Note

Enantioselective Conjugate Addition of Diethylzinc to Chalcone Catalyzed by Ni(acac)$_2$ and Chiral β-Amino Alcohols

WANG, Heng-Shan[†,a](王恒山)   DA, Chao-Shan[a](达朝山)   XIN, Zhuo-Qun[a](辛卓群)
SU, Wu[a](粟武)   XIAO, Yi-Nan[a](肖亦男)   LIU, Da-Xue[a](刘大学)   WANG, Rui[*,a,b](王锐)

[a] *Department of Biochemistry & Molecular Biology, School of Life Sciences, Lanzhou University, Lanzhou, Gansu 730000, China*

[b] *State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, Gansu 730000, China*

Enantioselective conjugate addition of diethylzinc to chalcone was carried out in the presence of Ni(acac)$_2$ complexed with five pyrrolidinylmethanols derived from *L*-proline. (*S*)-*N*-Benzyl-2-(1-hydroxy-1-methylethyl) pyrrolidine was found to be the best ligand in asymmetric conjugate addition among the five ligands. The products were obtained with up to 70% *ee*. The configuration of the product was determined jointly by the substituents on the carbon of the hydroxy group and the nitrogen atom.

Keywords   asymmetric conjugation addition, Ni(acac)$_2$, pyrrolidinylmethanols

Introduction

Recently increasing interest has been focusing on the enantioselective induction in conjugate addition by catalytic method.[1] Among others, ligand design is important for successful enantioselective processes. In searching efficient chiral catalyst for conjugate addition of diethylzinc to enones, ligands with a wide variety of main structural types have been studied.[2] Great improvements have been made by chiral ligands complexed with Cu(OTf)$_2$,[2a-b,3] but reports on Ni(II) complexed with chiral ligands are limited, and the results are less desirable.[4] It is necessary to do more work on this subject. Pyrrolidinylmethanols have been proved to be effective ligands for asymmetric addition of diethylzinc to aldehydes,[5] however, only a few of them have been used in asymmetric 1,4-addition of diethylzinc to enones.[6] Our interest in this area derived from our previous work on the enantioselective addition of diethylzinc to aldehydes catalyzed by pyrrolidinols.[7] Herein, we report our results on the nickel catalyzed addition of diethylzinc to chalcone employing pyrrolidinols as ligands.

In order to examine the effect of ligand structure on the enantioselectivity we applied a series of chiral pyrrolidinylmethanols **3a**—**3e** derived from (*S*)-proline, which had successfully been applied to asymmetric addition of diethylzinc to aldehydes. At beginning, we briefly examined a set of reaction systems, and found that Ni(II) catalyzed reaction gave the best results.[8]

To optimize the reaction conditions for pyrrolidine ligands, effects of solvents and ligand-nickel-chalcone ratio on the enantioselectivity were examined (Table 1). MeCN and Et$_2$O were found to be suitable solvents, while MeCN gave better reactivity and stereoselectivity (Table 1, Entries 1—5).

Scheme 1   1,4-Addition of Et$_2$Zn to chalcone.

3a: R^1 = Bn, R^2 = Me
3b: R^1 = Bn, R^2 = Et
3c: R^1 = Bn, R^2 = Ph
3d: R^1 = H, R^2 = Ph
3e: R^1 = Me, R^2 = Ph
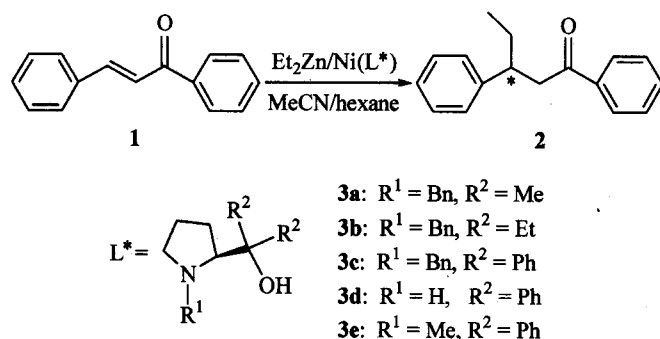
As shown in Table 1 (Entries 6—11), the enantioselectivity is optimized when ligand : Ni ratio is 2 : 1. In addition, the asymmetric induction was related with the molar ratio of substrate to ligand (Table 2, Entries 1—6). Finally, as expected, enantioselectivity was increased when the reaction was performed by addition of 2,2′-bipyridine (Table 2, Entries 6, 7).[9] Thus, optimized ligand-Ni(acac)$_2$-

Table 1 Effect of reaction conditions on the enantioselectivity of asymmetric conjugate addition of diethylzinc to chalcone using chiral pyrrolidinylmethanols[a]

Entry	Ligand	Solvent	Ligand:Ni	Temp. (°C)	Time (h)	Yield[c](%)	ee[d](%)	Config.[e]
1	3c	Et_2O^b/hexane	2:1	−45	8	77	33	R
2	3c	$CH_2Cl_2^b$/hexane	2:1	−23	2.5	85	17	R
3	3c	THF^b/hexane	2:1	−35	2.5	88	17	R
4	3c	MeCN/hexane	2:1	−23	3	87	40	R
5	3c	MeCN/toluene	2:1	−23	7	45	19	R
6	3a	MeCN/hexane	1:1	−23	1	89	19	S
7	3a	MeCN/hexane	1.5:1	−23	2	80	25	S
8	3a	MeCN/hexane	2:1	−23	2	80	42	S
9	3a	MeCN/hexane	5:1	−23	2.5	76	31	S
10	3a	MeCN/hexane	7:1	−23	3	77	26	S
11	3a	MeCN/hexane	20:1	−23	8	25	<5	S

[a] Ligand:chalcone:Et_2Zn = 1.5:10:15. [b] Solvent in which reaction was carried out after refluxing of ligand and Ni(acac)$_2$ in MeCN for 1 h and then MeCN was removed off. [c] Isolated yield. [d] Determined by HPLC using Daicel Chiracel OD column. [e] Assigned by comparing the HPLC retention time of the major peak (Ref. 9).

Table 2 Asymmetric addition of diethylzinc to chalcone using chiral pyrrolidinylmethanols

Entry	Ligand	Ligand: Chalcone	Time (h)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	3a	1:10	2	81	41	S
2	3a	3:20	2	90	42	S
3	3a	1:5	2	89	55	S
4	3a	1:2	2	94	53	S
5	3a	1:1	2	69	70	S
6	3a	1:5	2.5	90	55	S
7	3a[a]	1:5	2.5	87	59	S
8	3b	1:5	2.5	87	21	S
9	3c	1:5	2.5	89	40	R
10	3d	1:5	4	73	13	S
11	3e	1:5	2	82	33	R

[a] In the presence of 5% 2,2'-bipyridine. [b] Isolated yield. [c] Determined by HPLC using chiral OD column. [d] Assigned by comparing the HPLC retention time of the major peak (Ref. 9).

chalcone ratio of 2:1:10 and MeCN as solvent were used for further studies.

To elucidate the structure-enantioselectivity relationship, steric effect of the alcohol (R^2) and amino (R^1) moieties of pyrrolidine ligands were estimated by conducting reactions using *N*-benzyl derivatives (ligands 3a—3c) pyrrolidinyl and diphenylmethanols (ligands 3d, 3e).[5] It could be seen from the results (Table 2, Entries 6, 8, 9) that increase in the bulkiness of R^2 group reduced the degree of asymmetric induction. When 3a was used in the asymmetric reaction, higher enantioselectivity was observed than 3b and 3c. For the effect of substructure in the amino part, it was shown from the results (Table 2, Entries 9—11) that relatively higher optical yield of 2 was achieved by using *N*-protected ligands than the *N*-deprotected one. These observations are in accordance with those made in the asymmetric addition of diethylzinc to

aldehydes.[7]

It was more important to note from the results that the configuration of the product was determined jointly by the substituents on the carbon of the hydroxy group and the nitrogen atom. When R^1 = Bn, the substituent of the nitrogen atom, and R^2 which was substituent on the carbon of the hydroxyl group was methyl or ethyl group, configuration of the adducts was S. However, when R^1 was not changed but R^2 was phenyl group, the asymmetric induction direction was changed to R. When R^1 = H, R^2 = Ph, the configuration of the product was S. As for ligands 3e, R^1 = Me, and R^2 = Ph, the configuration of the conjugation adduct was R. So the two enantiomers of the asymmetric adducts were obtained by ligands only derived from the natural proline. Based on the data and from previous studies,[5,7] it could be revealed that when S enantiomer of 1-phenyl-1-propanol in excess was inducted by a ligand in addition of Et_2Zn to benzaldehyde, R enantiomer of 2, 3-diphenylpentan-1-one in excess was inducted by the same ligand in Ni-catalyzed addition of Et_2Zn to chalcone. This meant that in these two reactions prochiral face selection was ligand dependent but not dependent upon reaction type. This phenomenon could also be seen in reports of addition of Et_2Zn to aldehydes[11] and in nickel catalyzed addition of Et_2Zn to chalcone[4] using the same ligand, with no exception yet to be found.

The results indicated that very specific ligand properties is required for enantioselective catalysis.[12] Although many asymmetric reactions required steric bulk chiral catalysts in order to reach high enantioselectivity, ligand 3a, which is the smallest subsititutent on the carbon of the hydroxy group, obviously behaved the best catalytic activity among these ligands. This was possible that the *N*-atom possessed bulkier substitutent. For steadier intermediate complex of this asymmetric reaction, this bulkier substitutent probably needed relatively smaller substituted group on the carbon atom of the hydroxyl group.

So we applied pyrrolidine derivatives to promote asymmetric addition of diethylzinc to chalcone, and moderate to good enantioselectivity were obtained. More interesting was that the two enantiomers of the asymmetric adducts of chalcone could be obtained when the reaction were promoted by ligands only derived from the natural L-proline.

Typical procedure of asymmetric conjugation addition of diethylzinc to chalcone

A mixture of Ni(acac)$_2$ (6.4 mg, 0.024 mmol) and **3a** (11 mg, 0.05 mmol) in MeCN (2 mL) was stirred at 80 ℃ under argon for 1 h, then cooled to room temperature. Chalcone (52 mg, 0.25 mmol) in MeCN (1.0 mL) was added. The mixture was stirred for 20 min then cooled to − 23 ℃. Et$_2$Zn (1.0 mol·L^{-1} solution in hexane, 0.37 mmol) was added dropwise, the resulting mixture was stirred at − 23 ℃ for another 2.5 h .The reaction was quenched with 10% hydrochloric acid (2 mL), and the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$. After evaporating the solvent, the residue was purified by preparative TLC over silica gel (hexane : EtOAc = 15:1, V/V) to afford product 53 mg (81%). The *ee* value was measured by HPLC with a Daicel chiralcel OD column (hexane : ^{i}PrO = 99.8:0.2, 1.0 mL/min). The retention time is: major peak 15.5 min, minor peak 17.4 min, and the configuration was determined according to this retention time of the major peak as S.

References

1   For review see:
    (a) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186.
    (b) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283.
    (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

2   (a) Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645.
    (b) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron : Asymmetry* **1998**, *9*, 1179.
    (c) Bennett, S. M. W.; Brown, S. M.; Muxworthy, J. P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767.
    (d) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron : Asymmetry* **1999**, *10*, 2007.

    (e) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron : Asymmetry* **1997**, *8*, 3193.
    (f) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron : Asymmetry* **1997**, *8*, 3987.

3   (a) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E. Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104.
    (b) De Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374.
    (c) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620.
    (d) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429.

4   (a) De Vries, A. H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron : Asymmetry* **1997**, *8*, 1467.
    (b) Jansen, J. F. A.; Feringa, B. L. *Tetrahedron : Asymmetry* **1992**, *3*, 581.
    (c) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011.
    (d) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyoma, S. *Chem. Lett.* **1988**, 1571.

5   Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

6   (a) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040.
    (b) Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1990**, *55*, 4168.
    (c) Gibson, C. L. *Tetrahedron : Asymmetry* **1996**, *7*, 3357.
    (d) Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* **1992**, *33*, 7193.

7   Yang, X. W.; Shen, J. H.; Da, C. S.; Wang, R.; Choi, M. C. K.; Yang, L. W.; Wong, K. Y. *Tetrahedron : Asymmetry* **1999**, *10*, 133.

8   Results from other systems are: (1) 1,4-addition could be promoted in the mixture of **3a—3e** and Et$_2$Zn in hexane at room temperature (24 h), but gave 2 in 5%—0% *ee*; (2) Li salts of **3a** catalyzed the reaction and furnished 2 in 21% yield with 8% *ee* (S form); (3) addition product 2 with 15% *ee* was obtained in CH$_2$Cl$_2$ using chiral Cu(I) catalyst of **3c**.

9   Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516.

10 Brienne, M. J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613.

11 Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.

12 De Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479.