The nonlinear effect observed[3,16,28,29] is clear in Fig. 4(a), which shows the *e.e.* of the product (*S*)-**9b** as a function of the *d.e.* of the chiral auxiliary (*R,R*)-**2e**. The enormous convexity of the

Table 3
Enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes promoted by enantiopure *o*-hydroxybenzylamine (*R,R*)-**2e**[a]



Entry	Aldehyde	8	Time (h)	9	Yield (%)[b]	% *e.e.*[c]	$[\alpha]_D^{20}$ (*c*, solvent)
1	*m,p*-$(MeO)_2C_6H_3CHO$	**8a**	4	**9a**	92	94[d]	−31.4 (1.1, C_6H_6)
2	PhCHO	**8b**	4	**9b**	93	89	−41.8 (2.3, $CHCl_3$)[8]
3	*m,m′,p*-$(MeO)_3C_6H_2CHO$	**8c**	5	**9c**	88	86[d]	−18.5 (1.7, C_6H_6)
4	*p*-MeC_6H_4CHO	**8d**	4	**9d**	92	86	−35.4 (1.9, $CHCl_3$)[5]
5	*p*-$MeOC_6H_4CHO$	**8e**	5	**9e**	92	94	−34.8 (2.1, C_6H_6)[5]
6	*p*-BrC_6H_4CHO	**8f**	5	**9f**	85	83	−35.2 (1.3, C_6H_6)
7	1-Naphthaldehyde	**8g**	3	**9g**	92	83	−42.3 (2.7, C_6H_6)[10]
8	2-Naphthaldehyde	**8h**	4	**9h**	87	81	−28.3 (1.6, C_6H_6)[6]
9	*o*-$MeOC_6H_4CHO$	**8i**	2	**9i**	89	80	−17.8 (1.1, C_6H_6)[11]
10	9-Anthraldehyde	**8j**	23	**9j**	81	78[d]	−7.46 (1.6, $CHCl_3$)
11	2-Furaldehyde	**8k**	4	**9k**	89	73	−13.9 (2.6, $CHCl_3$)[6]
12	2-Thiofuraldehyde	**8l**	5	**9l**	83	70	−14.5 (2.1, $CHCl_3$)[13]
13	*p*-ClC_6H_4CHO	**8m**	7	**9m**	93	86	−17.9 (1.8, C_6H_6)[8]
14	C_6F_5CHO	**8n**	6	**9n**	94	51	+1.6 (2.1, C_5H_{12})[9]
15	Et_2CHCHO	**8o**	8	**9o**	83	94	−0.40 (1.9, $CHCl_3$)[7]
16	Me_2CHCHO	**8p**	8	**9p**	86	97	−15.2 (1.3, EtOH)[30]
17	*c*-$C_6H_{11}CHO$	**8q**	4	**9q**	82	93	−9.19 (1.4, Et_2O)[7]
18	(*E*)-$C_6H_5CH{=}CMeCHO$	**8r**	5	**9r**	82	83	+29.2 (1.1, $CHCl_3$)[10]
19	(*E*)-$C_6H_5CH{=}CHCHO$	**8s**	21	**9s**	83	76	−5.7 (2.5, $CHCl_3$)[8]
20	$nC_6H_{13}CHO$	**8t**	6	**9t**	95	75	+6.3 (1.6, $CHCl_3$)[8]
21	$PhCH_2CH_2CHO$	**8u**	4	**9u**	92	72	+18.7 (1.9, EtOH)[7]

[a] Conditions: [(*R,R*)-**2e**] = 0.050 M; [DEZ] = 1.00 M; [BzH] = 0.83 M; toluene; 20°C.
[b] GC yield on the mixture of the two enantiomers.
[c] Determined by capillary chiral GC analysis using the chiral column MEGADEX DMP β.[39]
[d] Determined by HPLC analysis using the chiral column LiChroCART® 254-4 (*S,S*)-Whelk-01.[40]



Scheme 2. Proposed mechanism for the catalytic cycle in the addition of dimethylzinc to benzaldehyde [R* = (*R*)-(+)-l-phenylethylamine]

curve with respect to a linear correlation is due to diastereomer recognition in the binuclear catalyst precursors **11**, as shown in Scheme 3. The initial reaction rate (V_o) appeared to be sensitive to diastereomeric purity of the auxiliary ligand (see Fig. 4(b)).

The auxiliary (*R*,*R*)-**2e** gives the ethylation of benzaldehyde four times faster than the reaction with (1*S*,1′*R*)-**2e**, and with a better *e.e.* The nonlinearity is a result of noticeable difference in chemical properties of the catalyst. On the basis of the experimental evidences observed, the heterochiral binuclear complex (*R*,*R*)·(*S*,*R*)-**11e** must be thermodynamically more stable than the homochiral (*R*,*R*)·(*R*,*R*)-**11e** and (*S*,*R*)·(*S*,*R*)-**11e**;[17] the major (*R*,*R*)-**10e** sequestrate the minus (1*S*,1′*R*)-**10e** (see Scheme 3). The complex (*R*,*R*)·(*R*,*R*)-**11e**, less stable, possesses the major tendency to dissociate into the active monomer (*R*,*R*)-**10e**.

3. Conclusions

These results demonstrate that the *o*-hydroxybenzylamines **2**, very accessible materials obtained through a short stereoselective synthetic route, are ligands that may be of general use in asymmetric Lewis acid catalysis. In summary, I have developed a practical and convenient synthesis and application of *o*-hydroxybenzylamines **2** as ligands for chiral catalysts in the enantioselective addition of dialkylzincs to aldehydes with high asymmetric amplification.

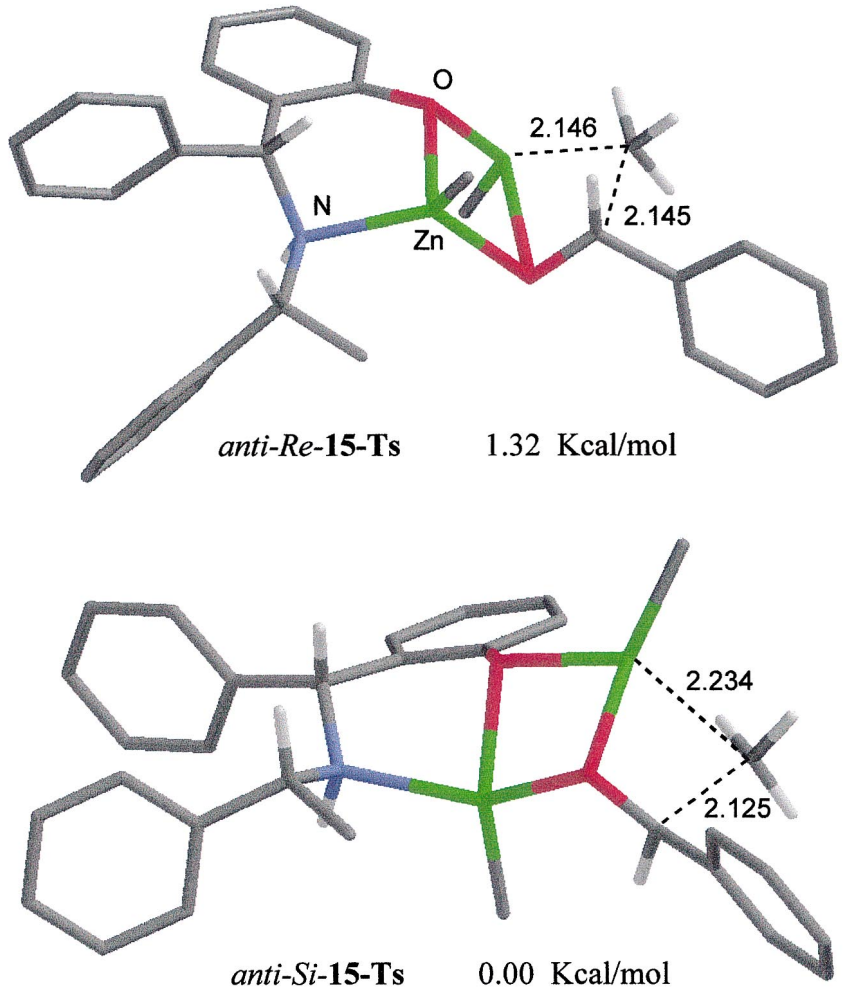


Figure 3. The lowest energy selected transition structures proposed for the methyl migration to the *Re* and *Si* face of benzaldehyde, optimised at the PM3 level[38]

4. Experimental

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in hertz. IR spectra were recorded with a Perkin–Elmer 257 spectrometer. GC–MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. All melting points are uncorrected. THF was dried by refluxing over sodium wires until the blue colour of benzophenone ketyl persisted and then distilled into a dry receiver under a nitrogen atmosphere. All reagents and solvents were distilled prior to use or were of commercial quality from freshly opened containers. Commercial methyllithium and butyllithium solutions (Aldrich) were employed under a dry atmosphere.

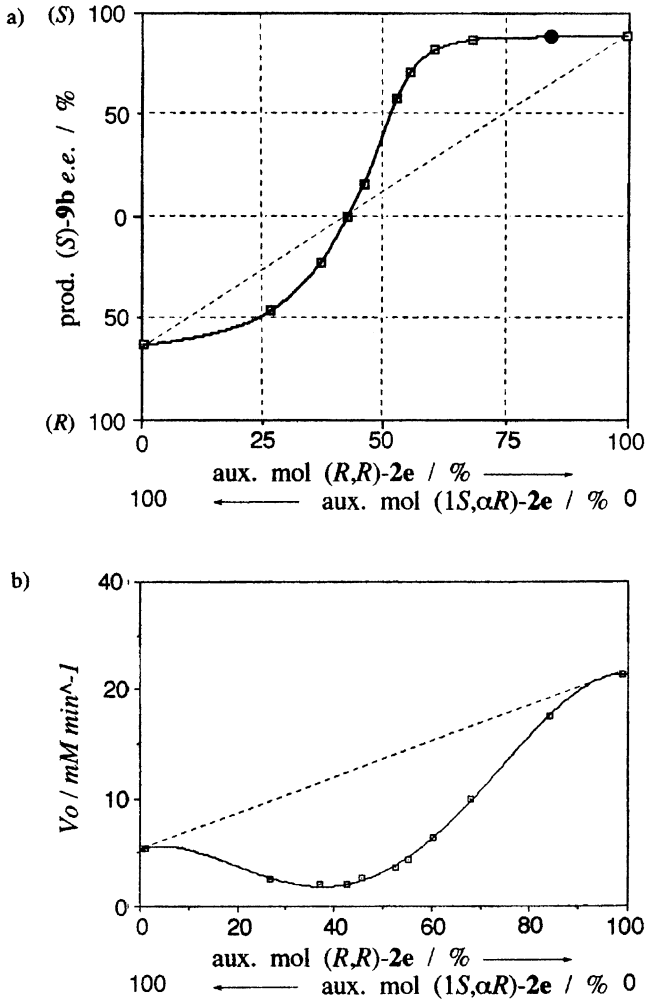
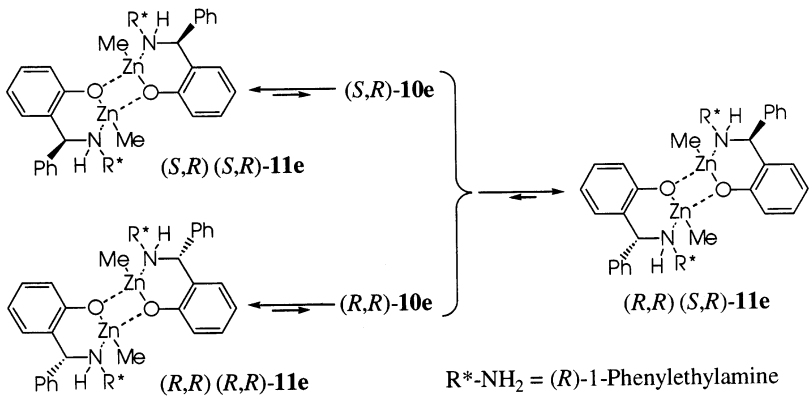


Figure 4. Curves obtained for the product (*S*)-**9b** *e.e.* (a) The initial rate of the reaction V_o; (b) as a function of the composition of auxiliary chelant (*R*,*R*)-**2e** *d.e.*% (black point 68% *d.e.*, such as resulting from the reduction of (*R*)-**1e**[18]). Conditions: [**2e**] = 0.050 M; [DEZ] = 1.00 M; [BzH] = 0.83 M; toluene; 20°C



Scheme 3. The homo- [(*R*,*R*)·(*R*,*R*)-**11e**, (*S*,*R*)·(*S*,*R*)-**11e**] and heterochiral [(*R*,*R*)·(*S*,*R*)-**11e**] dimeric species of the catalyst

The 2-imidoyl phenols **1** and **5** were prepared by direct condensation of the appropriate *o*-acylphenol[34] and (*R*)-(+)-1-phenylethylamine (99%) according to described procedure.[35–37] The 2-imidoyl phenol **1c** was prepared by methylation of the 2-imidoyl phenol **1b**.[19] The *o*-hydroxybenzylamines **2a**–**f** and **6** were prepared by reduction of the corresponding 2-imidoyl phenols **1** and **5**.[18]

4.2. Synthesis of o*-hydroxybenzylamines (*R,R*)-**4e** by reduction of the intermediate 3,4-dihydro-2*H*-1,3-benzoxazine (*R,R*)-**3e***

The benzoxazine (*R*,*R*)-**3e** (0.63 g, 2.0 mmol), prepared following a described procedure,[18] was dissolved in ethanol (8 mL) and treated with sodium borohydride (0.114 g, 3.0 mmol). After 90 min at room temperature the reduction was complete. The reaction mixture, diluted with CH_2Cl_2 (100 mL), was treated with a saturated aqueous solution (20 mL) of ammonium chloride. The organic layer was dried and evaporated. The residue, purified by flash chromatography (cyclohexane/ethyl acetate: 95/5 as eluent), gave (*R*,*R*)-**4e** (0.58 g, yield 92%).

*4.2.1. (4*R*)-4-Phenyl-3-[(1′*R*)-1′-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (*R,R*)-**3e***

Yield 91% colourless crystals, mp 98–100°C (hexane). $[\alpha]_D^{20} = -36.1$ ($c = 1.6$, $CHCl_3$). IR (Nujol): 1608, 1491, 1227, 940 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$ (d, 3H, $J = 6.6$ Hz), 3.98 (q, 1H, $J = 6.6$ Hz), 4.72 (br s, 1H), 4.83 (d, 1H, $J = 10.9$ Hz), 5.07 (dd, 1H, $J = 10.9$, 2.0 Hz), 6.80–7.50 (m). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.5$, 58.8, 59.3, 74.4, 116.5, 120.1, 120.3, 127.1, 127.5, 127.7, 128.0, 128.2, 128.6, 128.9, 130.2, 143.8, 145.2, 155.0. $C_{22}H_{21}NO$ (315.4): calcd C, 83.78, H, 6.71; N, 4.44; found: C, 83.92, H, 6.81; N, 4.27.

*4.2.2. 2-[(*R*)-{Methyl[(1′*R*)-1′-phenylethyl]amino}(phenyl)methyl]phenol (*R,R*)-**4e***

Colourless oil. $[\alpha]_D^{20} = -147.6$ ($c = 1.9$, $CHCl_3$). IR (film): 2977, 1587, 1255, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (d, 3H, $J = 7.0$ Hz), 2.09 (s, 3H), 4.08 (q, 1H, $J = 7.0$ Hz), 4.71 (s, 1H), 6.60–7.60 (m, 14H), 12.52 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 33.9, 57.6, 73.7, 117.5, 119.8, 128.0, 128.4, 128.6, 128.8, 128.9, 129.0, 129.1, 129.4, 129.6, 130.2, 141.1, 157.4. $C_{22}H_{23}NO$: calcd C, 83.24; H, 7.30; N, 4.41; found: C, 83.37; H, 7.41; N, 4.49.

4.3. Synthesis of o*-hydroxybenzylamines (*R*)-**6e** by reduction of the imidoyl phenol **5** and resolution of the racemic (±)-**6** with (*R,R*)-(+)-tartaric acid*

A mixture of the racemic *o*-hydroxybenzylamine (±)-**6** (1.44 g, 5.0 mmol), prepared following a described procedure,[18] and (*R*,*R*)-(+)-tartaric acid (0.75 g, 5.0 mmol) were dissolved in ethanol (5 mL) by delicate heating. A white precipitate, collected after 15 h (1.02 g, yield 46%), was treated with 2 M K_2CO_3 (1.4 g in 5 mL of H_2O) with stirring for 30 min. The resulting mixture was extracted with CH_2Cl_2 and the organic phase was dried and evaporated under reduced pressure. The crystalline white residue was purified by crystallisation from hexane (0.61 g, 2.1 mmol, yield 42%).

*4.3.1. 2-[(*R*)-(Benzylamino)(phenyl)methyl]phenol (*R*)-**6e***

Colourless crystals, mp 68–70°C (CH_2Cl_2/hexane). $[\alpha]_D^{20}$ −34.9 ($c = 2.3$, $CHCl_3$). IR (film): 3271, 1621, 1238, 1077, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (s, 1H), 3.80 and 3.95 (two d, 2H, $J_{AB} = 12.9$ Hz), 5.00 (s, 1H), 6.70–7.45 (m, 14H), 12.30 (br s, 1H). ^{13}C NMR (75

MHz, $CDCl_3$): $\delta = 52.5$, 67.4, 117.6, 119.8, 124.8, 127.9, 128.2, 128.4, 129.0, 129.3, 129.4, 129.5, 129.8, 138.6, 142.0, 158.2. $C_{20}H_{19}NO$: calcd C, 83.01; H, 6.62; N, 4.84; found: C, 82.92; H, 6.74; N, 5.02.

4.4. Synthesis of 1-((R)-phenyl{[(1′R)-1′-phenylethyl]amino}methyl)-2-naphthol (R,R)-7e

A mixture of 2-naphthol (0.72 g, 5.0 mmol), benzaldehyde (0.64 g, 6.00 mmol) and (*R*)-(+)-1-phenylethylamine (0.64 g, 5.25 mmol) was stirred at 60°C for 8 h under a nitrogen atmosphere. Following the progress of the reaction by TLC and ^{1}H NMR, it can be seen that the formation of the product occurs in the first two hours, but the initial *d.e.* of (*R*,*R*)-**7e** (44% at 2 h) increases in time (98% at 8 h) with the formation of a solid and crystalline reaction mixture. The reaction mixture was triturated at room temperature with EtOH (5 mL). The white crystals separated were collected and washed with EtOH (3×3 mL). The crystalline white residue, purified by crystallisation from EtOAc/hexane, gave the pure (*R*,*R*)-**7e** (1.64 g, 4.65 mmol, yield 93%).

4.4.1. 1-((R)-Phenyl{[(1′R)-1′-phenylethyl]amino}methyl)-2-naphthol (R,R)-7e

Colourless crystals, mp 155–156°C (EtOAc/hexane). $[\alpha]_D^{20} = -220.7$ ($c = 2.1$, $CHCl_3$). IR (film): 3271, 1621, 1238, 1077, 743, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (d, 3H, $J = 6.9$ Hz), 2.35 (br s, 1H), 3.92 (q, 1H, $J = 6.9$ Hz), 5.47 (s, 1H), 7.15–7.83 (m, 16H), 13.70 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.0$, 56.7, 60.3, 113.1, 120.1, 121.1, 122.4, 126.4, 126.7, 127.7, 127.9, 128.0, 128.7, 128.8, 129.0, 129.1, 129.7, 132.6, 141.5, 143.1, 157.3. *M*/*z* 232 (M^+−121, 38), 231 (100), 202 (23), 116 (21). $C_{25}H_{23}NO$: calcd C, 84.95; H, 6.56; N, 3.96; found: C, 85.21; H, 6.37; N, 3.77.

4.4.2. 1-((S)-Phenyl{[(1′R)-1′-phenylethyl]amino}methyl)-2-naphthol (1S,1′R)-7e

^{1}H NMR (300 MHz, $CDCl_3$) (minus diastereomer, deduced from the spectra of the crude reaction mixtures): $\delta = 1.60$ (d, 3H, $J = 6.7$ Hz), 2.35 (br s, 1H), 3.99 (q, 1H, $J = 6.7$ Hz), 5.90 (s, 1H), 7.15–7.83 (m, 16H), 13.70 (br s, 1H).

4.5. Enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes 8a–u promoted by enantiopure o-hydroxybenzylamine (R,R)-2e

Under a nitrogen atmosphere, a toluene solution of Et_2Zn (6.0 mmol, 1.1 M) was added to a mixture of aldehyde **8** (5.0 mmol) and *o*-hydroxybenzylamine (*R*,*R*)-**2e** (0.30 mmol) at 0°C and the whole solution was stirred at room temperature for 2–23 h. The progress of the reaction was monitored by GC analysis of aliquots of the reaction mixture, after quenching. Aqueous hydrochloric acid (2N) was added to quench the reaction under cooling with ice-water. The resulting mixture was extracted with CH_2Cl_2, and the extract was dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc) and then bulb-to-bulb distillation. The product was identified by spectroscopic methods and the optical rotation was measured. Enantiomeric excesses (% *e.e.*) were determined by GC analyses of the resulting alcohols on a chiral capillary column MEGADEX DMP β (30% dimethylpentil-β-cyclodedextrine on OV1701, 25 m, 0.25 mm ID, 0.25 μm film)[39] or by HPLC analysis using the chiral column LiChroCART® 254-4 (*S*,*S*)-Whelk-01 and mixtures *n*-hexane/2-propanol as eluent.[40] Yields are reported in Table 3. The data for the characterisation of a number of unknown alcohols follows.

4.5.1. 1-(3,4-Dimethoxyphenyl)propan-1-ol (S)-***9a***

Colourless crystals, mp 36–38°C (hexane). $[\alpha]_D^{20} = -31.4$ ($c = 1.6$, $CHCl_3$). IR (Nujol): 3401, 1593, 1027, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, 3H, $J = 7.4$ Hz); 1.60–1.90 (m, 2H), 1.93 (br s, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.52 (t, 1H, $J = 6.7$ Hz); 6.75–6.93 (m, 3H). ^{13}C NMR: $\delta = 10.2$, 31.8, 55.8, 55.9, 75.9, 109.0, 110.8, 118.2, 137.3, 148.3, 149.0. $C_{11}H_{16}O_3$: calcd C, 67.32; H, 8.22; found: C, 67.44; H, 8.07.

4.5.2. 1-(3,4,5-Trimethoxyphenyl)propan-1-ol (S)-***9c***

Colourless oil, $[\alpha]_D^{20} = -18.55$ ($c = 2.1$, $CHCl_3$). IR (film): 3428, 1593, 1234, 1128 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, 3H, $J = 7.4$ Hz); 1.60–1.90 (m, 2H), 2.10 (br s, 1H), 3.83 (s, 3H), 3.87 (s, 6H), 4.53 (t, 1H, $J = 6.5$ Hz); 6.75 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.7$, 32.4, 56.6, 61.3, 76.7, 103.3, 137.6, 141.0, 153.7. $C_{12}H_{18}O_4$: calcd C, 63.70; H, 8.02; found: C, 3.51; H, 8.17.

4.5.3. 1-(4-Bromophenyl)propan-1-ol (S)-***9f***

Colourless oil, $[\alpha]_D^{20} = -35.2$ ($c = 1.9$, $CHCl_3$). IR (film): 3350, 1487, 1071, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (t, 3H, $J = 7.4$ Hz); 1.58–1.89 (m, 2H), 2.19 (br s, 1H), 4.53 (t, 1H, $J = 6.6$ Hz); 7.19 and 7.45 (two d, 4H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.4$, 32.4, 75.7, 121.6, 128.2, 131.9, 144.0. $C_9H_{11}BrO$: calcd C, 50.26; H, 5.15; found: C, 50.04; H, 5.32.

4.5.4. 1-(9-Anthryl)propan-1-ol (S)-***9j***

Colourless crystals, mp 98–100°C (EtOAc/hexane), $[\alpha]_D^{20} = -7.46$ ($c = 1.2$, $CHCl_3$). IR (Nujol): 3308, 1459, 1014, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (t, 3H, $J = 7.4$ Hz); 2.10–2.55 (m, 3H), 6.16 (t, 1H, $J = 7.3$ Hz); 7.40–8.75 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.9$, 31.2, 73.1, 125.2, 125.5, 125.9, 127.7, 128.5, 129.8, 134.6, 135.4. $C_{17}H_{16}O$: calcd C, 86.40; H, 6.82; found: C, 86.64; H, 6.94.

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40. Optical purities (% *e.e.*) were determined by HPLC analyses of the resulting alcohols on a LiChroCART® 250-4, (*S*,*S*)-Whelk-01 chiral column. Chiral selector: (3*S*,4*S*)-4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenantrene. E. Merck 64271 Darmstadt, Germany.