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New chiral tetraaza ligands for the efficient enantioselective addition of dialkylzinc to aromatic aldehydes

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ABSTRACT

A series of chiral tetraaza ligands were studied for the enantioselective addition of dialkylzinc to aldehydes. These bis(amino amide) ligands show high enantioselectivity in the addition of organozincs to aromatic aldehydes. Different structural elements on the ligands seem to play an important role in determining the observed enantioselectivity. Ligand **4b** (*N*,*N*′-bis(*N*-L-valinyl)-1,3-diaminopropane, with an aliphatic spacer with 3C atoms) catalyzed the addition of Et_2Zn to benzaldehyde, 1-naphtaldehyde, 4-methoxybenzaldehyde, and 4-chlorobenzaldehyde to give the corresponding alcohol products with excellent conversions and selectivities and with enantioselectivities of 99, 97, 98, and 82%, respectively. DFT calculations provide an understanding of the mechanism of the enantioselection process.

1. Introduction

The search for new ligands in asymmetric catalysis is a field of continuous interest.[1] In this regard, the use of nitrogen-containing ligands in catalysis has received increasing attention in the last years.[2] For practical applications it is convenient that these ligands can be easily prepared through simple synthetic pathways from easily accessible starting materials. Special attention has been given to the synthesis of C_2-symmetric molecules since this kind of molecules is generally considered advantageous in catalysis because of the associated reduction in the number of possible transition states for enantioselective reactions.[3] Among the catalytic C–C bond-forming reactions, the enantioselective addition of diorganozinc reagents to aldehydes represents one of the most important and fundamental asymmetric reactions.[4] Since the first report by Oguni and Omi,[5] different families of chiral ligands have been used for this type of reaction. In this regard, β-amino alcohols are probably the most used chiral ligands for this kind of asymmetric reactions.[6] Nevertheless, examples of the use of other C_2 ligands include diols,[7] such as TADDOLs[8] and BINOLs,[9] diamines, bis-sulfonamides,[10] bis-oxazolines,[11] bis(amino alcohol)-oxalamides,[12] etc.

The design, preparation, and study of tetraaza ligands and their transition metal complexes has been a field of extensive investigation since the initial report by Jäger.[13] The presence of tetraaza ligands in important biological systems, such as metalloporphyrins, clearly illustrates their potential for the development of efficient and selective catalysis.[14] Due to their easy accessibility, bis(amino amides) derived from natural amino acids and having structure **1** represent an attractive family of C_2-symmetric tetradentate tetraaza ligands (see Fig. 1). Cu complexes of simple α-amino amides **2** have allowed us to develop interesting citrate sensors.[15a] Although they do not directly promote the addition of dialkyl zinc reagents to aldehydes, the corresponding Ni complexes have shown to be very versatile catalysts for this reaction.[15b,c] On the other hand, Polt has studied in detail the use of bis(imino amides) derivatives **3** containing an aromatic spacer derived from 1,2-diaminobenzene for the same reaction.[16] This author could demonstrate by NMR studies that a tetradentate complex with zinc is formed by those ligands in the presence of ZnR_2 species.

Simple bis(amino amides) **1** containing aliphatic spacers provide ligands with a higher structural and conformational flexibility. This kind of compounds have been prepared by our group as precursors of macrocyclic pseudopeptides being able to display organogelating properties[17a–c] or acting as 'in vivo' fluorescent pH

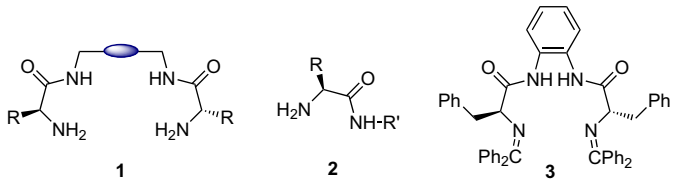

Figure 1. Structures of bis(amino amides) **1**, α-amino amide **2**, and Polt ligand **3**.

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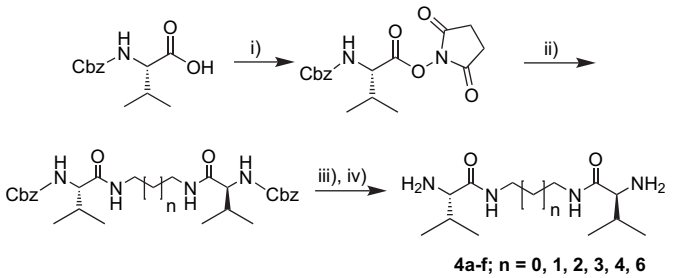
probes.[17d] On the other hand, homogeneous and supported Cu (II) complexes of compounds related to **1** have been studied as enantioselective catalysts for the chiral cyclopropanation reaction.[17e,f] Here we report on a combined experimental and theoretical study of those ligands for the catalytic enantioselective alkylation of aldehydes with dialkylzinc.

2. Results and discussion

2.1. Synthesis of ligands

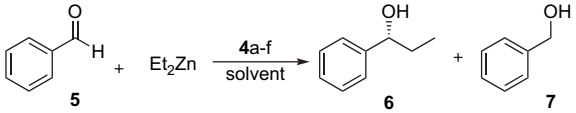
Open-chain peptidomimetics **4** derived from L-valine can be easily prepared starting from the corresponding *N*-Cbz protected amino acid through the initial formation of its activated *N*-hydroxysuccinimide ester, coupling with a variety of diamines and final N-deprotection, following previously reported procedures.[18] This synthetic procedure is outlined in Scheme 1 and allows an easy variation of the structural diversity components, i.e., the length of the aliphatic spacer and the amino acid residue. This is important in order to improve the optimization, using an iterative process, of the efficiency of the catalyst, in particular enantioselectivity. Overall yields for the preparation of compounds **4**, after the final deprotection step, were in the range 80–90%, being essentially independent of the nature and length of the aliphatic spacer.



Scheme 1. Synthesis of chiral bisamide ligands. Reagents: (i) DCC, *N*-hydroxysuccinimide, THF, rt; (ii) $H_2NCH_2(CH_2)_nCH_2NH_2$, DME, rt; (iii) HBr/AcOH; (iv) NaOH aq.

2.2. Enantioselective additions of diethylzinc to aldehydes

Since benzaldehyde has been the most extensively studied substrate, we focused our effort on the diethylzinc addition to benzaldehyde in our initial studies (Scheme 2). The enantioselective addition of diethylzinc to benzaldehyde was evaluated in the presence of a catalytic amount of the chiral ligand **4b**. Ligand **4b**, which is based on L-valine and an aliphatic spacer with 3 carbon atoms was used to optimize the reaction conditions for the addition of alkylzinc reagents to aldehydes. For these studies the catalytic Zn (II) complex was formed in situ from Et_2Zn and ligand **4b**.[19] Complex formation was found to be complete after 1 h at reflux. Different solvents were initially assayed in order to study their effect and to select the optimal one for the reaction. The reaction was carried out at 0 °C using 5 mol % of ligand **4b**.



Scheme 2. Diethylzinc addition to benzaldehyde.

As can be seen from Table 1, the addition of diethylzinc to benzaldehyde at 0 °C in hexanes afforded, after 24 h, an 87% conversion with 86% selectivity toward 1-phenyl-1-propanol, providing a 75% yield for **6** with 99% ee (entry 1). Under the same conditions, but after 72 h, the reaction was essentially complete (86% yield for **6**) (entry 3). When different solvents were considered, a remarkable effect was found on the enantioselectivity and the conversion. Non-coordinating solvents such as hexanes and toluene gave higher enantioselectivities than coordinating solvents such as THF (entry 4), although differences in selectivity were lower. When changing the solvent from hexanes to toluene (entry 6), the enantioselectivity decreased from 99 to 90%, but conversion decreased even more significantly. In the case of THF a good yield but moderate-low enantioselectivity was obtained after 24 h, in good agreement with the results reported by Soai with bidentate ligands.[20] It is interesting to note that the opposite effect (enhancement of the enantioselectivity) has been found by Dangel and Polt in the case of tetradentate ligands **3** containing aromatic spacers and imino groups.[16a] In the case of $CHCl_3$ and CH_3CN, conversions were low for both solvents after 24 h (entries 5 and 7). A good enantioselectivity was detected, however, for CH_3CN (53% yield, 91% ee), while it decreased to 76% ee for $CHCl_3$. Since hexanes gave the best enantioselectivity, this solvent was selected for the rest of the study.

Table 1
Enantioselective addition of Et_2Zn to benzaldehyde with ligand **4b**[c]

Entry	Solvent	Temp (°C)	Time (h)	Conversion[a] (%)	Selectivity[a]	ee[b] (%)
1	Hexanes	0	24	87	86	99 (*S*)
2	Hexanes	0	48	90	87	99 (*S*)
3	Hexanes	0	72	99	87	99 (*S*)
4	THF	0	24	87	76	68 (*S*)
5	CH_3CN	0	24	69	77	91 (*S*)
6	Toluene	0	24	65	82	90 (*S*)
7	$CHCl_3$	0	24	59	79	76 (*S*)
8	Hexanes	−20	24	64	89	99 (*S*)
9	Hexanes	+25	24	91	65	79 (*S*)

[a] Conversions and selectivities were determined by NMR. Selectivity=(**6**/(**6**+**7**))×100.
[b] Determined by chiral HPLC (Chiralcel OD); the major enantiomer obtained is indicated in parenthesis.
[c] Yield can be calculated as (conversion (%)×selectivity (%))/100.

The effect of the temperature was also investigated. Initial experiments were carried out by slow addition of Et_2Zn in hexanes over the solution containing **4b** at 0 °C. After 30 min the mixture was allowed to reach room temperature, benzaldehyde (in hexanes) was added, and the reaction was kept at room temperature for 24 h. Decreasing the reaction temperature to −20 °C resulted only in a slight increase of the selectivity, but at the expenses of much lower reaction rates. On the other hand, when the reaction (including the addition step) was carried out at room temperature, the enantioselectivity decreased to 79%. According to the former results, all subsequent reactions were carried out according to the initial protocol in hexanes at 0 °C.

In order to determine the optimal amount of the ligand needed for the addition of diethylzinc to benzaldehyde, initial experiments using variable quantities of ligand **4b** were carried out. In these studies, the concentrations of benzaldehyde and diethylzinc were kept constant at 0.3 and 0.6 mM, respectively, and the reaction was conducted at 0 °C in hexanes. Low conversions (yields lower than 50%) and enantiomeric excesses were observed when using loadings of **4b** ranging from 0.1 to 0.05 mol % of the catalyst (24 h reaction time). At 0.5% loading, the ee observed was 87%, with an 87% conversion (66% yield). Optimum results, in terms of conversion and enantioselectivity were achieved when 5 mol % of **4b** were used (76% yield, 99% ee). An increase of the quantity of ligand up to 10 mol % only improved slightly the yield, but not enantioselectivity (83% yield, 99% ee). Thus, for all subsequent reactions loadings of the chiral ligands were kept at 5 mol % (Fig. 2).

The optimized reaction protocol was then used for the enantioselective addition of diethylzinc to benzaldehyde using other

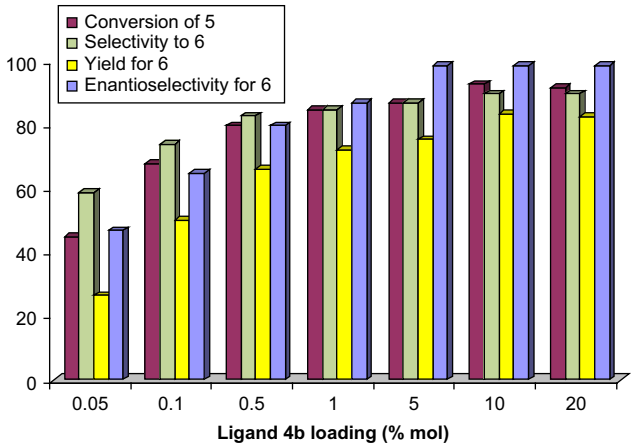


Figure 2. Effect of ligand loading (**4b**) on the conversion and ee of the addition of diethylzinc (0.6 mM) to benzaldehyde (0.3 mM) (24 h).

ligands (**4a**–**f**) containing spacers of different lengths. All reactions were carried out in hexanes at 0 °C. Selectivities ranged for all cases from 80 to 87%.

As can be seen from Table 2, the addition of diethylzinc to benzaldehyde at 0 °C afforded (*S*)-1-phenyl-1-propanol with excellent enantioselectivities when using those chiral open-chain pseudopeptides. Although conversions ranged from 72 to 87% after 24 h, almost quantitative conversions (higher than 95%) were obtained after 48 h. Rather surprisingly, the results show that the effect of the spacer is not very significant. Only when a very large spacer derived from 1,8-octanediamine was used (**4f**) the enantioselectivity decreased to 89% (entry 6). In this regard, modeling studies suggest that the flexible coordination sphere of Zn(II) allows to easily accommodate those structural changes with only minor distortions on the tetrahedral coordination of the metal. As a matter of fact, ESI-MS experiments confirmed the formation of the corresponding 1:1 complexes for all the ligands.[19]

The catalytic efficiency of ligands **4** for the addition of Me_2Zn to benzaldehyde was also examined. Reactions were run using 2 equiv of Me_2Zn and 5 mol % of the corresponding bis(amino amide) ligand. Results obtained showed similar trends to those found in the case of Et_2Zn. In both cases, ligands **4b** and **4c**, containing C3 and C4 spacers, seem to provide slightly superior catalytic efficiencies.

Those results encouraged us to apply this reaction to other aldehydes. Thus, the performance of ligands **4b** (*N*,*N*′-bis(*N*-L-valinyl)-1,3-diaminopropane) and **4f** (*N*,*N*′-bis(*N*-L-valinyl)-1,3-diaminooctane) were examined for the enantioselective addition of diethylzinc to a variety of aldehydes under the optimized (see Table 4). Bulky aromatic aldehydes such as 1-naphthaldehyde also gave excellent ee values (97%, Table 4, entry 3). The best enantioselectivity (98% ee) was obtained for 4-methoxybenzaldehyde, a substrate bearing an electron-donating substituent at the *para*-position (Table 4, entry 5). However, attempts to alkylate aliphatic aldehydes, such as hexanal, with diethylzinc or dimethylzinc in the presence of ligands **4b** or **4f** were unsuccessful. No conversion was detected after 24 h, neither at 0 °C nor at room temperature. The lower basicity of the oxygen atom of aliphatic aldehydes can be, most likely, at the origin of this behavior. As in the case of benzaldehyde, all the additions to aromatic aldehydes provided the corresponding *S*-alcohols as the major isomer with excellent enantioselectivities (82–98% ee) and in moderate to high yields (Table 3, entries 1–6). In all cases, again, **4b** showed a slightly better performance than **4f** (Table 4).

The relationship between the enantiomeric composition of the chiral ligand **4b** and that of the product arising from the addition of diethylzinc to benzaldehyde was also investigated. The complete absence of non-linear effects is in full agreement with the participation of 1:1 catalytic molecular complexes and allows to rule out the presence of aggregates species.

Table 2
Enantioselective addition of Et_2Zn to benzaldehyde with ligands **4a**–**f**[a]

Entry	Ligand	*n*	Yield[a,b] (%)	ee[c] (%)
1	**4a**	0	72 (98)	92 (*S*)
2	**4b**	1	87 (99)	99 (*S*)
3	**4c**	2	85 (99)	99 (*S*)
4	**4d**	3	77 (99)	97 (*S*)
5	**4e**	4	72 (98)	95 (*S*)
6	**4f**	6	77 (97)	89 (*S*)

[a] All reactions were carried out in hexanes at 0 °C using 5 mol % of **4**.
[b] Conversions (after 24 h) were determined by NMR. Conversions for 48 h are given in parentheses.
[c] Determined by chiral HPLC (Chiralcel OD).

Table 3
Enantioselective addition of Me_2Zn to benzaldehyde with ligands **4a**–**f**[a]

Entry	Ligand	*n*	Yield[a,b] (%)	ee[c] (%)
1	**4a**	0	71 (99)	89 (*S*)
2	**4b**	1	83 (99)	90 (*S*)
3	**4c**	2	82 (99)	92 (*S*)
4	**4d**	3	74 (99)	90 (*S*)
5	**4e**	4	72 (99)	89 (*S*)
6	**4f**	6	75 (99)	85 (*S*)

[a] All reactions were carried out in hexane at 0 °C.
[b] Conversions after 24 h, 5% of catalyst was used; conversions were determined by NMR. Conversions for 48 h are given in parentheses.
[c] Determined by GC analysis (capillary column VF-5ms).

2.3. DFT mechanistic analysis

In order to obtain a more detailed understanding of the mechanism involved, DFT studies were carried out.

Noyori and co-workers have studied the reaction mechanism extensively, both experimentally[21] and theoretically[22] for the addition of diethylzinc to benzaldehyde mediated by amino alcohols. In 1995, based on the molecular orbital calculations at the restricted Hartree–Fock level, Yamakawa and Noyori established the participation of two 5/4/4-fused tricyclic transition states (the numbers refer to the size of the rings involved in the process) and one bicyclic TS (see Fig. 3). Among the three possible stereoisomeric TSs, the tricyclic *anti*-configuration is the most favored, being 2.9–3.1 kcal/mol more stable than the tricyclic *syn*-configuration and 6.9 kcal/mol more stable than the bicyclic TS. In the tricyclic *anti*-TS, alkyl migration takes place with retention of configuration, whereas the high-energy bicyclic pathway would give inversion of the migrating alkyl group. Similar results were obtained by

Table 4
Enantioselective R_2Zn addition to aromatic aldehydes with ligand **4b**[a]

Entry	Ligand	Aryl group	R′	Yield[b] (%)	ee[c] (%)
1	**4b**	Phenyl	Et	87	99 (*S*)
2	**4f**	Phenyl	Et	77	89 (*S*)
3	**4b**	1-Naphthyl	Et	80	97 (*S*)
4	**4f**	1-Naphthyl	Et	73	89 (*S*)
5	**4b**	4-Methoxyphenyl	Et	90	98 (*S*)
6	**4f**	4-Methoxyphenyl	Et	83	91 (*S*)
7	**4b**	4-Chlorophenyl	Et	68	82 (*S*)
8	**4f**	4-Chlorophenyl	Et	60	81 (*S*)
9	**4b**	Phenyl	Me	83	90 (*S*)
10	**4f**	Phenyl	Me	75	85 (*S*)

[a] All reactions were carried out in hexanes at 0 °C.
[b] Yields after 24 h, 5% of catalyst was used; yields were determined by NMR. Quantitative yields were obtained after 48 h.
[c] Determined by chiral HPLC (Chiralcel OD).

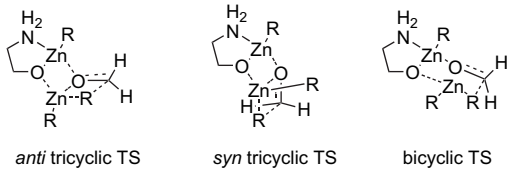


Figure 3. Transition states characterized by Yamakawa and Noyori. The terms *anti* and *syn* are used to define the relative disposition of the two terminal rings in the tricyclic TSs.

Goldfuss and Houk by means of ONIOM (RHF/LanL2DZ:UFF) calculations.[23]

Taking those studies as a starting point, rationalization of the observed enantioselectivity of enantioselective dialkylzinc additions to benzaldehyde catalyzed by amino alcohols has been carried out by different research groups.[24] However, the situation can be very different for the related reaction using tetradentated ligands such as **4**, and theoretical approaches to understand the corresponding mechanism have not been reported up to now. Following the mechanism described by Yamakawa and Noyori, it can be rationalized that, the first step must be the coordination of benzaldehyde to the catalytic zinc. For this, the oxygen can use either of its two lone pairs (cis or trans to Ph) giving place to two possible (cis or trans) complexes. In the case of amino alcohols, coordination to zinc takes place through displacement of a solvent molecule to afford tetrahedral zinc complexes like the trans complex **8** (Fig. 4).

This seems unreasonable in the case of Zn-bis(amino amide) complexes for the stronger coordination ability of amine nitrogen atoms. Accordingly, the oxygen atom of benzaldehyde is expected to coordinate to zinc in an apical position to give place to a complex like **9** (trans complex), taking into consideration that this metal ion, Zn(II), is able to present bi-, tetra-, and pentacoordination numbers.[25] In both cases, the chiral ligand favors the approach of benzaldehyde and the Et_2Zn moiety by one of the faces of the mean plane of the complex. Thus, the configuration shown in **9** with the Et_2Zn fragment located trans to the isopropyl group of the neighboring ring stereogenic center seems the most reasonable.

As in the case of amino alcohols, the *anti*-trans TS **10a** will provide access to the *S* enantiomer. The *R* enantiomer could be formed via the *syn*-trans (**10b**) or *anti*-cis pathway. The *syn*-cis TS would favor the formation of the *S* enantiomer, but this is always highly disfavored due to steric crowd (Fig. 5).

In order to check this hypothesis and examine the origin of the enantioselectivity of the alkylation of benzaldehyde and other aldehydes promoted by ligands **4**, the reaction mechanism was theoretically investigated by means of DFT methods (see Section 4). The system investigated was the same as the experimental one, corresponding to complex **9**. First of all, calculations confirmed the hypothesis for the generation of the initial product forming complex **9**. When a tetrahedral complex was investigated upon decoordination of an amine group, a high-energy intermediate was found (+25.8 kcal/mol) whereas the benzaldehyde coordination to form a pentacoordinated complex was found to be much more favorable (−13.6 kcal/mol). Upon this coordination, the aldehyde is

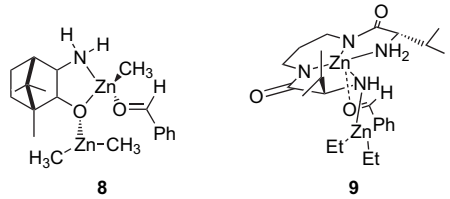


Figure 4. Initial complexes for amino alcohols, as characterized by Yamakawa and Noyori (**8**) and for bis(amino amides) (**9**).

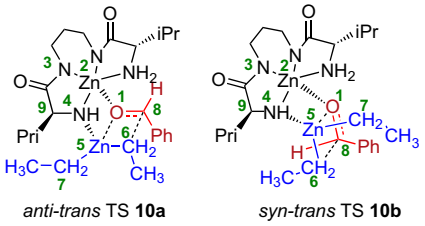


Figure 5. Schematic representation of the *anti* and *syn* transition states in the bis(amino amide) promoted addition of diethylzinc to benzaldehyde. Numbering is arbitrary and has been used in geometry discussions.

electrophilically activated, as suggested by the longer C=O bond of 1.233 Å in **9**, compared with 1.216 Å in free benzaldehyde. On the other hand, diethylzinc becomes significantly more nucleophilic upon coordination, as suggested by the increase on the Zn–C bonds in contrast with free diethylzinc (2.105 vs 2.023 Å). Complex **9** is formed with an exothermicity of 8.1 kcal/mol from ligand **4**, benzaldehyde, and diethylzinc. Among the two possible benzaldehyde coordinations, the trans configuration is 0.9 kcal/mol more stable than the cis one. The trans complex alternative to **9** in which the benzaldehyde approaches from below the six-membered chelate ring was calculate to be 0.3 kcal/mol less stable by DFT calculations.

The stereochemical outcome of the alkylation reaction was rationalized by transition state modeling. Comparison of the structures of the diastereomeric transition states **10** provides an understanding of the mechanism of enantioselection. Each transition state structure found possesses a single imaginary frequency, which corresponds to the migration of the suitably oriented ethyl group to the carbonyl carbon (Fig. 6). As can be seen in Table 5, the most favored structure is the *anti*-trans structure. These results are in agreement with the previous studies by Noyori and co-workers, despite of the fact that in this case the catalytic Zn(II) is pentacoordinated.

The *anti*-cis TS is calculated to be 4.0 kcal/mol higher in energy relative to the *anti*-trans TS. The energy difference between these diastereomeric structures can be provided by several steric interactions, in particular one taking place between the phenyl ring in benzaldehyde and one isopropyl group from a valine fragment. In the *anti*-trans structure, attack of diethylzinc can take place without a significant deformation in the O1–Zn2–N4–Zn5 ring system with a dihedral angle of −3.8°. On the contrary, in the *anti*-cis structure, to reduce the above-mentioned steric interaction, the Zn2–O1–C8 bond angle becomes wider compared to *anti*-trans structure (*anti*-trans, 126°; *anti*-cis, 145°) and the benzaldehyde molecule rotates; the O1–C8–C7–Zn5 also increases from 27.7° to 34.5°. The distortion is also reflected by the increase in the O1–Zn2–N4–Zn5 dihedral angle from −3.8° to 10.4°. The C6–C8–Ph angle increases from 94.9° to 102.3° in the *anti*-cis TS.

The *syn*-trans transition structure is 3.4 kcal/mol higher in energy than the *anti*-trans structure. The *syn*-cis TS is 4.1 kcal/mol higher in energy due to a steric interaction between phenyl ring in benzaldehyde and the propylene spacer. To avoid a high steric interaction, the C6–C8–Ph angle increases significantly from 100.0° to 110.3° in the *syn*-cis TS and the Zn2–O1–C8 bond angle becomes wider compared to the *anti*-trans structure as was observed for the *anti* transition states (*syn*-trans, 122°; *syn*-cis, 149°).

An important point is the flexibility of the 5/4/4 ring system core of the transition states. In agreement with the findings of Noyori and Yamakawa, the O1–Zn2 distance representing the common edge of the four-membered rings is shorter in *syn* transition states than in *anti* type ones. A geometrical characteristic that shows this flexibility is the value of the C9–N4–Zn5 angle. This angle notably increases from 113.4° in the *anti*-trans TS to 122.2° in the *anti*-cis

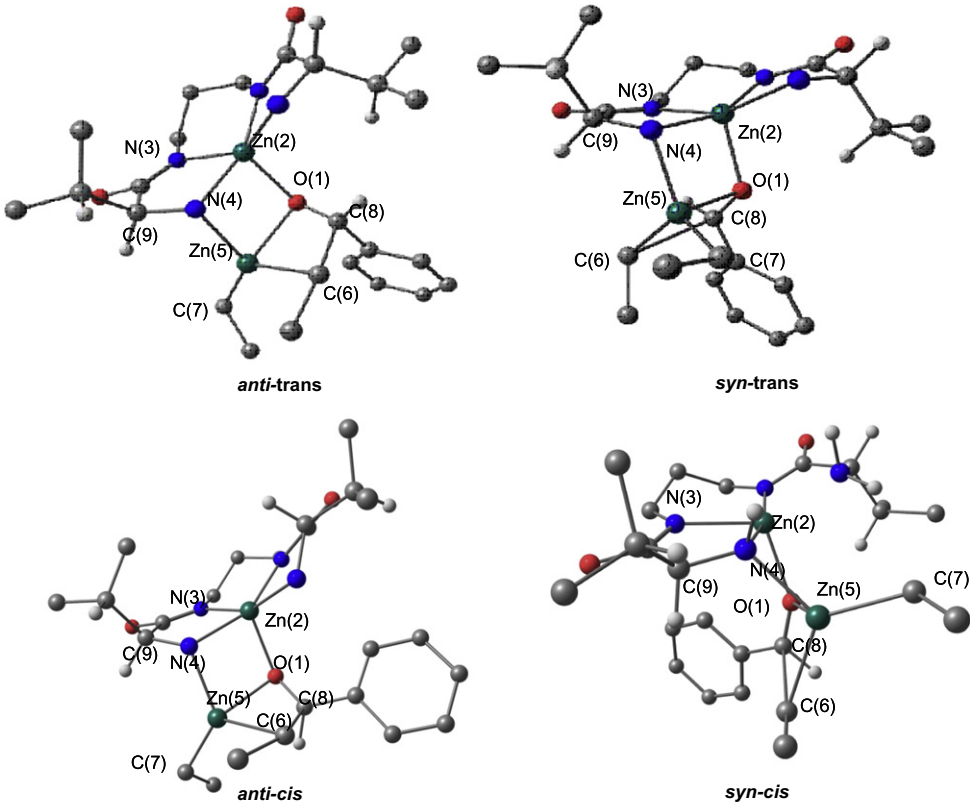


Figure 6. Transition state structures **10**, for *anti* and *syn*-models calculated from complex **9**. Hydrogen atoms omitted for clarity.

one to avoid unfavorable steric interactions. In both *syn* TSs, the C9–N4–Zn5 angle is increased in comparison with the *anti*-trans value. In the *syn* TSs this angle remains essentially constant (119.6°–120.4°) (Fig. 6).

The product forming complex **9** (Fig. 7) is regenerated from the final complex **11** (Zn-bound alkoxylate) upon reaction with diethylzinc and benzaldehyde, where the formation of a stable dialkylzinc alkoxide dimer or tetramer is a crucial step for the completion of the catalytic cycle. The stereochemistry of the alkoxide product is kinetically determined by the relative energy of the alternative diastereomeric transition states **10**. The energy difference (3.4 kcal/mol) between the two lowest energy transition states *anti*-trans and *syn*-trans would indicate that this ligand should induce a high degree of enantioselectivity in the alkylation reaction. From a qualitative point of view, the predicted enantioselectivity assuming a Boltzmann distribution at room temperature (99%) shows a good concordance with the experimentally observed one at 0 °C (99%).[26]

To check the effect of the R group in the bis(amino amide) ligands (see Fig. 1), we performed the theoretical analysis for R=CH_3. This is the smallest R group keeping asymmetry in the ligand and is based on the alanine residue. Some geometrical parameters and relative energies of the corresponding *anti* and *syn* transition states are shown in Table 6. The energy difference between the transition states decreases, which, as expected, reflects the importance of the steric bulk of the amino acid residue in determining the enantioselectivity. The *anti*-trans and *syn*-trans transition structures are again the most stable ones, originating from the aldehyde coordination at the less hindered face of the five-membered chelate ring. The energy difference between the more stable *anti*-trans and *syn*-trans transition structures accounts in favor of the formation of (*S*)-1-phenyl-1-propanol. In the case of the *anti*-cis TS, the presence

Table 5
Relevant geometrical parameters (Å and °) for the four possible transition states in the addition of diethylzinc to benzaldehyde for the L-valine-based tetraaza ligand **4b**

Parameter	*anti*-trans	*anti*-cis	*syn*-trans	*syn*-cis
Relative energy	0.0	4.0	3.4	4.1
O1–Zn2	2.268	2.265	2.252	2.245
C6–C8	2.348	2.349	2.426	2.419
Zn5–C6	2.329	2.278	2.284	2.224
O1–C8	1.293	1.293	1.294	1.293
C6–C8–O1	114.4	115.3	115.6	113.6
C6–C8–Ph	94.9	102.3	100.0	110.3
C9–N4–Zn5	113.4	122.2	119.6	120.4
O1–C8–C6–Zn5	27.7	34.5	−6.7	−20.1
O1–Zn2–N4–Zn5	−3.8	10.4	49.6	19.2

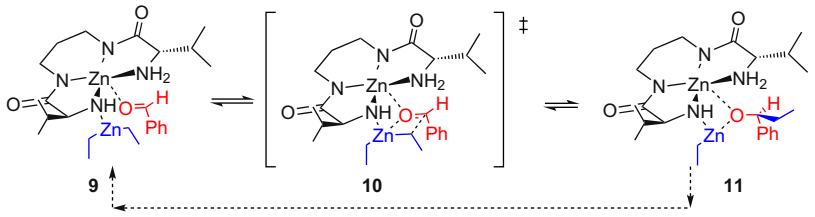


Figure 7. Mechanism of the ethyl transfer reaction.

Table 6
Relevant geometrical parameters (Å and °) of the four possible transition states in the addition of diethylzinc to benzaldehyde for the alanine-based tetraaza ligand **13b**

Parameter	*anti*-trans	*anti*-cis	*syn*-trans	*syn*-cis
Relative energy	0.0	1.8	0.7	1.9
O1–Zn2	2.294	2.265	2.286	2.281
C6–C8	2.348	2.349	2.422	2.361
Zn5–C6	2.329	2.278	2.286	2.337
O1–C8	1.293	1.293	1.295	1.292
C6–C8–O1	114.4	115.3	115.7	113.5
Zn5–C6–C8	66.2	66.1	66.2	65.3
C6–C8–Ph	102.5	92.3	95.1	94.1
C9–N4–Zn5	114.5	116.2	120.6	121.9
O1–C8–C6–Zn5	27.7	34.5	−2.3	−30.9
O1–Zn2–N4–Zn5	−3.8	10.4	12.3	12.2

Table 7
Effect of the steric bulk of the amino acid residue[a]

Entry	Aldehyde	Compound	Yield[b] (%)	ee[c] (%)
1	Benzaldehyde	**4b**	85	99 (*S*)
2	4-Methoxybenzaldehyde	**4b**	90	98 (*S*)
3	Benzaldehyde	**4b′**	83	99 (*R*)
4	Benzaldehyde	**12b**	96	95 (*S*)
5	4-Methoxybenzaldehyde	**12b**	91	98 (*S*)
6	Benzaldehyde	**13b**	96	62 (*S*)
7	4-Methoxybenzaldehyde	**13b**	91	70 (*S*)
8	Benzaldehyde	**14b**	87	97 (*S*)
9	4-Methoxybenzaldehyde	**14b**	89	99 (*S*)

[a] All reactions were carried out in hexanes at 0 °C.
[b] Yields after 24 h, 5% of catalyst was used; yields were determined by NMR.
[c] Determined by chiral HPLC (Chiralcel OD).

of the unfavorable steric interaction forces a deformation in the ring system to favor the attack of diethylzinc to benzaldehyde.

The theoretically determined transition state energies reveal that, for the two ligands studied, the effect of the steric bulk of the amino acid residue can have a remarkable effect on the enantioselectivity of the ethylation process. As can be seen from Tables 5 and 6, a decrease in the steric bulk of the amino acid residue, when changing from valine to alanine, causes a significant decrease in the energy difference of the transition state structures. In both cases, however, the *anti*-trans configuration is preferred over the *syn*-trans one. The energy values were also obtained at MP2 level by single point calculations on the DFT optimized geometries with no significant differences.

In order to check experimentally the validity of those calculations, we synthesized three additional chiral ligands related to **4b** and differing on the size and nature of the amino acid side chain. Thus, a further study was carried out with **12b**, **13b**, and **14b** (derived from alanine, phenylalanine, and isoleucine)[17a,18a] to evaluate the efficiency of the catalytic process and the effect of the steric bulk of the amino acid residue on the enantioselectivity of the reaction (Fig. 8).

As expected, the experimental results confirmed the predictions from calculations.[27] Table 7 gathers some results for the addition of Et_2Zn to benzaldehyde and 4-methoxybenzaldehyde. All catalysts except **4b′** (entry 3) were derived from L-amino acids and gave the (*S*)-secondary alcohol as the major product. Since **4b′** was derived from D-valine, the corresponding product had the (*R*)-configuration. Furthermore, an additional experiment with an *S*/*R* ligand (derived from L-valine and D-valine) was carried out to support the mechanistic results. As expected, this complex showed to be active but not enantioselective in the reaction under study. No significant differences in ee values were detected for the ligands with bulky side chains (**12b**, **13b**, **14b**). Nevertheless, a sharp decrease in the enantioselectivity was observed for the ligand derived from L-alanine (**13b**), therefore confirming the theoretical predictions. Interestingly, the predicted enantioselectivity assuming a Boltzmann distribution at room temperature (65%) shows a good concordance with the observed one at 0 °C (62%).[26]

3. Conclusions

Chiral tetradentate ligands **4**, **12**, **13**, and **14** having aliphatic spacers of different lengths can be easily prepared from simple amino acids in good yields. All ligands were tested for the enantioselective alkylation of dialkylzinc to aromatic aldehydes, showing excellent enantioselectivities (up to 99%). The origin of the enantioselectivity for bisamides was analyzed using high level theoretical calculations. The calculations predict that the (*S*) alcohol should be the predominant product for these ligands, in agreement with the experimental results. The proposed transition states can be compared with those proposed by Noyori and others. Four different 5/4/4-fused tricyclic TSs can be detected and derived from coordination of Et_2Zn to one amino group trans to the side chain and simultaneous trans coordination of benzaldehyde to an axial position of the central zinc. From those TSs, the *anti*-trans is the most stable one for **4b** (ΔE=−3.4 kcal/mol relative to *syn*-trans) favoring the formation of (*S*)-1-phenyl-1-propanol, which is in good agreement with experiments. The nature of the TSs agrees well with our experimental observations on the influence of the bulkiness of the substituents on the amino acid residue of bisamide ligands on the enantioselectivity of the catalytic process. Further studies are in progress in order to study the scope of this process and the potential application of these catalytic systems to other synthetically useful transformations.

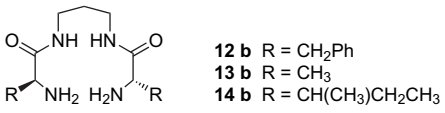


Figure 8. Tetraaza ligands prepared using different amino acids.

4. Experimental

4.1. Addition of diethylzinc to aldehydes. General procedure

Ligand **4b** (100 mg, 0.37 mmol) was placed in a Schlenk tube, dissolved in anhydrous hexanes (10 mL), and a 1 M solution of Et_2Zn in hexanes (0.41 mL, 0.41 mmol) was added. The solution was stirred and heated at 50 °C for 1 h. The reaction mixture was then cooled and benzaldehyde (0.75 mL, 7.4 mmol) was added at 0 °C. The mixture was stirred for 30 min, a 1 M solution of the Et_2Zn in hexanes (9.0 mL, 9.0 mmol) was added dropwise, and the reaction mixture was allowed to warm to rt. The reaction mixture was stirred at rt for 24 h, quenched by the addition of a 1 M solution of HCl, and the product was extracted into Et_2O (3×10 mL). The combined extracts were washed with $KHCO_3$, dried with anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate as the eluent) to give the pure alcohol as a colorless oil. The yield and the selectivity of the reaction were determined by NMR and the enantiomeric excess was determined by chiral HPLC.

4.2. Chiral HPLC analyses of the 1-arylpropan-1-ols

4.2.1. 1-Phenyl-1-propanol

HPLC analysis (Chiralcel OD column), hexanes/2-propanol=95:5, 1 mL/min, 254 nm (UV detector), t_R=9.45 min for (*R*) and t_R=11.35 min for (*S*).

4.2.2. 1-(1-Naphthyl)-1-propanol

HPLC (Chiralcel OD column), hexanes/2-propanol=90:10, 0.5 mL/min, 254 nm (UV detector), t_R=16.5 min for (*R*) and t_R 27.5 min for (*S*).

4.2.3. 1-(4′-Methoxyphenyl)-1-propanol

HPLC analysis (Chiralcel OD column), hexanes/2-propanol=97:3, 1 mL/min, 254 nm (UV detector), t_R=18.34 min for (*R*) and t_R=20.79 min for (*S*).

4.2.4. 1-(4′-Chlorophenyl)-1-propanol

HPLC analysis (Chiralcel OD column), hexanes/2-propanol=99:1, 0.5 mL/min, 254 nm (UV detector), t_R=28.86 min for (*R*) and t_R=27.15 min for (*S*).

4.2.5. 1-(4′-Tolyl)-1-propanol

HPLC analysis (Chiralcel OD column), hexanes/2-propanol=95:5, 1 mL/min, 254 nm (UV detector), t_R=7.87 min for (*R*) and t_R=11.52 min for (*S*).

4.2.6. 1-Phenyl-1-ethanol

GC analysis, capillary column VF-5ms; 30m×0.25 mm, 0.25 μm, 15 psi; temperatures: injector 230 °C, detector 300 °C, oven t_i=60 °C, t_f=130 °C, 10 °C/min, t_R=12.18 min for (*R*) and t_R=12.51 min for (*S*).

4.3. Computational details

DFT calculations were performed using the Gaussian 03 software package.[28] All structures were computed using density functional theory using the non-local hybrid Becke's three-parameter exchange functional (denoted as B3LYP)[29] with LanL2DZ pseudopotential and the associated basis set for Zn[30] and the 6-31G (d)[31] basis set for the rest of atoms. Initially, conformers of the compounds were constructed and computed using the semi-empirical method PM3 in Spartan.[32] The most stable ones were selected for the full DFT calculation. Transition state structures were confirmed by intrinsic reaction coordinate (IRC)[33] calculations to the corresponding reactants and products. All transition states and local minima were validated through frequency analysis. The single point energies were also computed using the MP2 method (6-31+G (d,p) for C, H, O, and N and LanL2DZ for Zn), showing that the potential energy surface at the MP2 level is quite similar to that at the B3LYP level.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.099.

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