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Enantioselective nickel-catalyzed conjugate addition of dialkylzinc to chalcones using chiral α-amino amides

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ABSTRACT

A series of α-amino amides derived from natural amino acids (alanine, valine, phenylalanine, isoleucine, and phenylglycine) have been synthesized and fully characterized. Their Ni(II) complexes prepared from $Ni(acac)_2$ catalyze the enantioselective conjugate addition of diethylzinc to chalcones in high yields and in good enantioselectivities (up to 84%). The side chain of the amino acid and the substituents in the amide nitrogen govern the enantioselectivity of the catalytic process.

Development of catalytic processes for enantioselective C–C bond formation is of great interest,[1] and the 1,2-addition of organozinc reagents to aldehydes is one of such processes.[2] The conjugate addition of dialkylzinc reagents to α,β-unsaturated prochiral enones is also of importance for the synthesis of optically active β-substituted carbonyl compounds,[3] and it has allowed the successful synthesis of biologically active compounds.[4] Copper and nickel chiral complexes have been the most widely investigated for the enantioselective addition of Grignard and dialkylzinc reagents to enones.[5] In the case of nickel, a variety of amino alcohols,[6] pyridine,[7] borneol,[8] proline,[9] and pyrrolidine derivatives,[10] and other ligands[11] have been used (Fig. 1). Nitrogen-containing ligands have recently gained increasing importance in this area.[12]

Recently, we reported that Ni(II) complexes derived from chiral α-amino amides are very versatile catalysts for the 1,2-enantioselective addition of dialkylzinc reagents to aldehydes.[13] Those

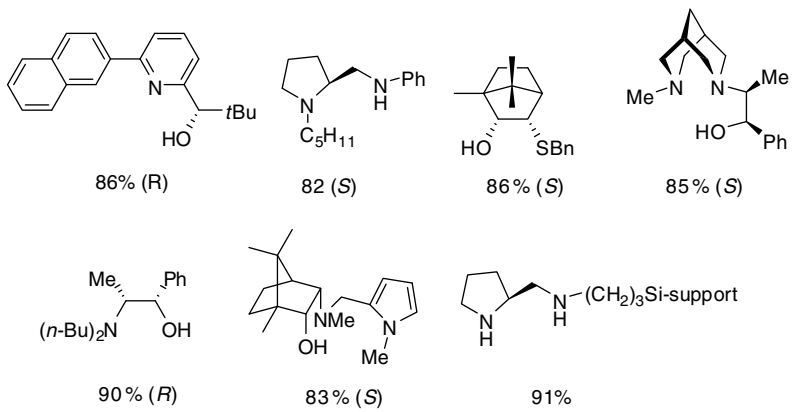

Figure 1. Ligands reported for the nickel-catalyzed conjugate addition of dialkylzinc to α,β-unsaturated prochiral enones.

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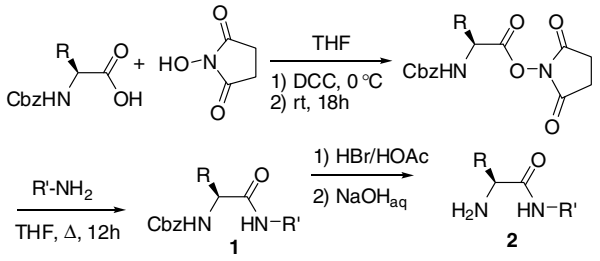
ligands **(2)** are promising as they (i) can be easily prepared; (ii) contain two nitrogen atoms with different coordination capabilities connected through a chiral backbone; (iii) their properties can be tuned by the selection of the substituents; (iv) can form robust metal complexes with transition metals under the appropriate conditions. However, only a few nickel,[9,13] copper,[14] and ruthenium[15] complexes of some α-amino amides have been reported for different applications.

1,4-Additions to cyclic enones using Grignard or dialkylzinc reagents can occur with high enantioselectivity in the presence of Cu complexes. Nevertheless, reports on the successful Et_2Zn addition to acyclic enones are less common giving lower enantioselectivities. Here, we report on the use of α-amino amides for the enantioselective Ni-catalyzed conjugate addition of Et_2Zn to chalcones.

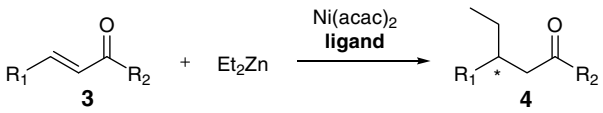
α-Amino amide ligands **2** were prepared using previously reported procedures for related systems.[16] Initial formation of the activated *N*-hydroxysuccinimide ester of the Cbz-(*S*)-amino acid followed by coupling with a variety of aliphatic, aromatic, and benzylic amines and final N-deprotection, using HBr/AcOH, of the N-protected α-amino amides **1**, afforded compounds **2** in 70–85% overall yields after purification (Scheme 1).

In order to examine the efficiency of those ligands for the nickel-catalyzed enantioselective conjugate addition of diethylzinc to α,β-unsaturated ketones, the chiral ligand **2a** (R = Phe, R′ = Phe) was initially selected, and chalcone (**3**, $R_1 = R_2$ = Phe) was used as a model substrate. In this case, best results were obtained when $Ni(acac)_2$ was used as the nickel source at a 2:1 ligand:Ni ratio. From the different solvents assayed, the use of CH_3CN at −20 °C was selected.[17] Thus, when a solution of 5 mol % of $Ni(acac)_2$ and 10 mol % of the chiral ligand **2a** in CH_3CN was heated at reflux for 1 h, and the chalcone was added at rt followed by the slow addition of a solution of Et_2Zn in hexane (1 M) at −20 °C, 1,3-diphenylpentan-1-one (**4a**, $R_1 = R_2$ = Phe) was isolated by standard techniques in 99% yield after 18 h. The enantiomeric excess was determined to be 75% (77% at −50 °C, but at the expenses of reducing the yield below 70%) by chiral HPLC analysis (Chiralcel OD column) (Scheme 2).

The use of $NiBr_2$, instead of $Ni(acac)_2$, resulted in a significant decrease of yield and enantioselectivity. This can be associated to the low solubility of $NiBr_2$ in CH_3CN and to the lower basicity of bromide for deprotonating the NH amide moiety, reducing the initial formation of the active complex. The order of addition of the reactants is also important. If the order of addition of Et_2Zn and chalcone is reversed, a significant amount of Ni(II) is reduced decreasing the amount of active chiral complex and reducing the



Scheme 1. Synthesis of α-amino amides.



Scheme 2. Ni-catalyzed conjugate addition of diethylzinc to chalcones.

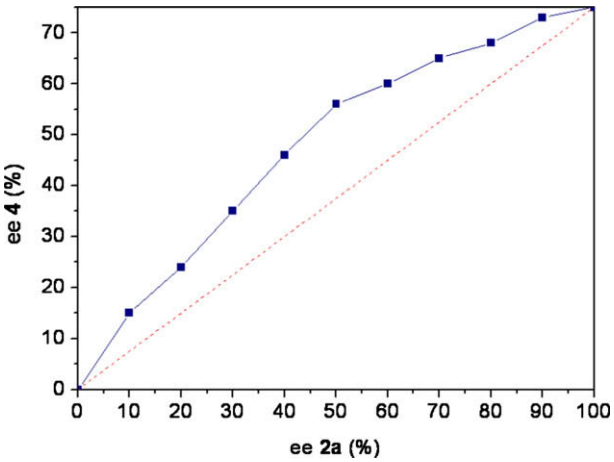


Figure 2. Correlation between the ee of ligand **2a** and the ee of **4a**.

enantioselectivity and yield.[18] In order to optimize the reaction time, the kinetic profile was studied under the former conditions. Samples of the reaction mixture were taken at various intervals of time, and the conversions were determined by GC analysis, revealing that just 6 h at −20 °C in CH_3CN was necessary to achieve an almost complete conversion (97% yield). According to this study, all subsequent reactions were carried out for 6 h.

The study of nonlinear effects in enantioselective catalysis has become an important mechanistic tool.[19] In order to understand the nature of the catalytic species, we examined the relationship between the enantiomeric composition of the chiral ligand **2a** and that of the resulting product **4a**. The positive nonlinear effect (asymmetric amplification) found in this system (Fig. 2) can be explained by the difference in chemical properties of diastereomeric complexes.[7a] It is reasonable to assume that 2 equiv of α-amino amide ligand replaces acetylacetonate anions from $Ni(acac)_2$, forming diastereomeric homochiral or heterochiral nickel complexes of general structure NiL_2. Replacement of one of those ligands by the chelating substrate should occur for the reaction to take place.

A positive nonlinear relationship can be explained by a greater stability of the *meso* complex compared to its chiral diastereoisomers.[20] Thus, the minor enantiomer of the ligand is trapped in this *meso* complex (*S*/*R*)-**2a**, and it becomes less available for the catalytic conjugate addition. This is corroborated by DFT studies that reveal that the *meso* 2:1 (*R*/*S*) complex from **2a** is slightly more stable (1.3 kcal mol^{-1}) than either the *R*/*R* or the *S*/*S* complex.[21] The structure calculated for the 2:1 complexes was suggested experimentally to be the most stable, in the case of **2b**, as suitable crystals for X-ray analysis were only obtained for the *meso* complex from a mixture containing the (*S*)-**2b** ligand contaminated with a minor amount of the *R*-enantiomer (Fig. 3).

In an attempt to improve the efficiency of the conjugate addition to chalcone, we synthesized a library of α-amino amides derived from (*S*)-phenylalanine by modification of the amine used in the α-amino amide synthesis. The results are summarized in Table 1.

In all cases, (*S*)-**4a** was the major enantiomer obtained with **2a** being superior to other ligands. Yields and enantioselectivities decreased, in some cases very significantly, for ligands **2k** and **2l** derived from aliphatic amines (entries 11 and 12) and in the case of ligands derived from bulky amines. This is particularly true for R′ substituents such as naphthyl (**2e**), anthryl (**2f**), or *tert*-butyl (**2l**) (entries 5, 6, and 10). Substituents in the *para* position of the phenyl group of the amide moiety had only a minor influence on the outcome of the reaction, except in the case of the *tert*-butyl substituent (**2b**, entry 2).

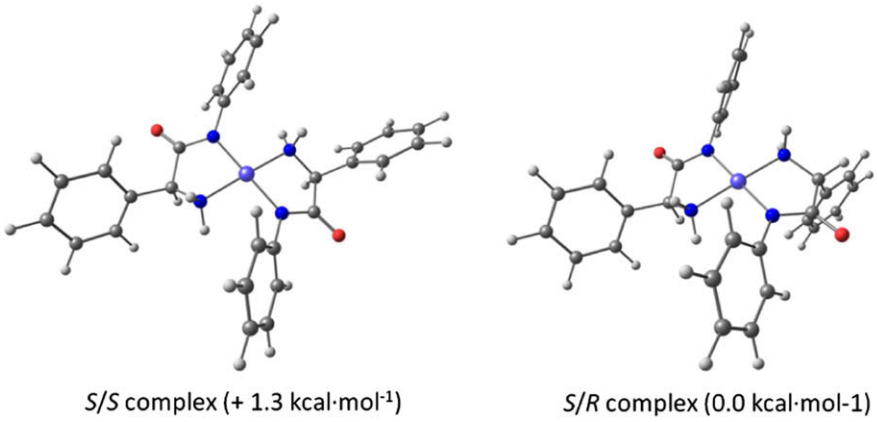
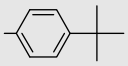
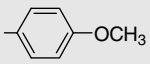
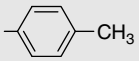
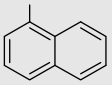
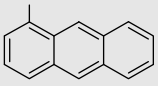
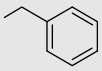
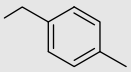
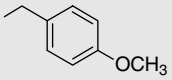
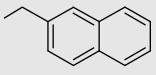


Figure 3. Optimized geometries of *S*/*S* and *S*/*R* Ni(II) complexes.

Table 1
Effect of the amine in the Et_2Zn conjugate addition to chalcone

Entry[a]	Ligand	R′	Yield (%)	ee[b] (%)
1	**2a**		97	75 (*S*)
2	**2b**		83	23 (*S*)
3	**2c**		96	67 (*S*)
4	**2d**		89	35 (*S*)
5	**2e**		63	15 (*S*)
6	**2f**		60	6 (*S*)
7	**2g**		95	66 (*S*)
8	**2h**		91	64 (*S*)
9	**2i**		87	65 (*S*)
10	**2j**		83	33 (*S*)
11	**2k**		86	43 (*S*)
12	**2l**		81	29 (*S*)

[a] All reactions were carried out at −20 °C for 6 h.
[b] Determined by HPLC analysis (Chiralcel OD column).[19]

In a second step, we examined the conjugate addition to chalcone using α-amino amide ligands derived from different amino acids differing on the size and nature of the side chain, while keeping R′ = Phe. Thus, a further study was carried out with ligands **2m, 2n, 2o**, and **2p** (derived from alanine, valine, isoleucine and phenylglycine). Table 2 summarizes the results, and as can be seen, no significant differences in ee values could be detected for the ligands with bulky side chains (entries 1, 3, and 4). Nevertheless, a slight decrease in the enantioselectivity was observed for the ligand derived from L-alanine (entry 2) containing the less bulky side chain. The best result was obtained when phenyglycine (entry 5) was used.

Using the conditions established, we explored the scope of Ni-catalyzed conjugate addition of Et_2Zn to various substituted α,β-unsaturated chalcones using ligand **2p**. The results are summarized in Table 3. Substituted chalcones were alkylated with good yields and interestingly, the stereoselectivity was affected by the electronic nature of the substituent. Chalcones with an electron-donating group (OMe) at the 4-position of one of the aromatic rings afforded the highest enantioselectivities (84% and 81% ee, entries 2 and 4), while chalcones with an electron-withdrawing group (Cl) gave slightly lower enantioselectivities (70% and 67% ee, entries 3 and 5). It is worth mentioning that the enantioselectivities obtained (ranging from 67% to 84% ee) are within the best ee up

Table 2
Effect of the steric bulk of the amino acid residue

Entry[a]	Ligand	R	Yield (%)	ee[b] (%)
1	**2a**	CH_2Ph	97	75 (*S*)
2	**2m**	CH_3	95	51 (*S*)
3	**2n**	$CH(CH_3)_2$	96	69 (*S*)
4	**2o**	$CH(CH_3)CH_2CH_3$	96	68 (*S*)
5	**2p**	Ph	97	78 (*S*)

[a] All reactions were carried out at −20 °C for 6 h.
[b] Determined by HPLC analysis (Chiralcel OD column).

Table 3
Scope of the conjugate Et_2Zn addition to substituted α,β-unsaturated chalcones using ligand **2p**

Entry[a]	R_1	R_2	Yield (%)	ee[b] (%)
1	Ph	Ph	97	78 (*S*)
2	4-$CH_3OC_6H_4$	Ph	99	84 (*S*)
3	4-ClC_6H_4	Ph	96	70 (*S*)
4	Ph	4-$CH_3OC_6H_4$	95	81 (*S*)
5	Ph	4-ClC_6H_4	93	67 (*S*)
6	Ph	Ph	99	75 (*S*)[c]

[a] All reactions were carried out at −20 °C for 6 h.
[b] Determined by HPLC analysis (Chiralcel OD column).
[c] Me_2Zn was used.

to now reported for the Et_2Zn conjugate addition to chalcones. The conjugate additions of Me_2Zn, due to the lower reactivity of this organometallic reagent, were carried out under different experimental conditions, that is, longer reaction time (24 h) in order to obtain complete conversion (entry 6).

As described for other nickel-derived catalysts, enantioselectivity was only observed in the conjugate addition of Et_2Zn to chalcones. For example, with ligand **2p**, the nickel-catalyzed addition of Et_2Zn to 2-cyclohexen-1-one and 2-cyclopenten-1-one gave the 1,4-product in 72% and 69% yield, respectively, but no enantioselectivity was observed.

In summary, we have shown that chiral α-amino amides derived from natural amino acids catalyzed the conjugate addition of diethylzinc to chalcones with good enantioselectivities in the presence of $Ni(acac)_2$. Different structural modifications were examined in order to optimize the enantioselectivity of the nickel-catalyzed conjugate addition. This process resulted in the selection of phenylglycine-based ligand **2p**, with a phenyl group in the amide moiety, which catalyzed the addition of diethylzinc to substituted chalcones with enantioselectivities up to 84%. Those enantioselectivities can be ranged between the best obtained for this reaction. Further studies are in progress to study the scope and mechanism of this process, and the potential application of these catalytic systems using other metals and for other synthetic transformations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.120.

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21. Structures were computed using density functional theory using the nonlocal hybrid Becke's three-parameter exchange functional (denoted as B3LYP) with LanL2DZ pseudopotential and the associated basis set for Ni and the 6-31G (d) basis set for the rest of atoms using the GAUSSIAN 03 software package (see Supplementary data for Gaussian citation).