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Catalytic enantioselective conjugate addition of diethylzinc to chalcones using chiral amino alcohol–nickel complexes

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Abstract—A series of chiral β-amino alcohols derived from (*S*)-leucine, valine, and phenylalanine were examined as chiral ligand in nickel-catalyzed conjugate addition of diethylzinc to chalcones. The (*S*)-valine-derived amino alcohol **1d** possessing a piperidine ring and two flexible phenethyl groups was found to be an efficient ligand to catalyze the conjugate addition with high enantioselectivity (up to 92% ee).

1. Introduction

Catalytic enantioselective conjugate additions of organometallic reagents to enones have been intensively investigated as synthetic methods for chiral carbon–carbon bond formation. Recently, Feringa and co-workers[1] reported that copper-catalyzed conjugate addition of diethylzinc using chiral phosphoramidite proceeded with good to excellent enantioselectivity for acyclic chalcones (up to 89% ee) and cyclic enones (up to 98% ee).[2] A variety of chiral amino alcohols such as ephedrine derivatives,[3] chiral pyridine derivatives,[4] borneol derivatives,[5] proline derivatives,[6] pyrrolidine derivatives,[7] and others[8] has been also used in nickel-catalyzed conjugate addition of diethylzinc to chalcones. Quite recently, we reported that chiral β-amino alcohol derived from (*S*)-leucine bearing two flexible phenethyl groups catalyzed the addition of diethylzinc to aldehydes with excellent enantioselectivity (up to 97% ee).[9] Moreover, the systematic studies of the substituent effect and nonlinear effect revealed that 'chiral relay'[10] system played an important role in controlling the enantioselectivity, where flexible moieties (R^2) should relay and amplify the stereochemical information of the stereogenic center of the amino acid residue (R^1) as shown in Fig. 1. This prompted us to employ this series of β-amino alcohols as chiral ligand in nickel-catalyzed conjugate addition to chalcones as shown in Scheme 1. In this paper, we report the enantioselective conjugate addition of diethylzinc to acyclic chalcones, which was realized by optimizing chiral amino alcohol ligands, the solvent, and the amount of ligand and $Ni(acac)_2$.

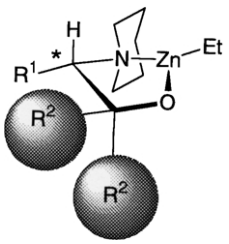
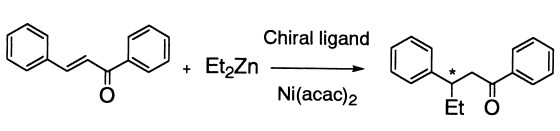
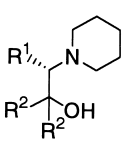


Figure 1.

2. Results and discussion

The ligands **1a–f** were easily prepared from commercially available (*S*)-leucine, valine, and phenylalanine ester via addition of various Grignard reagents to the (*S*)-amino acid esters and alkylation with 1,5-diiodopentane as described previously.[9] We examined the enantioselective conjugate addition of diethylzinc to chalcone as a model substrate with 16 mol% of the chiral ligands **1a–f** and 7 mol% of





1a R^1= *i*-Bu, R^2= Ph
1b R^1= *i*-Bu, R^2= CH_2CH_2Ph
1c R^1= *i*-Pr, R^2= Ph
1d R^1= *i*-Pr, R^2= CH_2CH_2Ph
1e R^1= CH_2Ph, R^2= Ph
1f R^1= CH_2Ph, R^2= CH_2CH_2Ph

Scheme 1. The nickel-catalyzed conjugate addition and chiral ligands.

Keywords: conjugate addition; asymmetric synthesis; enantioselection; chiral relay; amino alcohol.

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Table 1. Enantioselective conjugate addition of diethylzinc to chalcone using ligands **1a–f**

Entry	Ligand	Yield (%)	ee (%)[a]
1	**1a**	71	37
2	**1b**	91	74
3	**1c**	48	22
4	**1d**	65	87
5	**1e**	50	34
6	**1f**	91	74

All reactions were carried out with 7 mol% $Ni(acac)_2$ and 16 mol% ligand in MeCN at −30°C.

[a] Determined by HPLC analysis using DAICEL Chiralcel OD. The absolute configurations of the resulting adducts were determined to be *S* by comparison of the retention time.[4a]

$Ni(acac)_2$ in acetonitrile[3c] at −30°C. These results are summarized in Table 1.

Comparison between the amino alcohol ligands **1a**, **1c**, and **1e** (entries 1, 3, and 5) and ligands **1b**, **1d**, and **1f** (entries 2, 4, and 6), reveals that the ligands with a flexible phenethyl group as the relay group (R^2) afford good yields and higher enantioselectivites in the conjugate addition of diethylzinc to chalcone. These results are the same trend as were observed with the ligands derived from (*S*)-leucine for its addition to aldehydes.[9b] However, with respect to the chiral group (R^1), the use of isopropyl group derived from (*S*)-valine provided the highest enantioselectivity (entry 4). Thus, the amino alcohol **1d** was found to be the most efficient ligand in the conjugate addition to chalcone.

Next, the effects of additive, solvents, and the amount of $Ni(acac)_2$ and ligand were examined as shown in Table 2. Addition of 2,2-bipyridine did not improve the enantioselectivity as observed in the conjugate addition using ephedrine derivatives and Ni(II)[3] (entry 2). On the other hand, the solvent significantly affected the enantioselectivity of the conjugate addition and propionitrile afforded the slightly high enantioselectivity at lower Ni(II) loading (entries 3–6). The similar solvent effect on the enantioselectivity was also observed in the conjugate addition catalyzed by *cis-endo-N,N*-dimethyl-3-aminoborneol.[5b] Furthermore, decreasing the amount of $Ni(acac)_2$ to

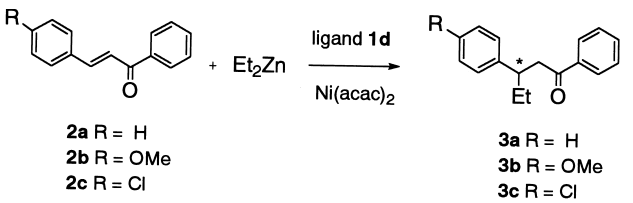
Table 2. Enantioselective conjugate addition of diethylzinc to chalcones **2a–c** using ligands **1d**

Entry	Substrate	Solvent	Ni/ligand (mol%)	Yield (%)	ee (%)[a]
1	**2a**	MeCN	7:16	65	87
2[b]	**2a**	MeCN	7:16	79	85
3	**2a**	MeCN	2:16	76	86
4	**2a**	EtCN	2:16	82	88
5	**2a**	*n*-PrCN	2:16	61	77
6	**2a**	*i*-PrCN	2:16	78	80
7	**2a**	EtCN	1:16	64	90
8	**2a**	EtCN	1.5:20	71	91
9	**2b**	EtCN	2:16	80	83
10	**2b**	EtCN	1.5:20	65	92
11	**2c**	EtCN	2:16	86	79
12	**2c**	EtCN	1.5:20	57	86

Reactions were carried out at −30°C.

[a] Determined by HPLC analysis using DAICEL Chiralcel OD and OD-H. The absolute configurations of the resulting adducts **3b** and **3c** were determined to be *S* by comparison of the optical rotations.[8e]

[b] Additive, 2,2-bipyridine (7 mol%), was used.



Scheme 2.

1 mol% resulted in the increase of the enantioselectivity and the decrease of the chemical yield (entry 7). Finally, 1.5 mol% of $Ni(acac)_2$ and 20 mol% of chiral ligand **1d** were found to be the best reaction conditions, producing (*S*)-1,3-diphenylpentan-1-one with 91% ee in 71% yield (entry 8).

In addition, we examined the conjugate addition to the substituted chalcones using the optimal experimental conditions (Scheme 2). Chalcone **2b** with an electron-donating group (OMe) at 4-position afforded the highest enantioselectivity (92% ee, entry 10) and chalcone **2c** with an electron-withdrawing group (Cl) gave slightly lower enantioselectivity (86% ee, entry 12). This substituent effect on the enantioselectivity is identical to that of the conjugate additions catalyzed by pyrrolidine derivative[8b] and is contrast to that of *N*-trityl aziridine derivative.[8e] Since the electronic effect of chalcones was not significantly important for the enantioselectivity of the copper-catalyzed conjugate addition,[2] it might be an alternative explanation that the observed poor solubility of 4-chlorochalcone **2c** in propionitrile at −30°C might affect the enantioselectivity of the nickel-catalyzed conjugate addition.

Although the actual active species are unclear, the following transition state model (Fig. 2) is suggested, based on the reaction mechanism for the nickel-[5c] and copper-catalyzed conjugate addition.[2] Chiral amino alcohol ligand **1d** might form the similar nickel complex to ethylzinc complex in the addition of diethylzinc to aldehydes, in which one of the phenethyl groups should locate in a *pseudo*-axial position. Furthermore, we assume that acyclic chalcones would coordinate to the nickel in the *s–cis* conformation as shown in Fig. 2, where the carbonyl oxygen of chalcones and the oxygen of chiral amino alcohol would locate in a *trans* position. Thus, the chalcones might be attacked on its *Si* face at the upper side of the square planar nickel complex to produce the corresponding (*S*)-adduct. This is consistent with the observed enantioselection.

3. Conclusion

We have demonstrated that the chiral amino alcohol derived from (*S*)-valine, which possesses a piperidine ring and two phenethyl groups, catalyzed the conjugate addition of

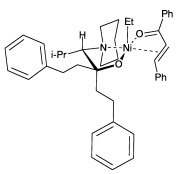


Figure 2. The transition state model.

diethylzinc to acyclic chalcones with high enantioselectivity. Thus, we clearly indicated that chiral relay system of these amino alcohol ligands is also operative in the nickel-catalyzed conjugate addition. Further studies are underway to apply to other related asymmetric reactions.

4. Experimental

IR spectra were determined using a Shimadzu IR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using a JEOL JNM-A400 spectrometer, respectively. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer. Optical rotations were determined on a Yanagimoto OR-50 polarimeter. The HPLC analysis was carried out using a DAICEL Chiralcel OB or OD column (0.46×25 cm) with a Shimadzu LC-6A. Acetonitrile, propionitrile, *n*-butyronitrile, and *i*-butyronitrile were dried over MS 4A. TLC was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm) and column chromatography was performed using Merck 23-400 mesh silica gel. Diethylzinc was purchased from the Aldrich Chemical. (*S*)-leucine ethyl ester hydrochloride, (*S*)-valine methyl ester hydrochloride, (*S*)-phenylalanine methyl ester hydrochloride, and the other reagents were obtained from Tokyo Kasei Kogyo or Wako Pure Chemical Industries. Chiral β-amino alcohols were prepared according to the previously described procedure.[9]

4.1. Typical procedure for enantioselective conjugate addition of diethylzinc to chalcones

4.1.1. (*S*)-1,3-diphenylpentan-1-one. A solution of **1d** (75.9 mg, 0.2 mmol, 20 mol%) and Ni(acac)$_2$ (3.9 mg, 0.015 mmol, 1.5 mol%) in propionitrile (2 ml) was stirred and refluxed for 1 h under nitrogen atmosphere. The solution was cooled to room temperature and chalcone (208.3 mg, 1.0 mmol) was added. The mixture was stirred and cooled to −30°C. Diethylzinc (1.0 M solution in hexane, 1.5 ml, 1.5 mmol) was added (the color changed from a clear green to dark brown) and stirring was continued at −30°C for 2 h (the color changed to pale yellow). The reaction mixture was quenched with aqueous 1N HCl solution, extracted with ether, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (pet. ether/ethyl acetate 25:1) to give (*S*)-1,3-diphenylpentan-1-one (168.3 mg, 71%); $[\alpha]_D^{25}$=+9.4 (c 2.47, EtOH), (lit.[11] $[\alpha]_D$=+10.5 (c 2.5, EtOH)). The ee was determined to be 91% by HPLC analysis using a DAICEL Chiralcel OD column (0.25% *i*-PrOH in hexane, flow rate: 1.0 ml/min, (*S*)-enantiomer: 17 min, (*R*)-enantiomer: 20 min).[4a] For 3-(4-chlorophenyl)-1-phenylpentan-1-one; $[\alpha]_D^{25}$=+6.2 (c 1.85, EtOH),[8e] OD-H column (0.25% *i*-PrOH in hexane, flow rate: 0.5 ml/min, (*S*)-enantiomer: 35 min, (*R*)-enantiomer: 37 min). For 3-(4-methoxyphenyl)-1-phenylpentan-1-one; $[\alpha]_D^{25}$=+14.5 (c 4.01, EtOH),[8e] OD column (0.25% *i*-PrOH in hexane, flow rate: 1.0 ml/min, (*S*)-enantiomer: 28 min, (*R*)-enantiomer: 25 min).

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