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C_2 symmetrical nickel complexes derived from α-amino amides as efficient catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes

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ABSTRACT

A series of C_2 symmetrical 1:2 Ni:L complexes derived from α-amino amides were studied for the enantioselective addition of dialkylzinc reagents to aldehydes. Different structural elements on the ligands seem to play an important role in determining the observed enantioselectivity. Through optimization of structure and reaction conditions, the best ligand provided secondary alcohols in excellent yields (up to 98%) and enantioselectivity of up to 99% ee for (*R*)-enantiomer. A transition state model has been proposed to explain the observed enantioselectivities based on computational calculations at the DFT level. Very interestingly, calculations suggest a coordination model of the aldehyde to the metal complex through association of a lone pair of the carbonyl oxygen to the hydrogen atom of an amino group.

1. Introduction

In the last decades, new synthetic methodologies have been developed for the successful generation of chiral carbon atom centers in a highly selective way, both in academia and industry, through the use of chiral auxiliaries, ligands, or catalysts.[1] In this regard, molecular catalysts consisting of a metal ion and a chiral organic ligand have been widely used in asymmetric synthesis.[2,3] Nowadays, catalytic enantioselective carbon–carbon bond forming reactions are extensively studied reactions in the field of asymmetric synthesis.[4] Among the catalytic reaction for C–C bond-forming, the enantioselective addition of organometallic reagents to aldehydes represents one of the most important and fundamental asymmetric reactions and serves as test for new catalysts. Furthermore, the asymmetric addition of dialkylzinc to aldehydes is a commonly used method for synthesizing chiral secondary alcohols.[5] Since the first report by Oguni and Omi,[6] different families of chiral ligands have been used for this type of reaction. In most cases, these ligands are extremely elaborate from a synthetic point of view, either due to their own structural complexity or because asymmetric synthesis or optical resolution processes are required for their preparation. This fact makes these new ligands expensive and, therefore, reduces the possibility of transferring them to industrial processes, as evidenced by the practically nonexistence industrial use of catalyzed, enantioselective addition of organozinc reagents to carbon electrophiles. From the hundreds of ligands for this asymmetric addition, only a small number of them are obtained by simple synthetic methods.

When designing ligands for enantioselective catalysis, special attention has been given to the synthesis of C_2-symmetric molecules as they are generally considered advantageous because of the associated reduction in the number of possible competing diastereomeric transition states for enantioselective reactions.[7] The use of nitrogen-containing ligands in asymmetric catalysis has received an important attention over the past years.[8] This is associated to the large availability of nitrogen containing chiral natural products, i.e., amino acids, which provides an appropriate starting point for the preparation of the corresponding ligands through short synthetic pathways from easily accessible starting materials.

In this regard, α-amino amides (Fig. 1) seem to appear promising ligands for several reasons: (a) they can be easily prepared by

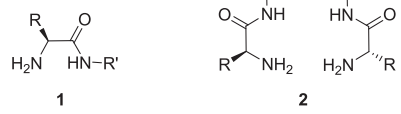

Fig. 1. Structures of α-amino amide **1** and bis(amino amide) **2** ligands.

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standard synthetic protocols; (b) they contain two nitrogen atoms with different coordination capabilities connected through a chiral backbone; (c) their steric properties can be tuned easily by the selection of the appropriate R-carbon substituents and the amine used for their synthesis (R′); (d) they can form robust metal complexes with transition metals. The ability of α-amino amides to form stable complexes with transition metals has recently focused the research in our group. Cu (II) complexes of simple α-amino amides **1** have allowed us to develop interesting fluorescent indicators for citrate with micromolar sensitivity.[9] The corresponding Ni (II) complexes, on the other hand, have shown to be highly active homogeneous catalysts for the addition of dialkylzinc reagents to aldehydes, providing an effective chirality switching associated to the metal-to-ligand ratio,[10] as well as efficient enantioselective catalysts for the conjugate addition of dialkylzinc to chalcones.[11] Zn(II) complexes of related bis(amino amide) ligands **2** (Fig. 1) gave high enantioselectivities in the addition of dialkylzinc reagents to aromatic aldehydes and their corresponding Cu (I) complexes were effective for the cyclopropanation reaction.[12] Furthermore, α-amino amides have been used as supporting ligands in the Ru (II)-catalyzed asymmetric transfer hydrogenation of acetophenone in the presence of *i*-PrOH/KOH.[13]

Taking into account our former results, here we report on the synthesis of new α-amino amide ligands, and their Ni (II) complexes having 2:1 (L:M) stoichiometries. Complexes with 2:1 (L:M) ratios have been selected for their higher thermodynamic stability providing some clear advantages for catalytic applications. These metallic complexes with C_2 symmetry can be easily prepared from commercially available amino acids in a cheap, rapid, and accessible way. Furthermore, we have examined the structural features responsible for their behavior. A transition state model is proposed in order to explain the observed enantioselectivities employing density functional theory calculations.

2. Results and discussion

As a part of our efforts to develop chiral catalysts based on cheap and easily available chiral sources, a family of Ni (II) complexes with 1:1 and 2:1 ligand:metal stoichiometries of α-amino amides derived from L-phenylalanine were prepared and screened in the enantioselective addition of Et_2Zn to benzaldehyde. Preliminary results showed that best results were obtained when *N*-benzylamine was used in the synthesis of α-amino amide (R=CH_2Ph), in particular for 2:1 complexes.[10]

Orange crystals of the 2:1 Ni complex derived from phenylalanine and benzylamine (**6a**) were grown by slow evaporation of a methanolic solution containing the ligand and $Ni(OAc)_2\cdot 4H_2O$, in a 2:1 molar ratio, at pH 12.0 (KOH in methanol). The structure consists of two practically equivalent neutral complex units. In each unit, the nickel atoms are coordinated with square-planar geometry to the two primary amines and to the two deprotonated amide nitrogen groups (Fig. 2).[14] The Ni(II) ion is optimally placed within the N4 basal plane with a deviation of only 0.002 Å. As expected, the Ni-deprotonated amide nitrogen distances (average 1.88 Å) are shorter than the Ni–amine ones (average 1.91 Å). Although all the N–Ni–N angles are close to 90°, it can be noticed that the angles of the five-membered chelate rings involving amide and primary amine nitrogens are lower than 90° (average 86°). The 2:1 complex shows a *trans* disposition of the ligands. The same disposition seems to be also present in solution, as the *trans* arrangement could be confirmed by NOE experiments. Theoretical calculations also indicated *trans* conformations to be more stable than those corresponding to *cis* isomers.[11] Interestingly, the crystal structure shows and extended network of hydrogen bonds between the carbonyl oxygen atoms and one hydrogen atom of the amine units (see ESI, Fig. S4).[15]

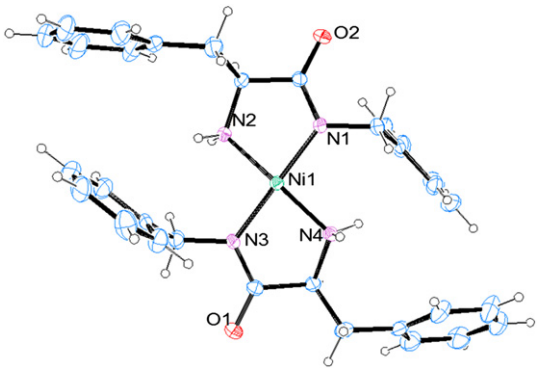
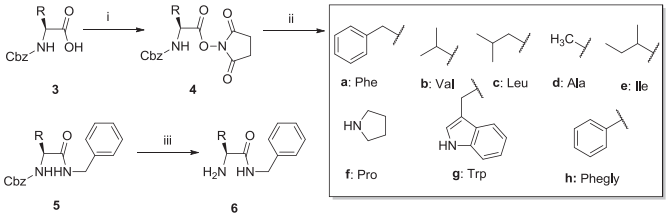


Fig. 2. ORTEP representation of the structure. Ni–N distances [Å]: Ni1–N1=1.869, Ni1–N2=1.901, Ni1–N3=1.884, Ni1–N4=1.914.

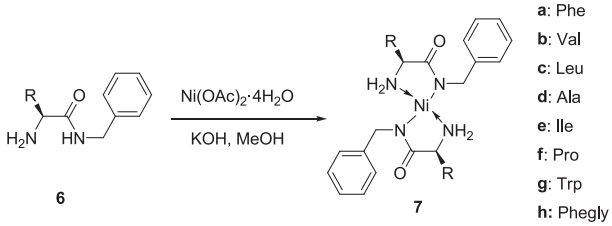
In order to optimize the ligand structure, our next step was to study the effect of the amino acid side chain (R, Fig. 1). For this purpose, a family of α-amino amides derived from a variety of natural and unnatural amino acids were synthesized, while the amide substituent was held constant as the benzyl group (R′=CH_2Ph). Those chiral α-amino amides were synthesized following the methodology previously developed by our group that allows the synthesis of pseudopeptidic compounds with high yields starting from simple amino acids (Scheme 1).[16]



Scheme 1. Synthesis of α-amino amides. Reagents: (i) DCC, *N*-hydroxysuccinimide, THF; (ii) $C_6H_5CH_2NH_2$, THF; (iii) (1) HBr/AcOH. (2) $NaOH_{aq}$.

From those amino amides, the corresponding nickel complexes with a 2:1 ligand:metal stoichiometry were prepared. For that, an appropriate amount of the α-amino amide dissolved in methanol was allowed to reflux under an inert atmosphere with $Ni(OAc)_2\cdot 4H_2O$ (0.5 equiv) in the presence of KOH (1 equiv) for 30 min (Scheme 2). The solution was filtered and concentrated to dryness. The resulting residue was washed with dichloromethane, recrystallized from ethanol, and dried in vacuum. The overall yields for the complexes were in the range of 84–91%. All Ni (II) complexes were fully characterized by IR, UV–vis, ESI-MS and EA (see ESI, Table S1). ESI-MS analyses only detected the presence of Ni (II) complexes with a 2:1 ligand:metal stoichiometry.

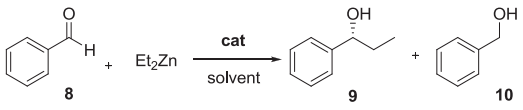
The formation of the corresponding nickel (II) complexes requires basic media (Scheme 2) for deprotonation of the amide N–H and the generation of square-planar Ni species. This is evidenced by



Scheme 2. Synthesis of Ni (II) complexes with 2:1 stoichiometry from α-amino amides.

the color change from green to orange, and by IR spectra having a significant shift of the C=O band to lower frequencies, indicating the participation of the deprotonated amide group in the coordination to Ni^{2+}.[17] UV–vis titrations revealed that 1 equiv of base (KOH) is needed for the formation of the corresponding square planar nickel (II) complex. The absorbance around 440 nm, assigned to the LMCT transitions, clearly revealed the existence complexes with square planar geometry. When the complexes were characterized by circular dichroism (CD) spectroscopy, a distinctive band associated to the d–d transition can be observed at 400–600 nm that may be attributed to the splitting of the energy levels of the d–d transitions of the metal located in the chiral coordination environment.[18]

In order to examine the catalytic activity of these complexes, the asymmetric addition of Et_2Zn to benzaldehyde to yield 1-phenyl-1-propanol was chosen as a model reaction (Scheme 3). For the optimization of the reaction conditions the nickel complex derived from ligand **6a** (R=R′=CH_2Ph) was used. The reaction was initially performed with a 1% mol of the nickel complex **7a** in toluene at 0 °C, using a commercially available solution of Et_2Zn (1.1 M in toluene). After the complete conversion of benzaldehyde, the mixture was quenched by the addition of 1 M aqueous HCl. After extraction with Et_2O, drying, and evaporation of the solvent, the product yield was directly determined on the crude mixture by ^1H NMR, while the ee of the product was measured by HPLC on a chiral stationary phase (Chiralcel OD). Under these conditions, the reaction was complete after 14 h and (*R*)-1-phenyl-1-propanol was obtained as the major product in 92% yield and 92% ee.



Scheme 3. Diethylzinc addition to benzaldehyde.

Initially, a screening of solvents was carried out under identical conditions to study the solvent effect, but no improvement was detected when changing to hexane, CH_3CN or THF (see ESI, Table S5). In order to determine the optimal amount of the ligand needed for the addition of diethylzinc to benzaldehyde, several experiments using variable quantities of nickel (II) complex **7a** were carried out. In these studies, the concentrations of benzaldehyde and diethylzinc were kept constant at 0.5 and 1.1 mM, respectively, and the reaction was conducted at 0 °C in toluene. When reducing the amount of catalyst below 1%, the conversion at 14 h is appreciably reduced and, accordingly, longer reaction times are needed (see ESI, Fig. S5). At the same time the selectivity starts to be slightly reduced. Only below 0.1% loadings an appreciable reduction in enantioselectivity was detected. At 0.1% loading, the ee observed was 92%, with 89% conversion. Increasing the amount of catalyst above 1% does not produce any improvement in enantioselectivity although an increase in selectivity and conversion (92% ee, 94% selectivity, and 98% conversion). Regarding the effect of the amount of Et_2Zn, best results were obtained using 1.2 equiv of Et_2Zn with 92% yield and 92% ee. Increasing the amount of Et_2Zn enhanced the undesirable reduction of benzaldehyde to benzyl alcohol.

Reducing the temperature to −20 °C allows slightly increasing selectivity and ee (with 1 mol % of catalyst: 99% and 94%, respectively) but at the expenses of a great reduction in conversion (69%). A further decrease in the temperature to −40 °C led to a dramatic decrease in both the conversion (25%) and the ee (36%). On the other hand, at room temperature a decrease in ee to 86% was observed. It must be noted that the addition of dialkylzinc to aldehydes usually reaches a maximum ee at a certain temperature, which is called the isoinversion temperature.[19] Thus, optimal conditions seems to correspond to the use of 1 mol % of the nickel complex **7a** in toluene at 0 °C for about 14 h.

In order to understand the mode of action of the catalyst, the standard reaction between diethylzinc and benzaldehyde was monitored over time for a total period of 18 h (see ESI, Fig. S6). The addition was complete in 14 h and the by-product **10** remained at a relatively low level throughout this period. The enantioselectivity of the desired product **9** remained relatively constant over time.[20]

To examine the influence of the amino acid side chain (R) in the ligands, Ni (II) complexes **7b**–**h** were studied, while the R′ group was held constant as benzyl. Results showed that for the conditions established, almost all of the catalysts afforded 1-phenyl-1-propanol in excellent yields, but ee values revealed a dependence on the amino acid substituent. The results after 14 h are presented in Table 1 and, as observed for similar systems, higher values of ee were achieved when bulky substituents were present.[21]

Table 1
Effect of the amino acid side chain on the addition of Et_2Zn to benzaldehyde

Entry	Catalyst	Amino acid	Conv. (%)[a]	Selectivity (%)[b,d]	ee (%)[c]
1	**7a**	Phe	99	94 (92)	92 (*R*)
2	**7b**	Val	99	85 (82)	58 (*R*)
3	**7c**	Leu	99	91 (88)	54 (*R*)
4	**7e**	Ileu	99	90 (87)	74 (*R*)
5	**7d**	Ala	99	81 (77)	47 (*R*)
6	**7g**	Trp	99	70 (68)	80 (*R*)
7	**7f**	Pro	42	50 (n.m.)	0
8	**7h**	PhGly	97	95 (90)	93 (*R*)

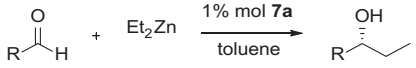
[a] Aldehyde (1 equiv), Et_2Zn (1.2 equiv), and catalyst (1% mol) in toluene at 0 °C. Determined by ^1H NMR.
[b] Determined by ^1H NMR. Selectivity=(**9**/**9**+**10**)×100.
[c] Determined by HPLC (Chiralcel OD).
[d] Isolated yields are given in parenthesis. n.m.=not measured.

Complexes derived from ligands with bulky aromatic groups, such as α-amino amides derived from phenylalanine (entry 1) and phenylglycine (entry 8) provided the highest ee values for the ethylation of benzaldehyde. Ligands with branched alkyl groups, such as those derived from valine (entry 2), leucine (entry 3), and isoleucine (entry 4) gave good enantioselectivities, being the branching at the α position of the side chain the most efficient substitution pattern. Other sterically less demanding side chain ligands gave, as expected, lower enantioselectivities (entry 5). Interestingly, when the catalyst derived from (*S*)-proline was used, a low activity (42% conversion and 50% selectivity) and no enantioselectivity were observed (entry 7).

As inferred from Table 1, the catalyst derived from phenylalanine (**7a**, R=CH_2Ph) gives the highest efficiency in terms of yield and stereoselectivity for the addition of diethylzinc to benzaldehyde. To study the scope and limitations of the process, this catalyst was screened for the addition of diethylzinc to a variety of aromatic and aliphatic aldehydes, using under the optimized reaction conditions. As seen in Table 2, good to excellent enantioselectivities could be achieved for aromatic and aliphatic aldehydes, with a reaction time significantly shorter than those reported in literature with other catalysts (usually from 15 h to some days).

The results reveal that complex **7a** is a highly efficient catalyst for the enantioselective addition of dialkylzinc to aldehydes to afford optically active secondary alcohols in high yields and with excellent enantioselectivities. Several trends have emerged from these experiments (Table 2). The presence of electron-donating or electron-withdrawing substituents on the aromatic ring is compatible with the selected reaction conditions. Aromatic substrates including 1-naphthaldehyde, 2-naphthaldehyde, 4-methoxy benzaldehyde, and 4-chloro benzaldehyde react with diethylzinc

Table 2
Results in the addition of diethylzinc to different aldehydes catalyzed by **7a**



Entry	R	Conv. (%)[a]	Selectivity (%)[b,d]	ee (%)[c]
1	Ph	98	96 (91)	92 (*R*)
2	2-Naphtyl	98	97 (91)	76 (*R*)
3	1-Naphtyl	95	96 (89)	80 (*R*)
4	4-MeO–Ph	98	99 (94)	99 (*R*)
5	4-Cl–Ph	92	93 (83)	79 (*R*)
6	2-Me–Ph	67	89 (n.m.)	71 (*R*)
7	3-Me–Ph	92	96 (88)	80 (*R*)
8	4-Me–Ph	94	99 (90)	95 (*R*)
9	Cyclohexyl	72	76 (n.m.)	41 (*R*)
10	Hexyl	75	88 (n.m.)	80 (*R*)

[a] Aldehyde (1 equiv), Et_2Zn (1.2 equiv), and catalyst **7a** (1% mol) in toluene at 0 °C, 12 h. Determined by ^1H NMR.
[b] Determined by ^1H NMR. Selectivity=(**9**/**9**+**10**)×100.
[c] Determined by HPLC (Chiralcel OD).
[d] Isolated yields are given in parenthesis. n.m.=not measured.

to give the corresponding (*R*)-alcohol with 76–99% ee values. An important steric substituent effect is observed at the *ortho* position (entries 6, 7, and 8). In the case of aliphatic aldehydes, this catalyst also gave good enantioselectivities for the addition of diethylzinc to cyclohexanecarbaldehyde and hexanal, but producing lower yields or conversions (entries 9 and 10).

Encouraged by these results, we investigated the addition of dimethylzinc to aldehydes. The small number of studies for the enantioselective addition of Me_2Zn to aldehydes, as compared with that of Et_2Zn, is in part due to the lower reactivity of Me_2Zn. However, in recent years, this reaction has received special attention,[22] as it allows the synthesis of the chiral 1-hydroxyethyl moiety that is widespread in the structure of natural products and drug compounds.[23] Firstly, the addition of dimethylzinc to benzaldehyde, under the same conditions used for diethylzinc, was examined. In the presence of 1 mol % of the Ni (II) catalyst **7a**, the reaction was complete after 24 h at 0 °C, with an excellent yield and enantioselectivity (Table 3). At room temperature the reaction afforded the desired addition product in 98% conversion and 85% selectivity with 81% ee. Increasing the amount of ligand from 1 to 5 mol % led to a further improvement in the catalytic activity (quantitative conversion in 14 h, entry 2). No improvement was obtained by further increasing the catalyst loading to 10 mol % (entry 4). Thus, 1 mol % of the catalyst and 0 °C were selected as the best reaction conditions in toluene. As reported in most cases, the reactions with diethylzinc were significantly faster than with dimethylzinc.

Table 3
Variation of substrate and dimethylzinc

Entry	R	**7a** (% mol)	Conv. (%)[a]	Selectivity (%)[b,d]	ee (%)[c]
1	Ph	0.1	96	95 (89)	92 (*R*)
2	Ph	1	99	99 (96)	95 (*R*)
3	Ph	5	98	99 (95)	95 (*R*)
4	Ph	10	98	99 (95)	95 (*R*)
5	2-Naphtyl	1	97	99 (93)	81 (*R*)
6	1-Naphtyl	1	98	93 (89)	44 (*R*)
7	4-Me–Ph	1	94	98 (90)	82 (*R*)
8	4-MeO–Ph	1	99	99 (95)	82 (*R*)
9	4-Cl–Ph	1	94	93 (85)	76 (*R*)
10	Cyclohexyl	1	66	89 (n.m.)	32 (*R*)
11	Hexyl	1	77	80 (n.m.)	35 (*R*)

[a] Aldehyde (1 equiv), Et_2Zn (see Table 3), and catalyst **7a** in toluene at 0 °C. Determined by ^1H NMR.
[b] Determined by ^1H NMR.
[c] Determined by GC (column VF-5 ms).
[d] Isolated yields are given in parenthesis. n.m.=not measured.

Table 3 also displays the results for the enantioselective addition of dimethylzinc to a variety of aldehydes (entries 5–11). As can be seen, good to excellent enantioselectivities could be achieved for various aromatic aldehydes. It was also found that this catalyst was efficient for the addition of dimethylzinc to aliphatic aldehydes (entries 10 and 11), although with lower conversions and enantioselectivities.

In order to obtain a more detailed understanding of the mechanism involved, DFT calculations using the Gaussian 03 software package[24] were performed. A comprehensive preliminary mechanistic study of the nickel catalyzed diethylzinc addition to benzaldehyde was carried out by means of a medium-sized model: the Ni (II) complex was derived from the *N*-methylamino amide of *N*-L-alanine (**1**, R′=CH_3, R=CH_3) and diethylzinc and benzaldehyde were used as reagent and substrate. Structures were optimized at the B3LYP/6-31G level to obtain properly characterized minima and transition-state (TS) structures. As DFT studies suggest, diethylzinc can coordinate to the nickel catalyst through the carbonyl oxygen of the α-amino amide (Fig. 3) in a similar way as reported by Dangel and Polt in the case of zinc (II) complexes derived from bis(imino amides).[25] According to theoretical calculations, diethylzinc shifts from a linear geometry to an angular geometry (155.1°) and becomes significantly more nucleophilic upon coordination, as suggested by the increase on the Zn–C bonds when coordinated (2.069 vs 2.023 Å).

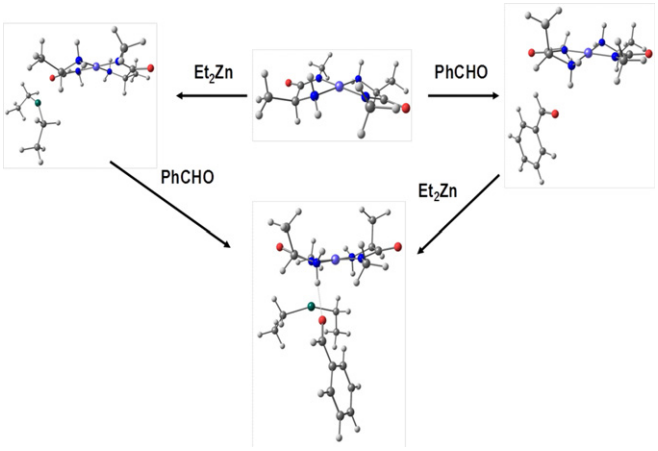


Fig. 3. Formation of the '*reactive-forming*' complex.

Coordination of benzaldehyde to the catalytic nickel complex through the carbonyl oxygen would give place to two possible 'reactive-forming' complexes, as it can use either of its two lone pairs (*cis* or *trans* to Ph). In the case of amino alcohols, coordination to zinc complexes takes place through displacement of a solvent molecule to afford tetrahedral zinc complexes, but this seems unreasonable in the case C_2 Ni complexes derived from α-amino amides for the stronger coordination ability of amine nitrogen atoms.

Very interestingly, calculations suggest that the lone pair of the carbonyl oxygen from the aldehyde does not coordinate to the Ni, but to the axial hydrogen of one of the amino groups, which acidity is increased upon coordination of the nitrogen atom to the metal (Fig. 3). As inferred from DFT calculations, upon coordination, the carbon–oxygen double bond length is increased 1.6%, which is proposed to increase the electrophilicity of the carbonyl compound. Based on this model, the ethyl transfer from diethylzinc to benzaldehyde will occur through two possible transition states to give the 'product forming' complex with the corresponding absolute configuration (Fig. 4).

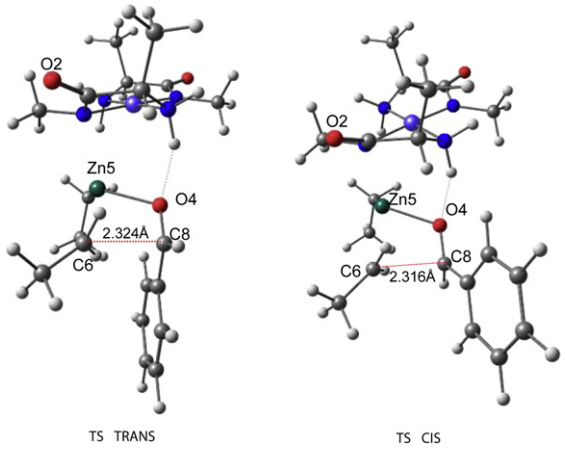


Fig. 4. Proposed transition states for enantioselective addition of organozinc to aldehydes.

Based on the model proposed by Noyori and co-workers, the product forming complex is regenerated from the final complex (Zn-bound alkoxylate) upon reaction with diethylzinc and benzaldehyde, where the formation of a stable dialkylzinc alkoxyde dimer or tetramer is a crucial step for the completion of the catalytic cycle.[26] The stereochemistry of the alkoxyde product is kinetically determined by the relative energy of the alternative diastereomeric transition states. In this case, an energy difference of 0.8 kcal/mol is calculated between the two transition states (Fig. 4). Thus, calculations predict the *R* stereoisomer to be the main product, which is consistent with the experimental results. From a qualitative point of view, the predicted enantioselectivity assuming a Boltzmann distribution at room temperature (60%) shows a reasonable concordance with the experimentally observed one at 0 °C (47%; Table 1, entry 5).[27]

To check the effect of the R group in the α-amino amide ligands (see Fig. 1), we performed a theoretical analysis for different amino acids containing side chains of different bulkiness. These calculations revealed that the effect of the steric bulk of the amino acid residue can have a remarkable effect on the enantioselectivity of the process. As reported by other authors, the steric bulk around the chiral carbon atom or the nitrogen atom in chiral β-amino alcohol ligands generally enhances the enantioselectivity of the Et_2Zn addition to benzaldehyde.[28] As can be seen in Table 4, the change from alanine to valine, causes a significant increase in the energy difference of the transition state structures (from 0.8 to 1.1 kcal/mol). Finally, when phenylalanine was used, the energy difference increased to 2.1 kcal/mol. In both cases, however, the (*R*) configuration in the final product is preferred.

Table 4
Variation of substrate and diethylzinc using ligand **1h**

Entry	R	ΔE[a]	ee calcd (%)[b]	ee exp (%)
1	CH_3	0.8	56	47
2	$CH(CH_3)_2$	1.1	78	64
3	CH_2Ph	2.1	97	92

[a] Values are given in kcal/mol.
[b] Predicted enantioselectivity assuming a Boltzmann distribution at 293 K.

3. Conclusions

In summary, we have shown that nickel complexes with 2:1 stoichiometry (L:M) derived from chiral α-amino amides catalyze the enantioselective addition of diethylzinc and dimethylzinc to aldehydes with good to high enantioselectivities. These catalysts can be easily obtained from cheap, commercially available, starting materials. Their modular structure allows an easy optimization of the catalytic system. Different structural modifications were examined in this regard, resulting in the selection of a phenylalanine-based ligand, with a benzyl group in the amide moiety. The corresponding 2:1 Ni (II) complex catalyzed the addition of diethylzinc to substituted aldehydes with enantioselectivities of up to 99%. Those enantioselectivities can be ranged between the best ones obtained for this reaction. According to DFT studies, a transition state model has been suggested to explain the enantioselectivities observed. 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 α-amino amide ligands on the enantioselectivity of the catalytic process. It deserves to be mentioned that calculations suggests that coordination of the aldehyde to the complex does not take place through the metal but with a hydrogen atom of the amino groups of the ligand that become increasingly acidic upon formation of the Ni (II) complex. This is a new catalytic model that had not been previously observed for related systems. Further investigation on the applications of these nickel complexes for other asymmetric reactions is ongoing in our laboratory.

4. Experimental section

4.1. General remarks

All reactions were carried out using standard Schlenk techniques unless specified other otherwise. All reagents were purchased from commercial suppliers and used without further purification. Dry hexane, CH_3CN and toluene were prepared by distillation from sodium and stored over sodium wire under N_2 atmosphere. Dry tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone as a moisture indicator under N_2 atmosphere before use. All liquid aldehydes were freshly distilled under reduced pressure. Degassed dry solvents were used for all experiments. The NMR experiments were carried out on a Varian INOVA 500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts (δ, parts per million) are relative to the resonance of the deuterated solvent as the internal standard ($CDCl_3$, δ=7.26 ppm for proton NMR, δ=77.00 ppm for carbon NMR). The data are reported as (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or unresolved, br s=broad singlet, coupling constant(s) in Hertz, integration). Infrared spectra were recorded with a Perkin–Elmer 2000 spectrometer. Chiral HPLC was performed using Diacel chiralcel OD column. Optical rotations were measured using a JASCO P-1020 polarimeter. Mass spectra (ESI) were recorded with a Micromass Quattro LC spectrometer equipped with an electrospray ionization source and a triple-quadrupole analyzer. Melting points were measured with a STUART SMP10 melting point apparatus.

4.2. General procedure for the preparation of *H*-hydroxysuccinimide ester of *N*-Cbz-L-amino amides 4a–h[10–12]

The *N*-Cbz-L-amino acid (1 mmol) and *N*-hydroxysuccinimide (1 mmol) were dissolved in dry THF at 0 °C. Once a clear solution had been obtained, DCC (1 mmol) in anhydrous THF was added in several aliquots and the resulting solution was stirred at 0–5 °C for 3 h. The dicyclohexylurea formed was filtered off and the filtrate was concentrated to dryness. The crude product was recrystallized from 2-propanol to furnish the pure product.

4.3. General procedure for the preparation of *N*-Cbz-L-amino amides 5a–h[10–12]

The *N*-hydroxysuccinimide ester of *N*-Cbz-L-amino acid (1 mmol) was dissolved in anhydrous THF (40 mL) and *N*-benzylamine (1 mmol) was added dropwise with stirring. The reaction

mixture was stirred at 50–60 °C for 8 h. The white solid formed was filtered and washed with cold basic water (3×10 mL) and then with cold water. The solid was dried under reduced pressure (60–70 °C) for 24 h.

4.4. General procedure for the deprotection of *N*-Cbz-L-amino amides 6a–h[10–12]

The *N*-Cbz-amino amide was treated with a solution of HBr/AcOH (33%) and the mixture was stirred at room temperature until CO_2 evolution ceased. At this point, dry diethyl ether was added to the clear solution, which led to the deposition of a precipitate. This was filtered and washed with additional ether and dissolved in distilled water; the resulting solution was extracted with chloroform (3×10 mL). Solid NaOH was then added up to a pH value of 12 and the resulting solution was saturated with NaCl and extracted with chloroform (3×10 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under vacuum to obtain a white solid.

*4.4.1. (S)-2-Amino-N-benzyl-3-phenylpropanamide (**6a**).* Yield=63%; mp=179.1–180.4 °C; $[\alpha]_D^{20}$ +21.1 (*c* 0.1, MeOH); ESI-MS *m*/*z*=255.3 ($M+H^+$), 277.3 ($M+Na^+$); IR (KBr) ν_{max}: 3320, 2895, 1953, 1667, 1542, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.74–2.82 (dd, 1H, *J*=8.7, 13.7 Hz, C*H*$_2$Ph), 3.26–3.32 (dd, 1H, *J*=7.0, 12.6 Hz, C*H*$_2$Ph) 3.66–3.70 (m, 2H, NHC*H*$_2$Ph, CH*), 4.43–4.45 (d, 1H, *J*=6.5 Hz, NHC*H*$_2$Ph), 6.85–6.88 (m, 2H, Ar–H), 6.87–6.98 (m, 2H, Ar–H), 7.11–7.14 (m, 6H, Ar–H), 7.57 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 41.0, 43.2, 56.5, 126.8, 127.0, 127.4, 127.8, 128.7, 129.4, 137.8, 138.4, 174.0; Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.49; H, 7.27; N, 11.22.

*4.4.2. (S)-2-Amino-N-benzyl-3-methylbutanamide (**6b**).* Yield=87%; mp=115.1–116.0 °C; $[\alpha]_D^{20}$ +37.4 (*c* 0.1, MeOH); ESI-MS *m*/*z*=207.1 ($M+H^+$); IR (KBr) ν_{max}: 3320, 2895, 1953, 1667, 1542, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.01–1.04 (dd, 6H, *J*=6.9 Hz, CH_3), 2.18 (m, 1H, C*H*$(CH_3)_2$), 3.68 (d, 1H, *J*=5.7 Hz, CH*), 4.36–4.50 (dd, 2H, *J*=14.7, 27.0 Hz, NHC*H*$_2$Ph), 7.26–7.34 (m, 10H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 16.8 (CH_3), 17.7, 30.4, 43.2, 58.7, 127.4, 128.3, 128.5, 138.2, 168.3; Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 70.01; H, 8.89; N, 13.42.

*4.4.3. (S)-2-Amino-N-benzyl-4-methylpentanamide (**6c**).* Yield=83%; mp=189.1–190.4 °C; $[\alpha]_D^{20}$ +27.9 (*c* 0.1, MeOH); ESI-MS *m*/*z*=221.3 ($M+H^+$); IR (KBr) ν_{max}: 3310, 2955, 1979, 1655, 1522, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.90–0.95 (d, 6H, *J*=6.6 Hz, CH_3), 1.34–1.58 (m, 2H, C*H*$_2$CH$(CH_3)_2$), 1.61–1.72 (m, 1H, C*H*$(CH_3)_2$), 3.33–3.36 (d, 1H, *J*=7.3 Hz, CH*), 4.37 (d, 2H, *J*=7.2 Hz, NHC*H*$_2$Ph), 7.27–7.31 (m, 5H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 22.8, 23.5, 26.1, 44.2, 45.9, 54.8, 128.5, 128.8, 129.7, 140.1, 178.1; Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 71.04; H, 9.22; N, 12.82.

*4.4.4. (S)-2-Amino-N-benzylpropanamide (**6d**).* Yield=92%; mp=179.0–180.5 °C; $[\alpha]_D^{20}$ +2.1 (*c* 0.1, MeOH); ESI-MS *m*/*z*=179.3 ($M+H^+$); IR (KBr) ν_{max}: 3294, 2937, 1955, 1682, 1534, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.31–1.34 (d, 3H, *J*=7.2 Hz, CH_3), 3.86–3.92 (dd, 1H, *J*=6.9 Hz, CH*), 4.15–4.30 (dd, 2H, *J*=15.3 Hz, NHC*H*$_2$Ph), 7.11–7.21 (m, 5H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 19.1, 45.7, 51.7, 129.9, 130.3, 131.5, 138.3, 172.7; Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.31; H, 7.97; N, 17.87.

*4.4.5. (2S,3S)-2-Amino-N-benzyl-3-methylpentanamide (**6e**).* Yield=88%; mp=164.1–166.0 °C; $[\alpha]_D^{20}$ +7.2 (*c* 0.1, MeOH); ESI-MS *m*/*z*=221.1 ($M+H^+$); IR (KBr) ν_{max}: 3290, 2935, 1953, 1684, 1532, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.92–1.01 (m, 6H, CH_3) 1.58–1.61 (m, 2H, CH_2), 1.87–1.96 (m, 1H, CH), 3.73 (d, 1H, *J*=5.4 Hz, CH*), 4.34–4.50 (dd, 2H, *J*=14.4 Hz, NHC*H*$_2$Ph), 7.28–7.33 (m, 5H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 10.5, 14.0, 24.3, 36.9, 43.1, 57.9, 127.4, 128.3, 128.5, 138.5, 168.1; Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.98; H, 9.19; N, 12.78.

*4.4.6. (S)-N-Benzylpyrrolidine-2-carboxamide (**6f**).* Yield=89%; mp=125.1–126.7 °C; $[\alpha]_D^{20}$ +13.6 (*c* 0.1, MeOH); ESI-MS *m*/*z*=205.3 ($M+H^+$); IR (KBr) ν_{max}: 3312, 2895, 1962, 1669, 1544, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.49–1.63 (m, 2H, CH_2), 1.77–2.05 (m, 2H, CH_2), 2.74–2.89 (m, 2H, CH_2), 3.62–3.68 (m, 1H, CH*), 4.51 (m, 1H, NHC*H*$_2$Ph), 6.85–6.90 (m, 3H, Ar–H), 7–23–7.28 (m, 3H, Ar–H), 7.32–7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 23.6, 29.8, 43.2, 47.6, 60.9, 126.4, 127.3, 128.1, 136.2, 170.1; Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.89; H, 7.84; N, 13.61.

*4.4.7. (S)-2-Amino-N-benzyl-3-(1H-indol-3-yl)propanamide (**6g**).* Yield=89%; mp=189.1–190.9 °C; $[\alpha]_D^{20}$ +10.8 (*c* 0.1, MeOH); ESI-MS *m*/*z*=294.7 ($M+H^+$); IR (KBr) ν_{max}: 3325, 2897, 1963, 1667, 1540, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 3.14–3.38 (ddd, 2H, *J*=6.8, 11.8 Hz, C*H*$_2$Ind), 4.20–4.34 (dd, 2H, *J*=8.9 Hz, NHC*H*$_2$Ph), 4.51 (m, 1H, CH*), 6.85–6.90 (m, 3H, Ar–H), 7–10–7.40 (m, 5H, Ar–H), 7.70 (br, 1H, Ar–H), 8.01 (br, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 43.7, 55.2, 107.2, 112.1, 118.5, 120.5, 125.0, 127.1, 127.3, 127.5, 128.5, 128.8, 131.3, 135.2, 136.6, 169.7; Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.89; H, 6.64; N, 14.21.

*4.4.8. (S)-2-Amino-N-benzyl-2-phenylacetamide (**6h**).* Yield=84%; mp=173–175 °C; $[\alpha]_D^{20}$ +34.8 (*c* 0.1, MeOH); ESI-MS *m*/*z*=240.3 ($M+H^+$); IR (KBr) ν_{max}: 3332, 2893, 1962, 1669, 1545, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 4.20 (d, 2H, *J*=8.9 Hz, NHC*H*$_2$Ph), 4.81 (s, 1H, CH*), 6.88–6.94 (m, 4H, Ar–H), 7–13–7.35 (m, 6H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 43.7, 55.2, 126.6, 127.0, 127.8, 128.5, 128.6, 130.3, 133.2, 136.3, 169.7; Anal. Calcd for $C_{18}H_{19}N_3O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.29; H, 7.18; N, 8.08.

4.5. General procedure for the preparation of 2:1 Ni complexes

An appropriate amount of α-amino amide (1 mmol) dissolved in methanol was allowed to reflux under an inert atmosphere with $Ni(OAc)_2 \cdot 4H_2O$ (0.5 mmol) in the presence of KOH (1 mmol) for 30 min. The solution was filtered and concentrated to dryness. The resulting residue was washed in dichloromethane, recrystallized from ethanol, and dried in vacuum.

*4.5.1. 2:1 Ni complex of (S)-2-amino-N-benzyl-3-phenylpropanamide (**7a**).* Yield: 79%; FTIR (KBr): 3442, 3046, 2951, 1590 (C=O), 1455, 1261 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 351 nm (260); ESI-MS (negative) *m*/*z* 599.2 $[M+Cl]^-$; Anal. Calcd for $C_{16}H_{16}N_2ONi$: C, 67.99; H, 6.06; N, 9.91. Found: C, 67.82; H, 6.25; N, 9.96.

*4.5.2. 2:1 Ni complex of (S)-2-amino-N-benzyl-3-methylbutanamide (**7b**).* Yield: 72%; FTIR (KBr): 3438, 3045, 2959, 1582 (C=O), 1465, 1259 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 438 nm (245); ESI-MS (negative) *m*/*z* 503.2 $[M+Cl]^-$; Anal. Calcd for $C_{12}H_{16}N_2ONi$: C, 61.43; H, 7.30; N, 11.94. Found: C, 70.01; H, 8.89; N, 13.42.

*4.5.3. 2:1 Ni complex of (S)-2-amino-N-benzyl-4-methylpentanamide (**7c**).* Yield: 70%; FTIR (KBr): 3440, 3049, 2933, 1589 (C=O), 1459, 1260 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 452 nm (210); ESI-MS (negative) *m*/*z* 531.2 $[M+Cl]^-$; Anal. Calcd for

$C_{13}H_{18}N_2ONi$: C, 62.79; H, 7.70; N, 11.27. Found: C, 62.57; H, 7.85; N, 11.14.

*4.5.4. 2:1 Ni complex of (S)-2-amino-N-benzylpropanamide (**7d**).* Yield: 82%; FTIR (KBr): 3437, 3042, 2947, 1587 (C=O), 1453, 1258 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 448 nm (235); ESI-MS (negative) *m/z* 447.1 $[M+Cl]^-$; Anal. Calcd for $C_{10}H_{12}N_2ONi$: C, 58.14; H, 6.34; N, 13.56. Found: C, 58.32; H, 6.45; N, 13.49.

*4.5.5. 2:1 Ni complex of (2S,3S)-2-amino-N-benzyl-3-methylpentanamide (**7e**).* Yield: 76%; FTIR (KBr): 3441, 3047, 1593 (C=O), 1458, 1255 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 432 nm (220); ESI-MS (negative) *m/z* 531.2 $[M+Cl]^-$; Anal. Calcd for $C_{13}H_{18}N_2ONi$: C, 62.79; H, 7.70; N, 11.27. Found: C, 62.99; H, 6.75; N, 11.39.

*4.5.6. 2:1 Ni complex of (S)-N-benzylpyrrolidine-2-carboxamide (**7f**).* Yield: 72%; FTIR (KBr): 3438, 3048, 2932, 1588 (C=O), 1461, 1259 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 445 nm; ESI-MS (negative) *m/z* 499.2 $[M+Cl]^-$; Anal. Calcd for $C_{12}H_{14}N_2ONi$: C, 66.36; H, 5.24; N, 5.24. Found: C, 66.62; H, 5.05; N, 5.36.

*4.5.7. 2:1 Ni complex of (S)-2-amino-N-benzyl-3-(1H-indol-3-yl) propanamide (**7g**).* Yield: 62%; FTIR (KBr): 3439, 3045, 2950, 1584 (C=O), 1460, 1261 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 437 nm (253); ESI-MS (negative) *m/z* 677.2 $[M+Cl]^-$; Anal. Calcd for $C_{18}H_{17}N_3ONi$: C, 61.96; H, 6.50; N, 12.04. Found: C, 61.85; H, 6.69; N, 11.99.

*4.5.8. 2:1 Ni complex of (S)-2-amino-N-benzyl-2-phenylacetamide (**7h**).* Yield: 71%; FTIR (KBr): 3440, 3048, 2944, 1595 (C=O), 1463, 1260 cm^{-1}; UV–vis absorption (MeOH): λ (ε, M^{-1} cm^{-1}) 431 nm (230); ESI-MS (negative) *m/z* 571.1 $[M+Cl]^-$; Anal. Calcd for $C_{18}H_{17}N_3ONi$: C, 67.66; H, 6.06; N, 10.43. Found: C, 67.44; H, 6.18; N, 10.56.

4.6. General procedure for the addition of ZnR_2 to aldehydes

The Ni complex (0.1 equiv) was dissolved in anhydrous toluene (10 mL) in a Schlenk tube. The solution was stirred and cooled at 0 °C for 30 min, and then a solution of Et_2Zn (1.1 M in toluene) or Me_2Zn (1.0 M in toluene) (12 equiv) was added dropwise via a syringe under N_2 atmosphere. After stirring the mixture for 30 min at room temperature, a solution of aldehyde (10 equiv) in dry toluene was added dropwise via a syringe. The mixture was stirred at room temperature for 8 h, quenched with 1 M HCl aqueous (5 mL), 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 evaporated under vacuum. Purification by column chromatography (silica gel, 9:1 hexane/AcOEt as eluent) gave the pure alcohol as a colorless oil. All reactions were carried out using 0.1–0.2 mL of aldehyde. The conversion and the selectivity of the reaction were determined by NMR spectroscopy, and the enantioselectivity was determined by HPLC or GC on a chiral stationary phase.

4.7. Conditions for the analysis of chiral secondary alcohols

GC: chiral capillary GC column VF-5 ms; 30 m×0.25 mm, 0.25 μm. Carrier Gas: H_2 (5 mL min^{-1}). Injector 230 °C, Detector (FID) 300 °C, oven 60–130 °C, 10 °C min^{-1}. Chiral HPLC: Chiralcel OD column; 254 nm UV detector. The conditions of analysis and retention times of the *R* and *S* isomers have been reported elsewhere.[22h,29]

4.8. Computational details

DFT calculations were performed using the Gaussian 03 software package. All structures were computed using density functional theory using the non local hybrid Becke's three-parameter exchange functional (denoted as B3LYP)[30] with LanL2DZ pseudopotential and the associated basis set for Ni and Zn[31] and the 6-31G (d)[32] basis set for the rest of atoms. Initially, conformers of the compounds were constructed and computed using the semi-empirical method PM3 in Spartan.[33] The most stable ones were selected for the full DFT calculation. Transition state structures were confirmed by intrinsic reaction coordinate (IRC)[34] 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

Characterization of Ni 2:1 (II) complexes. FTIR spectra for **6a** and **7a** complex. UV–vis and CD spectra for **7a**. Crystal data for **7a**. Results in the addition of diethylzinc to benzaldehyde using different solvents. Results in the addition of diethylzinc to benzaldehyde at different loadings of catalyst **7a**. Cartesian coordinates (for the minimized structures B3LYP/6-31G*) for reactive complexes. Supplementary data related to this article can be found online http://dx.doi.org/10.1016/j.tet.2012.11.025.

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14. Crystal data: $C_{32}H_{34}N_4NiO_2$, M_r=565.34, T=298 K, orthorhombic, space group $P2_12_12_1$, a=9.6064(3), b=10.1035(3), c=28.3643(7) Å, V=2752.99(14) Å^3, Z=4, 8100 unique reflections, final R_1=0.0531and wR_2=0.0549 for 4574 observed [$I>2\sigma(I)$] reflections. CCDC 775444 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk).
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