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Nickel complexes from α-amino amides as efficient catalysts for the enantioselective Et_2Zn addition to benzaldehyde

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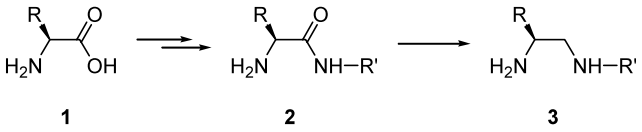
Abstract—Ni^{2+} complexes derived from simple α-amino amides catalyze very efficiently the addition of Et_2Zn to benzaldehyde, giving (*S*)-1-phenylethanol as the major isomer in most cases (94% yield, 97% ee for R = Bn). The nature of the substituent on the amide nitrogen atom seems to play a key role in determining the asymmetric induction observed.

Vicinal diamines represent a very interesting class of organic compounds that have found important applications in different fields.[1] The 1,2-diamino moiety can be found in many natural products such as biotin, and different synthetic compounds of this class have been developed for biomedical applications, in particular in chemotherapy since the initial studies with cisplatin-related compounds.[2] On the other hand, chiral 1,2-diamines are receiving increasing attention as starting materials for stereoselective synthesis and as chiral metal ligands and organocatalysts.[3] In connection with this target, most efforts have been devoted to the preparation and study of chiral vicinal diamines having C_2 symmetry. However, the preparation of enantiopure compounds of this class is not a trivial task and requires carefully controlled synthetic strategies and, in many cases, racemate separation. This has limited the general use of those chiral auxiliaries to a reduced number of structures, in particular 1,2-diphenyl-1,2-ethanediamine and 1,2-cyclohexanediamine.[4]

On the contrary, simple C_1 symmetric enantiomerically pure 1,2-diamines (**3**) can be efficiently prepared from easily available α-amino acids **1** according to the general route outlined in Scheme 1.[5] The presence of C_2 symmetry is generally considered an advantageous structural feature,[6] but many recent examples have shown the potential of C_1 symmetric ligands that, in some cases, can be even more efficient than related C_2 systems.[7]

Catalytic properties of metal complexes derived from amide or sulfonamide derivatives of C_2 symmetric 1,2-diamines, such as **5** and **6**, have been reported[8] (Fig. 1). Nevertheless, complexes **4** derived from the general structure **2** have not been very much studied in asymmetric catalysis, except, perhaps, some proline derivatives.[9] As a matter of fact, α-amino amides **2** present some structural features that make them very attractive in this respect. The presence of two nitrogen atoms with different coordination capabilities and the relative acidity of the N–H amide functionality can favor the formation of strong metal complexes with a very tightly defined steric and electronic environment that can be easily optimized through the appropriate selection of R



Scheme 1. Preparation of α-amino amides and diamines.

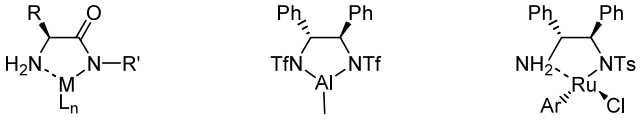


Figure 1.

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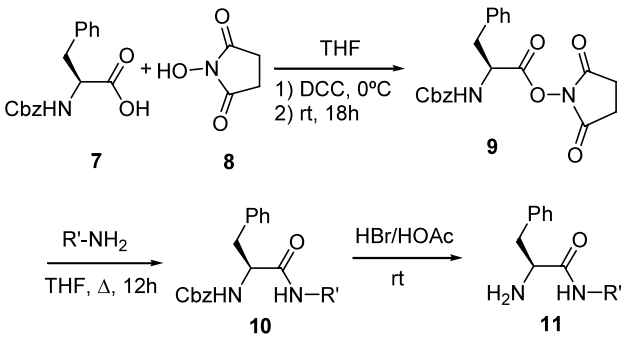
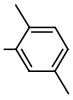
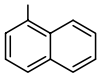
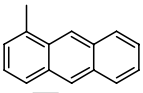
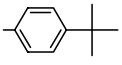


Scheme 2. Synthesis of α-amino amides

Table 1. Results for the synthesis of α-amino amides **11**

Entry	Ligand[a]	R'	Yield (%)
1	**11a**		61
2	**11b**		86
3	**11c**		72
4	**11d**		87
5	**11e**		70
6	**11f**		85
7	**11g**		97
8	**11h**		78
9	**11i**		67
10	**11j**		70
11	**11k**		62

[a] all compounds have been characterised by a full set of analytical data (elemental analysis, IR, NMR and MS)

and R′ groups, a behavior comparable to that found in β-amino alcohols.

As a part of our efforts to develop chiral catalysts based on cheap and easily available chiral sources and according to the former considerations,[10] a series of α-amino amides derived from L-phenylalanine were prepared as described in Scheme 2.

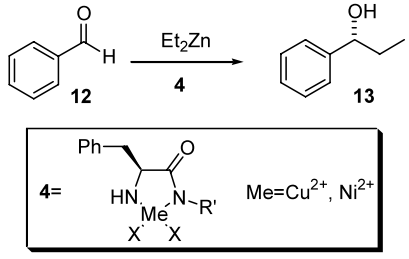
Taking into account our previous experience with related systems, the *N*-cbz protected amino acid **7** was converted into the activated ester **9** by reaction with *N*-hydroxy succinimide **8** in the presence of DCC (87% yield). Reaction of the intermediate **9** with different aliphatic and aromatic amines afforded *N*-protected α-amino amides **10**, in general in excellent yields. Deprotection using HBr/AcOH was almost quantitative and allowed us to obtain the desired products **11** with the overall yields shown in Table 1.

As can be seen in Table 1, yields were similar for aromatic and aliphatic amines and additional functional groups such as alcohol or ester can be present.

The addition of Et_2Zn to benzaldehyde in the presence of catalytic amounts of compounds **11** was selected as a well-known benchmark reaction to explore their potential in enantioselective catalysis. A wide range of chiral ligands such as β-amino alcohols, amino sulfur compounds, diols and some chiral amines has shown to act as efficient catalysts for this reaction.[11,12]

Preliminary experiments were carried out with ligand **11h**, a compound having two stereocenters with absolute configuration *S*. The results are gathered in Table 2 (entries 1–4). As can be seen in entry 1, no catalytic activity was observed when the ligand was added to the

Table 2. Results for the Et_2Zn addition to benzaldehyde in the presence of metal complexes of **11**



Entry	Ligand	Metal Salt	Yield (%)[a]	ee (%)[b]
1	**11h**	---	---	---
2	**11h**	$Zn(OAc)_2$	---	---
3	**11h**	$Cu(OAc)_2$	70	0
4	**11h**	$Ni(OAc)_2$	85	67 (*S*)
5	**11b**	$Ni(OAc)_2$	92	85 (*S*)
6	**11c**	$Ni(OAc)_2$	79	18 (*S*)
7	**11d**	$Ni(OAc)_2$	90	86 (*S*)
8	**11i**	$Ni(OAc)_2$	82	17 (*R*)
9	**11k**	$Ni(OAc)_2$	94	97 (*S*)

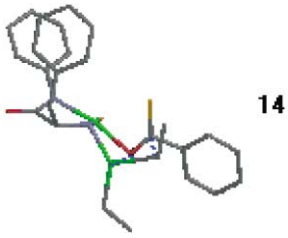


Figure 2.

reagent's mixture, and the same happened when **11h** was first stirred in the presence of $Zn(OAc)_2$ (entry 2). It is not easy to rationalize this behavior, but, most likely, it can be ascribed to the formation of oligomeric complex species of low activity. A similar situation has been described, for instance, when comparing the activity of soluble and supported catalysts derived from compounds with partly related structures.[13] In the same way, it has been observed that *N*-alkylated and sterically constrained β-amino alcohols show, in general, the higher activities for the same reaction.[11] A completely different behavior was observed, however, when **11h** was allowed to react first with $Cu(OAc)_2$ or $Ni(OAc)_2$ in a 1:1 ratio (entries 3 and 4) In both cases, a clear catalytic activity was observed.[14] This can be ascribed to the formation of the corresponding Cu or Ni complexes **4h**. The catalytic activity of some metal complexes, in particular Ti(IV) and Cu(II) complexes, for R_2Zn additions is well documented, and Ni(II) complexes have been used for conjugate carbonyl additions.[9c,15]

In the case of the copper complex, no asymmetric induction was observed, but a reasonable selectivity (85%) and enantioselectivity was obtained (67% ee, (*R*)-1-phenylpropanol **13** as the major isomer) when the nickel complex was used.

In view of the former results, other ligands were tested using similar conditions. As shown in Table 2, results obtained are dependent on the nature of the R′ substituent at the amide nitrogen atom. Very good activities and enantioselectivities were achieved for ligands **11b** (85% ee) and **11k** (97% ee) derived from simple amines containing an unsubstituted aromatic ring. The use of ligands derived from more bulky amines (**11c**, **11d**, **11i**) always gave complexes with lower activities and enantioselectivities. A remarkable result was that observed when using α-amino amide **11i** prepared from 4-*t*-butylaniline. In this case, the observed asymmetric induction was low (17% ee), but the major isomer obtained had an absolute configuration (*R*), opposite to that observed in other cases. Even if this ee value is low, this result opens the way to consider that a dual enantioselective control can be achieved with ligands **3** through an appropriate balance of the R and R′ groups, a situation of great interest in the development of efficient chiral catalysts.

The mechanism of the Et_2Zn addition to benzaldehyde in the presence of β-amino alcohols has been studied in detail,[11c,16] and several mechanistic studies have been carried out for the Ti mediated catalytic reaction,[11d,17] but much less is known for the mechanism involved in the reaction catalysed by Ni^{2+} complexes. In our case, all data indicate that upon addition of Et_2Zn the blue–green paramagnetic Ni^{2+} octahedral complex initially formed with UV–vis bands at 390, 650 and 1020 nm, is transformed into an orange diamagnetic Ni^{2+} square-planar complex with a maximum absorbance at 445 nm. Deprotonation of the amide hydrogen is required for this change, and this takes place even with weaker bases as shown in IR experiments by the significant shift of the C=O band to lower frequencies, but deprotonation of the primary amino group can also take place in the presence of Et_2Zn as has been observed in other related systems.[18,19]

Initially, the stereochemical outcome of the reaction can be rationalized in terms of a transition state (**14**) (Fig. 2) related to that generally accepted for the addition of diethylzinc to benzaldehyde in the presence of β-amino alcohols.[15] Coordination of benzaldehyde to the Ni atom should take place at the position more distant from the substituent on the amide nitrogen atom and using the lone pair of the oxygen *anti* to the C–aryl bond. From the two possible arrangements of this class, the *anti* TS **14** seems to be the most stable in agreement with theorical calculations,[16] giving place to the formation of the *S*-**13** enantiomer, the major isomer observed in most cases. The nature of the *N*-substituents at the amide group can affect to the energy differences between *syn* and *anti* TS, but, alternatively, a change in the conformation of the five-membered ring from envelope to planar could allow considering a six-membered chair TS similar to that recently reported by Norrby that would give place to the formation of the *R*-**13** enantiomer.[16d] As can be seen in Table 2, the bulkier *N*-substituents are those for which the prevalence of *S*-**13** as the major isomer is lower.

Nevertheless, the situation is more complicated. A spectrophotometric study was carried out using amino amide **11e** as a model, since it contains the strongly absorbing chromophore anthracene ($\varepsilon = 6.6\times10^5$ M^{-1} cm^{-1} at $\lambda = 365$ nm in methanol). The formation of the **11e**–Ni(II) complex in MeOH containing NaOH can be followed through the shift of its UV–vis absorption spectrum to longer wavelengths. In order to ascertain the stoichometry of the complex(es) formed in solution, the method of continuous variations (Job method) was applied,[20] monitoring the absorbance increment at $\lambda =$ 400 nm versus the molar fraction (f) of ligand. Preliminary results show that a stable 1:2 complex (metal:ligand) is formed in solution and actually it is the prevalent species at elevated concentrations. However at much lower concentrations there is an equilibrium between the 1:1 and the 1:2 complexes. Further work is presently being carried out to determine the role played by both species in the addition reaction, but the present results clearly reveal the very high potential of those simple α-amino amides as chiral auxiliaries in enantioselective catalysis.

Acknowledgements

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14. In a typical procedure, **11** and the metal salt (1:1 ratio) were stirred in MeOH for 30 minutes at rt. The solvent was then vacuum evaporated and the blue–green complex was dried and redisolved in anhyd. toluene. An excess of Et_2Zn (1.1 M in toluene, 20–25 times in excess over the catalyst) was added at 0°C and the color changed to orange. Then benzaldehyde (10 mol/mol of catalyst) was slowly added and the resulting mixture was stirred at rt for 24 h. After this period the reaction was quenched with HCl and the crude of the reaction was purified and analyzed using standard protocols.
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