

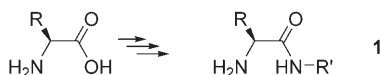
Efficient Chirality Switching in the Addition of Diethylzinc to Aldehydes in the Presence of Simple Chiral α -Amino Amides**

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Chiral catalysis is one of the most efficient approaches for the preparation of enantiopure compounds.^[1] For practical applications, the chiral ligands need to be accessible from simple starting materials and the process has to provide access to both enantiomers of the product, to guarantee that the desired isomer can be obtained.^[2] This last condition can be fulfilled through the preparation of both enantiomers of the corresponding ligand. A more challenging approach is the dual stereocontrol over the outcome of the reaction by modification of the reaction conditions or the nonchiral structural components, thereby allowing the preparation of either of the enantiomers from a single configuration of the chiral elements of the catalyst.^[3] This chirality switching has been achieved by using different Lewis acids coordinated to the ligands,^[4] by modification of the solvent system,^[5] and by introduction of structural features that modify the catalytic mechanism or the structure of the catalytic site,^[6] including variations in the nature of the support in heterogeneous catalysis.^[7] An example has recently been reported in which the reversal of topicity is obtained by a change in the molecularity of the catalytic species formed by the ligand and a Gd center.^[8] This is a promising possibility as many catalytic systems show a significant sensitivity to the molecularity of the catalysts and the catalytic complexes.^[9]

Starting from natural amino acids, α -amino amides **1** (Scheme 1) can be easily obtained through N protection,

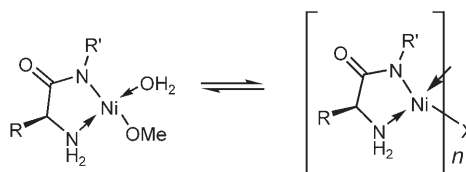


Scheme 1. General structure for α -amino amides.

activation of the carboxy group, coupling with a variety of amines, followed by N deprotection.^[10] We have also shown that the corresponding Ni complexes are able to efficiently catalyze the addition of diethylzinc to benzaldehyde.^[11–13]

The formation of the active complexes requires basic media and is accompanied by deprotonation of the amide (NH) group and the generation of square-planar Ni species (color change from blue to orange). The stoichiometry of the complexes was determined by the continuous variations method (Job plot).^[14] For this purpose, amino amides **1a** (R = CH₂Ph, R' = 1-anthryl) and **1b** (R = CH₂Ph, R' = 2-methylnaphthyl) containing strong chromophoric groups were selected: one derives from an aromatic amine and the second from a benzylic one. The results obtained from the absorbance at approximately 400 nm (MeOH, ca. 10^{−5} M) revealed the existence of complexes with two different stoichiometries, namely 1:1 and 1:2 (M/L).

Nickel complexes of different α -amino amides were prepared in MeOH/KOH for both M/L stoichiometries. The data obtained on complexes obtained from 1:1 metal/ligand ratios suggested the presence of monomeric and oligomeric species in equilibrium (Scheme 2). However, the presence of



Scheme 2. Structures of monomeric and oligomeric species for 1:1 nickel complexes of α -amino amides.

the correct M/L ratio was confirmed through acidic treatment of the complex and separate UV determination of the ligand and the metal. For the 1:2 complexes, the structure was confirmed by elemental analysis and ESI MS. The square-planar complexes also allowed their study by NMR spectroscopy. All data indicate that the 1:2 complexes are of higher stability than the 1:1 complexes, in particular those derived from aromatic amines, but interconversion is very slow under normal conditions.

The ligands in the 1:2 species can adopt either *cis* or *trans* dispositions (Figure 1). Theoretical calculations (RB3LYP/LACVP* level) using a simplified model derived from methylamine and alanine indicated the *trans* conformations to be more stable than those corresponding to *cis* isomers (by 7–9 kcal mol^{−1}, Figure 2).

The prevalence of *trans* dispositions in solution was confirmed by NOE experiments. The complex derived from **1c** (see Figure 1) showed positive NOE contacts between the aromatic protons at the 2-position of the *tert*-butylphenyla-

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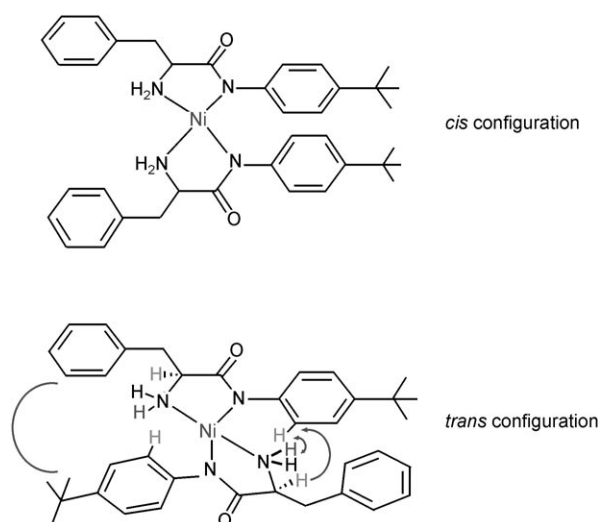


Figure 1. Alternative *cis* and *trans* disposition of the ligands in the 1:2 complex of amino amide **1c** ($R = \text{CH}_2\text{Phe}$; $R' = 4\text{-}t\text{BuC}_6\text{H}_4$). Experimental NOE effects are shown for the *trans* configuration.

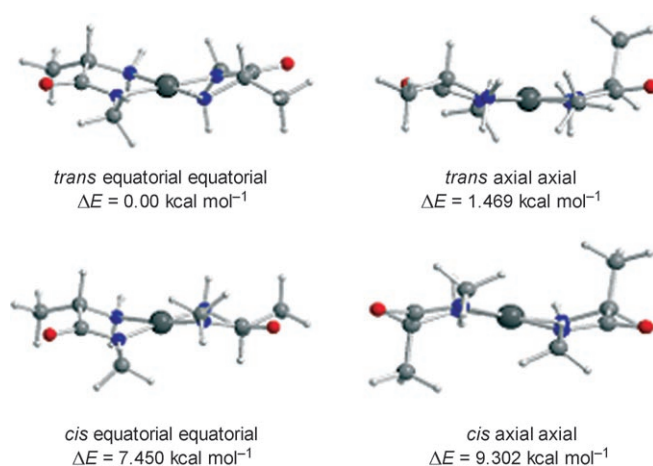


Figure 2. Calculated minimum energy structures for the *cis* and *trans* configurations in the model structure of the 1:2 complexes. Axial and equatorial refer to the disposition of the methyl group of alanine in the five-membered ring formed upon chelation to the nickel center.

mino fragment and the methine hydrogen atom at the stereogenic center as well as with one of the two amino hydrogen atoms. A small NOE interaction was also detected for the *tert*-butyl group and the aromatic protons of the side chain. Similar observations were found in other systems. This finding agrees with the structures of 1:2 nickel complexes reported for related ligands.^[15] The presence of the C_2 axis within these complexes can serve the important function of dramatically reducing the number of possible competing diastereomeric transition states.^[16]

Nickel complexes prepared under both metal/ligand stoichiometries (1:1 and 1:2) were efficient catalysts for the addition of diethylzinc to benzaldehyde. Initial studies were carried out with ligand **1d** ($R = R' = \text{CH}_2\text{Ph}$).^[11] Table 1 shows the results obtained after 24 h for the 1:1 and 1:2 complexes at different catalyst loadings.

Table 1: Addition of ZnEt_2 to benzaldehyde using 1:1 and 1:2 Ni/**1d** complexes.

Complex	Catalyst loading [mol %]	Conversion [%] ^[a]	Selectivity [%] ^[a]	<i>ee</i> [%] ^[b]
1:1	10	99	94	97 (<i>S</i>)
1:1	5	99	95	97 (<i>S</i>)
1:1	1	99	97	97 (<i>S</i>)
1:1	0.5	85	93	96 (<i>S</i>)
1:1	0.1	80	93	93 (<i>S</i>)
1:1	0.05	50	51	62 (<i>S</i>)
1:2	10	99	94	92 (<i>R</i>)
1:2	5	99	98	93 (<i>R</i>)
1:2	1	99	96	96 (<i>R</i>)
1:2	0.5	80	89	91 (<i>R</i>)
1:2	0.1	70	86	90 (<i>R</i>)
1:2	0.05	40	43	47 (<i>R</i>)

[a] Yields after 24 h; conversions and selectivities were determined by NMR spectroscopy. Selectivity: $100 \times [\text{1-phenylpropanol}]/[\text{benzyl alcohol}] + [\text{1-phenylpropanol}]$. [b] Determined by chiral HPLC (Chiralcel OD); the major enantiomer obtained is indicated in parenthesis.

Both complexes are active catalysts at low loadings, and reach turnover numbers (TONs) of almost 10^3 . Longer reaction times are required for complete conversion with catalyst concentrations below 1%, but the selectivity and enantioselectivity remain essentially unaffected. Only with catalyst loadings of about 0.05% were effects on the selectivity and *ee* values detected. The catalysts obtained from 1:1 stoichiometries are more active than the 1:2 complexes. In the first case, conversion is complete after 8 h at RT for a 1% molar ratio while, under the same conditions, the 1:2 complexes require 16–18 h. In the 1:2 complexes the Ni center achieves a more efficient coordination sphere and, accordingly, it is expected to be less active for coordination of additional ligands.

Nevertheless, the most significant observation is that the 1:2 complex affords (*R*)-1-phenylpropanol as the major enantiomer whilst the complex prepared with a 1:1 metal/ligand ratio produces (*S*)-1-phenylpropanol as the predominant species. Thus, a very effective chirality switching is achieved with this simple ligand just by using the corresponding Ni complexes with 1:1 or 1:2 stoichiometries as catalysts. To our knowledge, this represents the first example of this approach to dual stereocontrol, and the first case in which a single ligand allows both enantiomers to be obtained in the addition of dialkylzinc to aldehydes.

The relationship between the enantiomeric composition of the chiral complex derived from **1d** and that of the product arising from the addition of diethylzinc to benzaldehyde was investigated. The presence of very strong negative nonlinear effects for the 1:1 complex confirms the importance of aggregated species for this stoichiometry.^[17] Such nonlinear effects are completely absent for the 1:2 complex (Figure 3), which shows that, in this case, aggregate formation is not significant.^[18]

This dual stereocontrol seems to be quite general. A few examples with other α -amino amides and for other aldehydes are given in Table 2. The last two entries in Table 2 confirm that it also applies to other reagents such as ZnMe_2 .

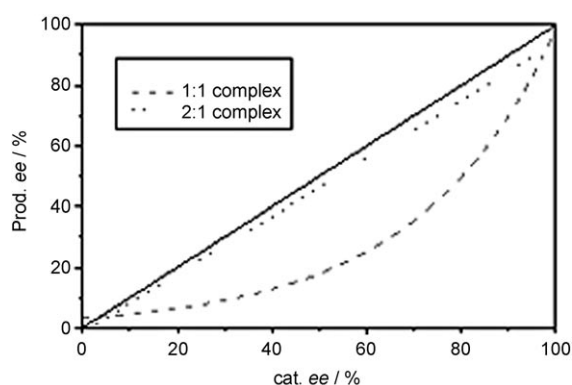


Figure 3. Enantioselectivity of the product as a function of the optical purity of the ligand **1d**.

Table 2: Addition of ZnEt_2 to benzaldehydes and 1-naphthaldehyde using 1:1 and 1:2 Ni/**1d–f** complexes.^[a]

Ligand	M/L	Aldehyde	Conv. [%] ^[a]	Select. [%] ^[b]	ee [%] ^[c]
1e	1:1	benzaldehyde	99	90	80 (S)
1e	1:2	benzaldehyde	99	88	85 (R)
1f	1:1	benzaldehyde	99	92	68 (S)
1f	1:2	benzaldehyde	99	89	85 (R)
1d	1:1	4-chlorobenzaldehyde	99	93	90 (S)
1d	1:2	4-chlorobenzaldehyde	99	96	92 (R)
1d	1:1	4-methylbenzaldehyde	99	96	83 (S)
1d	1:2	4-methylbenzaldehyde	99	95	85 (R)
1e	1:1	4-methoxybenzaldehyde	99	95	90 (S)
1e	1:2	4-methoxybenzaldehyde	99	95	88 (R)
1f	1:1	4-methoxybenzaldehyde	99	96	85 (S)
1f	1:2	4-methoxybenzaldehyde	99	96	92 (R)
1e	1:1	1-naphthaldehyde	99	93	78 (S)
1e	1:2	1-naphthaldehyde	99	89	82 (R)
1f	1:1	1-naphthaldehyde	99	90	76 (S)
1f	1:2	1-naphthaldehyde	99	91	84 (R)
1d	1:1	benzaldehyde ^[d]	99	98	87 (S)
1d	1:2	benzaldehyde ^[d]	99	96	87 (R)

[a] **1d**: $\text{R} = \text{R}' = \text{CH}_2\text{Ph}$, **1e** $\text{R} = \text{R}' = 4\text{-CH}_2(\text{C}_6\text{H}_4)\text{CH}_3$, and **1f** $\text{R} = \text{CH}_2\text{Ph}$, $\text{R}' = 4\text{-CH}_2(\text{C}_6\text{H}_4)\text{OCH}_3$. [b] Yields after 24 h; conversions and selectivities were determined by NMR spectroscopy. Selectivity: $100 \times [\text{1-phenylpropanol}]/[\text{benzyl alcohol}] + [\text{1-phenylpropanol}]$. [c] Determined by HPLC on a chiral stationary phase (Chiralcel OD); the major enantiomer obtained is indicated in parenthesis. [d] Addition of ZnMe_2 .

Explaining the observed enantioselectivities is difficult without calculating the relative energies of all reasonable transition states. For 1:1 complexes, the coordination of benzaldehyde at one square-planar position, by substituting one weakly coordinating ligand, or at one octahedral position allows a transition state to be considered that is similar to that described by Noyori and co-workers for the process catalyzed by amino alcohols. A tricyclic transition state with an *anti-trans* disposition could favor the formation of the *S* enantiomer.^[19] For 1:2 complexes, coordination must occur at one of the octahedral positions. Actually, an octahedral green complex is obtained by dissolving the complex in benzaldehyde. In this case, the presence of the R' substituent can favor a *syn-trans* disposition of the tricyclic transition state, thereby affording the *R* enantiomer.

In summary, the results presented herein reveal that efficient dual stereocontrol can be achieved by using simple α -amino amides derived from natural amino acids for the addition of ZnR_2 to aromatic aldehydes just by a straightforward adjustment of the stoichiometry of the Ni complexes. Thus, 1:1 Ni complexes provide the *S* enantiomer while the 1:2 Ni complexes afford the *R* enantiomer. Both catalytic systems are very active and can be used at very low concentrations (1% or lower). Further studies are in progress to study the scope of this process and the potential application of these catalytic systems to other processes.

Experimental Section

General procedure for the preparation of nickel complexes: A solution of nickel(II) acetate (1 equiv or 0.5 equiv) in methanol (ca. 10^{-2}M) was added to a solution of **1** (1 equiv) in methanol (ca. 10^{-2}M). After stirring the mixture for 20 min at RT, KOH (ca. 3 equiv) in methanol (1M solution) was added and the solution was maintained at RT overnight. The orange precipitate formed was isolated by filtration, washed, and dried to afford the complexes in almost quantitative yields.

General procedure for the addition of ZnR_2 to aldehydes: The Ni complex (1 mmol) 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 1.1M solution of ZnEt_2 in toluene (21 mmol) was added. After stirring the mixture for 30 min at RT, a solution of the aldehyde (10 mmol) in toluene was added slowly. The mixture was stirred at RT for 18 h, quenched with HCl (1M), and the product was extracted into Et_2O ($3 \times 10\text{ mL}$). 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 hexanes/AcOEt as the eluent) gave the pure alcohol as a colorless oil. The conversion and the selectivity of the reaction were determined by NMR spectroscopy, and the *ee* value was determined by HPLC or GC on a chiral stationary phase.

Determination of the *ee* values: Chiralcel OD column, hexanes/2-propanol (95:5; 1.0 mL min^{-1}), UV detection (210 nm). Phenyl-1-propanol: $t_R = 9.45\text{ min}$ (*R*) and 11.35 min (*S*); 1-(1'-naphthyl)-1-propanol: $t_R = 17.26\text{ min}$ (*R*) and 8.61 min (*S*); 4-methylphenyl-1-propanol: $t_R = 7.84\text{ min}$ (*R*) and 11.47 min (*S*); 4-chlorophenyl-1-propanol: $t_R = 36.21\text{ min}$ (*R*) and 39.57 min (*S*); 4-methoxyphenyl-1-propanol: $t_R = 13.69\text{ min}$ (*R*) and 14.85 min (*S*). Phenylethanol: GC, capillary column VF-5 ms; $30\text{ m} \times 0.25\text{ mm}$, $0.25\text{ }\mu\text{m}$, 15 psi; temperatures: injector 230°C , detector 300°C , oven $60\text{--}130^\circ\text{C}$, $10^\circ\text{C min}^{-1}$; $t_R = 12.18\text{ min}$ (*R*) and 12.51 min (*S*).

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