Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 133–138

TETRAHEDRON: *ASYMMETRY*

Chiral pyrrolidine derivatives as catalysts in the enantioselective addition of diethylzinc to aldehydes

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Received 6 November 1998; accepted 8 December 1998

Abstract

A series of pyrrolidine derivatives with β-amino alcohol moieties prepared from (*S*)-proline were found to catalyze the enantioselective addition of diethylzinc to aldehydes to yield optically active secondary alcohols with high enantioselectivities. A mechanism accounting for the configurational change with the bulkiness of chiral ligands is proposed.

1. Introduction

Catalytic asymmetric carbon–carbon bond formation is one of the most active research areas in organic synthesis.[1] In this field, asymmetric addition of diethylzinc (Et_2Zn) to aldehydes using a catalytic amount of chiral catalyst has attracted much attention.[2] In recent years, numerous efforts have been made to search for new effective chiral ligands such as chiral β-amino alcohols,[3] chiral amino thiols,[4] pyridyl alcohols,[5] amines[6] and titanium complexes[7] and to investigate the reaction mechanism.[8] It has been found that β-amino alcohols and titanium complexes are efficient in the reaction. Mechanistic studies show that the enantioselectivity of the addition of dialkylzincs to aldehydes is very sensitive to the steric and electronic properties of chiral catalysts. In this paper, we report the catalytic asymmetric addition of Et_2Zn to aldehydes using chiral pyrrolidine derivatives having β-amino alcohol moieties **1**–**7**[9] in order to elucidate the steric effect of chiral ligands on the enantioselectivity.

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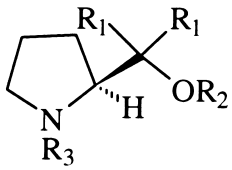
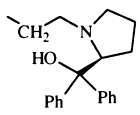
0957-4166/99/$ - see front matter
PII: S0957-4166(98)00497-2



1: R_1 = Me, R_2 = H, R_3 = $PhCH_2$
2: R_1 = Et, R_2 = H, R_3 = $PhCH_2$
3: R_1 = Ph, R_2 = H, R_3 = $PhCH_2$
4: R_1 = Ph, R_2 = R_3 = H
5: R_1 = Ph, R_2 = Me, R_3 = $PhCH_2$

6: R_1 = Ph, R_2 = Me, R_3 = H
7: R_1 = Ph, R_2 = H,
R_3 =



2. Results and discussion

2.1. Effect of the amount of catalysts and reaction temperature on the asymmetric reaction

Our first effort was to investigate the effect of the amount of catalysts **1**, **2** and **3** and reaction temperature on the catalyzed addition of Et_2Zn to benzaldehyde. The results are listed in Table 1. When 5 mol% of ligands (relative to benzaldehyde) was used, the optical purity (op) of 1-phenylpropan-1-ol was lower than those using 10 mol% chiral ligands (runs 1–2, 4–5, 7–8, and 10–11). The op decreased but the yields were nearly quantitative when the amount of the catalysts was increased to 15 mol% (runs 3, 6, 9, and 12). For example, the addition of Et_2Zn to benzaldehyde in hexane catalyzed by 5 mol%, 10 mol% and 15 mol% of β-amino alcohol **2** afforded (*R*)-1-phenylpropan-1-ol in 81.9%, 95.7% and 94.1% op, respectively, with high yields (runs 7–9). We attempted to lower the reaction temperature for higher enantioselectivity, but there was almost no reaction below 0°C. Thus, the optimum amount of chiral catalysts was 10 mol% relative to benzaldehyde and reaction temperature was 0°C.

Table 1
The effect of the amount of chiral ligands on asymmetric addition of Et_2Zn to benzaldehyde

run	ligand	mol %[a]	solvent	temp. and time	yield[b]	$[\alpha]_D$	op%[c]	config.
1	**1**	5	hexane	0°C-2h, rt-13h	98.9	+43.1(c 4.3)	94.8	*R*
2	**1**	10	hexane	0°C-2h, rt-13h	96.8	+44.0(c 4.1)	96.7	*R*
3	**1**	15	hexane	0°C-2h, rt-13h	95.3	+43.5(c 4.0)	95.6	*R*
4	**1**	5	toluene	rt-48h[d]	71.8	+13.5(c 4.6)	29.7	*R*
5	**1**	10	toluene	rt-48h[d]	40.1	+40.4(c 4.3)	88.9	*R*
6	**1**	15	toluene	rt-48h[d]	35.9	+22.6(c 4.4)	49.8	*R*
7	**2**	5	hexane	0°C-2h, rt-13h	98.7	+37.3(c 3.9)	81.9	*R*
8	**2**	10	hexane	0°C-2h, rt-13h	97.6	+43.6(c 4.4)	95.9	*R*
9	**2**	15	hexane	0°C-2h, rt-13h	97.8	+42.8(c 3.7)	94.1	R
10	**3**	5	hexane	0°C-2h, rt-1.5h	99.6	-29.4(c 5.3)	64.6	*S*
11	**3**	10	hexane	0°C-2h, rt-7h	96.6	-37.2(c 4.5)	81.8	*S*
12	**3**	15	hexane	0°C-2h, rt-13h	98.2	-36.1(c 3.8)	79.4	*S*

[a] Relative benzaldehyde

[b] Isolated yields.

[c] Determined by comparison of the optical rotation value with the literature value.[10]

[d] No reaction at 0°C.

2.2. Effect of solvents on the asymmetric reaction

It has been reported that solvents have a great effect on the enantioselectivity and yields.[7b] Thus, our second effort was to examine the effect of solvents using 10 mol% of chiral ligands **1**, **2**, and **3** on the reaction. As shown in Table 2, when **1** was used as a ligand, an identical op of 99.2% was obtained in benzene and cyclohexane with 97.7% and 97.2% yields (runs 2, 5).

Although a similar op could be obtained using mixed solvents, the yields were relatively low (runs 6–8). The highest op of 95.7% was obtained by employing hexane as a solvent in the presence of ligand **2** (runs 9–12). Using ligand **3** bearing the bulky diphenylmethanol moiety, up to 81.8% op was obtained of phenyl propanol with *S* configuration in hexane (runs 13–16). From the results, toluene and THF as solvents retarded the reaction and lowered the enantioselectivities and yields to some extent. Thus, the best solvents for the reaction are benzene and hexane.

Table 2
The effect of solvents on the asymmetric addition of Et_2Zn to benzaldehyde

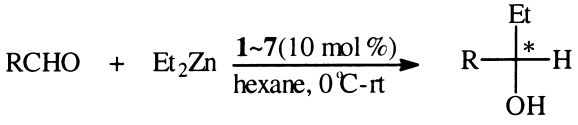
run	ligand[a]	solvent	temp. and time	yield[b]	$[\alpha]_D$	op%[c]	config.
1	**1**	hexane	0°C-2h, rt-13h	96.8	+44.0(c 4.1)	96.7	*R*
2	**1**	benzene	0°C-2h, rt-13h	97.7	+45.1(c 4.6)	99.2	*R*
3	**1**	THF	rt-48h	57.5	+35.7(c 4.0)	78.5	*R*
4	**1**	toluene	rt-48h	40.1	+40.4(c 4.3)	88.9	*R*
5	**1**	cyclohexane	0°C-2h, rt-13h	97.2	+45.1(c 4.4)	99.2	*R*
6	**1**	hexane:benzene 1:1	0°C-2h, rt-10h	80.1	+45.4(c 5.1)	99.8	*R*
7	**1**	hexane:toluene 1:1	0°C-2h, rt-13h	81.0	+45.2(c 4.7)	99.4	*R*
8	**1**	benzene:toluene 1:1	0°C-2h, rt-13h	91.8	+41.0(c 4.2)	90.2	*R*
9	**2**	hexane	0°C-2h, rt-13h	97.6	+43.6(c 4.4)	95.9	*R*
10	**2**	benzene	0°C-2h, rt-13h	97.6	+39.4(c 4.3)	86.6	*R*
11	**2**	cyclohexane	0°C-2h, rt-13h	76.2	+40.6(c 4.5)	89.3	*R*
12	**2**	THF	rt-48h	47.0	+27.1(c 4.1)	59.5	*R*
13	**3**	hexane	0°C-2h, rt-7h	96.6	-37.2(c 4.5)	81.8	*S*
14	**3**	hexane:toluene 5:1	-10°C-3h,0°C-4h	88.7	-28.7(c 3.9)	63.1	*S*
15	**3**	toluene	0°C-2h, rt-13h	91.5	-32.7(c 4.4)	71.9	*S*
16	**3**	benzene	0°C-2h, rt-13h	92.4	-25.4(c 4.1)	55.8	*S*

[a] 10 mol %
[b] Isolated yields.
[c] Determined by comparison of the optical rotation value with the literature value.[10]

2.3. Enantioselective addition of Et_2Zn to benzaldehyde and 4-methoxybenzaldehyde

Under the above optimum reaction conditions, the asymmetric catalytic capability of chiral ligands **1**–**7** was investigated (Scheme 1). The results are shown in Table 3. β-Amino alcohol **1** possessing a dimethylmethanol moiety at the α-position of the pyrrolidine ring (R_1=Me) gave (*R*)-1-phenylpropan-1-ol in 99.2% op and (*R*)-1-(4-methoxyphenyl)propan-1-ol in 95.3% op (runs 1–2). Chiral ligand **2** (R_1=Et) also provided good results (runs 3–4). However, on ligand **3** (R_1=Ph), while the bulkiness of

the α-position of the pyrrolidine ring was gradually increased, the op of the product decreased and the *S* configuration of the product was observed (runs 5–6). The ligand **5** (R_2=Me, R_3=$PhCH_2$) shows higher enantioselectivity than **3** (runs 5–6, 10–11) and the catalytic capability of **6** (up to 93.7% op, runs 12–13) containing the methoxy group (R_2=Me) is higher than **4** with the hydroxyl group (R_2=H, up to 55% op, runs 7–9). Chiral C_2-symmetric alcohol **7** also gave good results with the product having *S* configuration (91% op, 95% yield, run 15). Though the structure of the chiral ligands is very similar, the absolute configuration of the product and the enantioselectivity are very different, which prompts us to rationalize the mechanism of the addition reaction.



Scheme 1.

Based on our experimental findings and related mechanistic studies by Soai and Noyori,[8a,b] we proposed a mechanism as shown in Scheme 2. First, Et_2Zn reacts rapidly with the ligand to give the corresponding zinc monoalkoxide **8**, which does not ethylate benzaldehyde, and is then converted to the zinc monoalkoxide–diethylzinc complexes **9** and **10**.[11] The coordination geometry of the zinc atom is essentially tetrahedral[12] and this complex **10** is more stable than complex **9**. The nucleophilicity of the ethyl group of Et_2Zn would be increased by coordination of the zinc atom with the oxygen or the nitrogen atom of the catalyst.[13] Second, the *re* or *si* face of benzaldehyde may be reacted to give six-center transition states (TS) **11** and **12**, respectively. The TS **11** should be more stable than TS **12** because

Table 3
Enantioselective addition of Et_2Zn to aldehydes

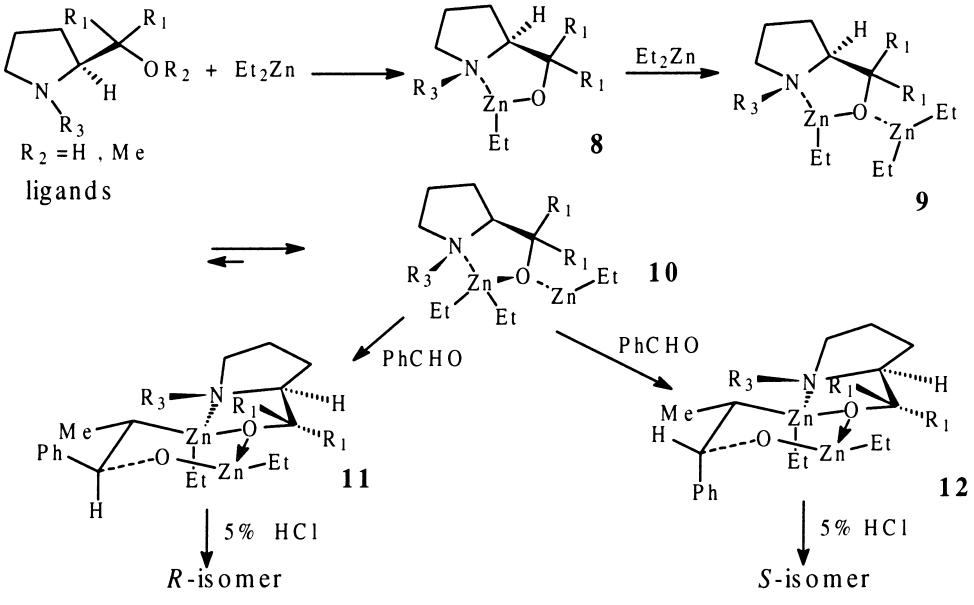
run	ligand	substrate	solvent	reaction time	yield[a]	$[\alpha]_D$	op%[b]	config.
1	**1**	PhCHO	benzene	0°C-2h, rt-13h	97.7	+45.1(c 4.6)	99.2	*R*
2	**1**	4-MeOPhCHO	benzene	0°C-2h, rt-15h	79.4	+32.9(c 3.7)	95.3[c]	*R*
3	**2**	PhCHO	hexane	0°C-2h, rt-13h	97.6	+43.6(c 4.4)	95.7	*R*
4	**2**	4-MeOPhCHO	hexane	0°C-2h, rt-15h	72.5	+29.3(c 3.4)	84.9[c]	*R*
5	**3**	PhCHO	hexane	0°C-2h, rt-7h	96.6	-37.2(c 4.5)	81.8	*S*
6	**3**	4-MeOPhCHO	hexane	0°C-2h, rt-13h	93.5	-27.4(c 3.9)	79.3[c]	*S*
7	**4**	PhCHO	hexane	0°C-2h, rt-48h	74.4	+16.4(c 4.8)	36.1	*R*
8	**4**	PhCHO	benzene	0°C-2h, rt-48h	70.3	+25.1(c 5.1)	55.2	*R*
9	**4**	4-MeOPhCHO	benzene	0°C-2h, rt-48h	66.8	+15.8(c 4.1)	45.8[c]	*R*
10	**5**	PhCHO	benzene	0°C-2h, rt-10h	94.6	-38.8(c 4.8)	85.3	*S*
11	**5**	PhCHO	hexane	0°C-2h, rt-10h	90.1	-43.2(c 4.7)	95.0	*S*
12	**6**	PhCHO	benzene	0°C-2h, rt-15h	95.9	+42.6(c 4.4)	93.7	*R*
13	**6**	PhCHO	hexane	0°C-2h, rt-15h	98.7	+41.7(c 4.5)	91.7	*R*
14	**7**	PhCHO	hexane	0°C-2h, rt-30h	78.1	-21.6(c 4.9)	47.5	*S*
15	**7**	PhCHO	hexane:toluene 5:1	0°C-2h, rt-13h	94.9	-41.4(c 5.2)	91.0	*S*
16	**7**	PhCHO	hexane:benzene 5:1	0°C-2h, rt-10h	93.3	-29.5(c 4.8)	64.8	*S*
17	**7**	4-MeOPhCHO	hexane:toluene 5:1	0°C-2h, rt-13h	87.2	-30.8(c 4.2)	89.3[c]	*S*

[a] Isolated yield.

[b] The op % was calculated based on the maximum rotation -45.45 (c 5.1,$CHCl_3$) for (*S*)-1-phenylpropan-1-ol[10].

[c] Determined by comparison of the optical rotation value with the literature value[3a].

the phenyl group is disposed equatorially in **11**.[14] Third, the six-center transition states **11** and **12** may explain the stereochemical course of the addition. When the α-substituent of the pyrrolidine ring is Me or Et (ligands **1** or **2**), the *re* face of benzaldehyde is attacked, leading to the *R* isomer (Table 3, runs 1–4). However, with the increase of the bulkiness of the α-substituent of the pyrrolidine ring, steric factors have to be taken into consideration. The bulky phenylmethanol moiety and bulky N-group in ligands **3** and **5** block the approach of benzaldehyde from the *re* face, and the ethyl group at complex **10** attacks benzaldehyde mainly from the *si* face through the transition state **12**, leading to the *S*-isomer.[14a] Owing to transition state **12** being unstable, less asymmetric induction was observed (runs 5–6, 10–11, 14–17). On the other hand, in case where the *N*-substituent is small (H in **4** and **6**), the steric effect is not sufficient to hinder attack of the *re* face of benzaldehyde, resulting in the *R*-isomer (runs 7–9, 12–13). The same trend was observed by Soai[8a] using β-amino alcohols with different N-substitutents as chiral catalysts in the reaction.



Scheme 2.

3. Experimental

3.1. General methods

Optical rotation ($[\alpha]_D$) was taken on a WZZ automatic polarimeter using $CHCl_3$ as a solvent. All reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvent under anhydrous condition. Hexane, benzene, cyclohexane, THF and toluene were distilled from sodium. Benzaldehyde and 4-methoxybenzaldehyde were distilled from calcium hydride under an argon atmosphere.

3.2. Typical procedure of asymmetric addition of Et_2Zn to benzaldehyde

To a solution of chiral β-amino alcohol (**1**) (14 mg, 0.064 mmol) in benzene (1.2 mL) was added dropwise a solution of Et_2Zn (1.28 mL, 1 M in benzene solution) at 0°C. After stirring for 0.5 h,

benzaldehyde (67.8 mg, 0.64 mmol) was added at 0°C, and the reaction was stirred for 2 h at 0°C and for 13 h at room temperature. The reaction mixture was quenched by 5% cold aqueous HCl solution and the mixture was extracted with ether (4×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give an oily residue. The residue was purified by silica gel TLC to give optically active 1-phenylpropan-1-ol (84.3 mg, 97.7%).

Acknowledgements

We thank the Hong Kong Polytechnic University, the National Natural Science Foundation of China, Fok Ying Tung Education Foundation (Hong Kong), and the Ministry of Education of China for financial support.

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