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Enantioselective additions of diphenylzinc to aldehydes using chiral pyrrolidinylmethanol derivatives as catalysts

Gang Zhao,[a,*] Xiang-Guo Li[b] and Xiu-Ran Wang[b]

[a]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 FengLin Lu, 200032 Shanghai, China*
[b]*Anhui Normal University, Institute of Organic Chemistry, Anhui, China*

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Abstract—The enantioselective addition of diphenylzinc to aldehydes using a series of chiral ligands derived from (*S*)-proline afforded secondary alcohols in high yields and with high enantiomeric excesses of up to 92.6%. The configuration of the secondary alcohol enantiomer obtained was found to be dependent on the catalyst used.

1. Introduction

The catalytic enantioselective addition of dialkylzinc reagents (ZnR_2, where R = methyl, ethyl and isopropyl) to aldehydes has been studied extensively in recent years[1] and dialkylzinc reagents have been used employing a variety of chiral ligands to yield the corresponding secondary alcohols with high enantioselectivity.[1,2] Few asymmetric diarylzinc additions to aldehydes have been reported,[3–5] because the uncatalysed diphenylzinc addition can compete with the catalysed reaction. The development of an enantioselective catalyst for diarylzinc addition is therefore much more challenging than the equivalent dialkylzinc reactions.

Soai et al. initially developed the enantioselective phenylation of prochiral aldehydes using a kinetically formed chiral complex between a phenyl Grignard reagent, a zinc halide and *N*,*N*-dibutylnorephedrine.[6] In 1997, Fu et al. reported the first enantioselective phenylation of aldehydes using a catalyst based on a planar chiral ligand.[3] Recently, Pu et al. presented the highly enantioselective phenylation reaction with chiral 1,1′-binaphthol based monomeric and polymeric catalysts.[4] Bolm et al. also reported good enantioselectivity in a reaction using a chiral ferrocenyl hydroxyoxazoline catalyst,[5] while Soai et al. recently reported the enantioselective addition of dialkylzinc reagents to aldehydes using **1a** as a chiral catalyst.[12] We recently investigated the use of sulfonyl (*S*)-prolinols as chiral catalysts to reduce aromatic ketones to the corresponding alcohols in high yields and with good enantioselectivities.[7] Herein, we report the use of the prolinol derivatives **1a**–**1l** (Scheme 1) as catalysts in the enantioselective addition of diphenylzinc to aldehydes.

2. Results and discussion

2.1. Effect of solvent and temperature on the asymmetric reaction

We first investigated the effect of solvent and reaction temperature on the catalytic addition of $ZnPh_2$ to *p*-chlorobenzaldehyde using 10 mol% of catalyst **1a**. The results are summarised in Table 1. In this study, obvious solvent effects were observed. The highest enantioselectivity of 89.1% was obtained by employing toluene solvent at −30°C (entry 4). When reactions were carried out in hexane, ether, THF or CH_2Cl_2, the enantioselectivity was poor. This could be a result of the strong coordinating ability of THF and Et_2O to the active catalyst complex. It is unclear why poor enantioselectivity is seen in the hexane and CH_2Cl_2 solvated reactions.

The best result was achieved at a reaction temperature of −30°C. Using the same conditions but at room temperature, the reaction was complete within 30 minutes but afforded a product with lower e.e. (entry 6).

* Corresponding author. Fax: 86 21 64166128; e-mail: zhaog@pub.sioc.ac.cn

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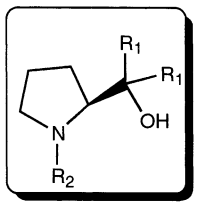
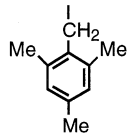


1

1a: R_1 = Ph R_2 = Me

1b: R_1 = Ph R_2 =



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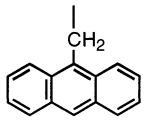
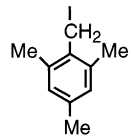


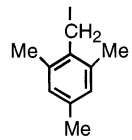
1d: R_1= *p*-F-C_6H_4 R_2 = Me

1e: R_1= Me R_2 = Bn

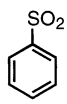
1f: R_1= Me R_2 =



1g: R_1= H R_2 =



R_1 = Ph R_2 =



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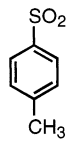

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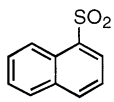

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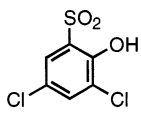

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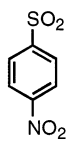


1l

Scheme 1.

2.2. Chiral catalysts and the amount of catalysts

Based on the above optimum reaction conditions, we chose *p*-chlorobenzaldehyde as the substrate to examine the effect of various catalysts. The results are listed in Table 2. All catalysts gave good yields. However, the e.e. varied from 92.6 to 6.1%. Moreover, the absolute configuration of the product was found to change on employing different catalysts. The sulfonyl (*S*)-prolinols **1h**–**1l** gave (*R*)-(*p*-chlorophenyl)phenylmethanols (entries 11–19) and, interestingly, though chiral ligands **1a**–**1g** have similar structures, they afforded products with different absolute configuration. A similar trend was observed by Wang[8] using β-amino alcohols with different α-substituents as chiral catalysts in the reaction of diethylzinc additions to aldehydes. A tentative mechanism proposed by Soai et al. could explain the stereochemical course of the addition reaction.[12]

We investigated the effect of catalyst loading on the reaction. From this it was found that the optimum amount was 15–20 mol%.

It is noteworthy that the catalyst is very stable and was recovered from the reactions in more than 90% yield and re-used in the same reaction without any loss of yield or e.e. The ^{1}H NMR spectra and specific rotation of the recovered catalyst proved that it was unchanged after the reaction. Of the catalysts examined, catalysts **1a**, **1e** and **1h** gave the highest enantioselectivities (entries 3, 8 and 14).

2.3. Enantioselective addition of various aldehydes using catalysts 1a, 1e or 1h

We applied catalysts **1a**, **1e** and **1h** to the additions of various aldehydes, and the results are shown in Table 3.

Table 1. The effect of solvents and temperature on asymmetric addition of $ZnPh_2$ to *p*-chlorobenzaldehyde

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	E.e. (%)[b]	Config.[c]
1	Hexane	−78 to 0	15	92	5.0	*S*
2	Hexane	−30	9	98	24.3	*S*
3	Toluene	−78 to 0	16	99	81.4	*S*
4	Toluene	−30	8	95	89.1	*S*
5	Toluene	0	4	96	83.1	*S*
6	Toluene	Rt	0.5	92	11.2	*S*
7	Toluene:hexane (v/v=1:1)	−30	8	98	72.5	*S*
8	Ether	−30	7.5	94	0.9	*S*
9	THF	−30	9	96	0.0	–
10	CH_2Cl_2	−30	7	97	3.1	*S*

[a] Yield of isolated pure product.
[b] E.e. was determined by HPLC with Chiralcel AD, with 10% 2-propanol in hexane as eluent.
[c] Configuration of products was established on the basis of the sign of the specific rotation.[4b]

Table 2. Chiral catalysts and the amount of catalysts

Entry	Catalysts	Mol %[a]	Time (h)	Yield (%)[b]	E.e. (%)[c]	Config.[d]
1	**1a**	5	8	91	87.8	*S*
2	**1a**	10	8	95	89.1	*S*
3	**1a**	15	10	96	**92.6**	*S*
4	**1a**	20	9	93	92.1	*S*
5	**1b**	15	10	97	70.3	*S*
6	**1c**	20	9	95	64.4	*S*
7	**1d**	20	8	91	36.6	*S*
8	**1e**	20	8	93	**70.6**	*R*
9	**1f**	20	13	93	6.1	*R*
10	**1g**	20	8	97	9.5	*R*
11	**1h**	5	9	93	39.0	*R*
12	**1h**	10	8	92	46.2	*R*
13	**1h**	15	10	95	71.2	*R*
14	**1h**	20	9	95	**83.5**	*R*
15	**1h**	25	8	93	68.1	*R*
16	**1i**	20	8	93	21.8	*R*
17	**1j**	20	8	91	11.3	*R*
18	**1k**	20	7	92	65.7	*R*
19	**1l**	20	9	93	32.9	*R*

[a] Molar ratio to *p*-chlorobenzaldehyde.
[b] Isolated yields.
[c] E.e. was determined by HPLC with a Chiralcel AD column, with 10% 2-propanol in hexane as eluent.
[d] Configuration of products was established on the basis of the sign of the specific rotation.[4b]

For the examined aryl aldehydes, the catalysts **1a**, **1e** and **1h** gave moderate to good e.e. and high chemical yields. Generally, higher selectivities were seen with *para*-substituted aryl aldehydes rather than their *ortho*- and *meta*-substituted analogues, which is probably a result of steric hindrance effects.

The absolute configuration of the product varied with the catalyst employed. The (*S*)-configured products resulted from reactions catalysed by **1a**. In contrast, the absolute configuration of products from reactions catalysed by **1e** and **1h** was found to be (*R*). The exception to this was the substrate *m*-Cl-C_6H_4CHO, where the same absolute configuration of product was observed irrespective of the catalyst used (runs 8, 19 and 30).

In conclusion, we have applied a series of chiral ligands derived from (*S*)-proline to the asymmetric addition of diphenylzinc to various benzaldehydes. Other ligands have been developed in our group and will be reported in detail soon.

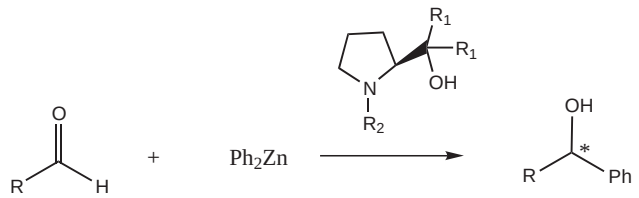
3. Experimental

3.1. General methods

All reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions. All solvents were purified according to standard methods. Aldehydes were purchased from Aldrich Ltd.

Catalysts **1h**–**1l** were synthesised by our method.[7] Catalysts **1a** and **1e** were synthesised according to the literature.[12,13] The synthesis of the other catalysts was similar to the reported methods.[12,13] Diphenylzinc was pre-

Table 3. Asymmetric addition of aldehydes using catalysts **1a**, **1e** and **1h**



Run	R	Yield (%)[a]	% E.e. (config.)[b]
		Cat. **1a** (15 mol%)	
1	4-Cl-C_6H_4	96	92.6 (*S*)[c]
2	4-Br-C_6H_4	94	50.2 (*S*)[c]
3	2-Naphthyl	93	60.5 (*S*)[d]
4	4-Me-C_6H_4	94	79.8 (*S*)[e]
5	2-Cl-C_6H_4	99	15.2 (*S*)[f]
6	*trans*-PhCH=CH	93	7.4 (*R*)[d]
7	*i*-Pr	94	56.8 (*R*)[g]
8	3-Cl-C_6H_4	92	53.7 (*R*)[h]
9	4-CH_3O-C_6H_4	95	92.2 (*S*)[e]
10	4-F-C_6H_4	93	90.5 (*S*)[i]
11	4-NO_2-C_6H_4	94	81.8 (*S*)[j]
		Cat. **1e** (20 mol%)	
12	4-Cl-C_6H_4	95	70.6 (*R*)[c]
13	4-Br-C_6H_4	96	71.5 (*R*)[c]
14	2-Naphthyl	91	43.9 (*R*)[d]
15	4-Me-C_6H_4	91	87.6 (*R*)[e]
16	2-Cl-C_6H_4	97	13.2 (*R*)[f]
17	*trans*-PhCH=CH	90	4.2 (*S*)[d]
18	*i*-Pr	92	6.5 (*S*)[g]
19	3-Cl-C_6H_4	91	7.9 (*R*)[h]
20	4-CH_3O-C_6H_4	98	19.6 (*R*)[e]
21	4-F-C_6H_4	96	71.8 (*R*)[i]
22	4-NO_2-C_6H_4	94	71.3 (*R*)[j]
		Cat. **1h** (20 mol%)	
23	4-Cl-C_6H_4	95	83.5 (*R*)[c]
24	4-Br-C_6H_4	97	75.1 (*R*)[c]
25	2-Naphthyl	90	45.9 (*R*)[d]
26	4-Me-C_6H_4	91	69.1 (*R*)[e]
27	2-Cl-C_6H_4	93	8.5 (*R*)[f]
28	*trans*-PhCH=CH	91	2.6 (*S*)[d]
29	*i*-Pr	93	6.9 (*S*)[g]
30	3-Cl-C_6H_4	92	10.9 (*R*)[h]
31	4-CH_3O-C_6H_4	91	48.2 (*R*)[e]
32	4-F-C_6H_4	95	55.4 (*R*)[i]
33	4-NO_2-C_6H_4	93	65.0 (*R*)[j]

[a] Isolated yields.
[b] The absolute configuration was determined on the basis of the sign of the specific rotation.[4b,9–11]
[c] Determined by Chiralcel AD column, 10% 2-propanol in hexane as eluent.
[d] Determined by Chiralcel OD column, 10% 2-propanol in hexane as eluent.
[e] Determined by Chiralcel OJ column, 20% 2-propanol in hexane as eluent.
[f] Determined by Chiralcel OD column, 20% 2-propanol in hexane as eluent.
[g] Determined by Chiralcel AS column, 5% 2-propanol in hexane as eluent.
[h] Determined by Chiralcel OD column, 9% 2-propanol in hexane as eluent.
[i] Determined by Chiralcel OB-H column, 20% 2-propanol in hexane as eluent.
[j] Determined by Chiralcel AD column, 20% 2-propanol in hexane as eluent.

pared according to the literature,[14] as a 0.5 M solution in toluene as determined by titration.[15]

3.1.1. Preparation of 1b. PhMgBr (1 mmol) in ether (11 mL) was added dropwise to a solution of (*S*)-1-(2,4,6-trimethyl)benzenemethyl-proline ethyl ester (5 mmol) in ether (10 mL) at room temperature. The mixture was stirred under reflux for 4 h and cooled to 0°C. The reaction was quenched with saturated aqueous ammonium chloride, the organic layer was separated and the aqueous extracted with ether (3×5 mL). The combined organic extract was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel to provide **1b** as a white solid (1.6 g, 84%): $[\alpha]_D^{20}=-7.1$ ($c=1.39$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.5–2.0 (4H, m), 2.1 (6H, s), 2.2 (3H, s), 2.4 (m, 1H), 2.6 (m, 1H), 3.1, 3.4 (2H, AB-system, $J=12.2$ Hz), 4.0 (1H, m), 4.9 (1H, br s), 6.7 (2H, s), 7.1–7.9 (10H, m). IR (KBr): 3401, 1613, 1491, 1368 cm^{-1}. Anal. calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.10; N, 3.63. Found: C, 83.63; H, 8.45; N, 3.66%. MS (*m*/*z*): 384 (M^+–1, 3), 368 (1), 202 (47), 133 (100), 77 (11).

3.1.2. Preparation of 1c. Prepared analogously to **1b** in 70% yield: white solid, $[\alpha]_D^{20}=+47.6$ (*c* 0.98, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.5 (2H, m), 1.7 (1H, m), 2.0 (1H, m), 2.2 (1H, m), 2.6 (1H, m), 4.1, 4.5 (2H, AB-system, $J=12.5$ Hz), 4.3 (1H, q, $J=4.9$), 4.9 (1H, br s), 7.0–8.2 (18H, m), 8.3 (1H, s); IR (KBr): 3371, 1624, 1523, 1490, 1340 cm^{-1}. Anal. calcd for $C_{32}H_{29}NO$: C, 86.64; H, 6.59; N, 3.16. Found: C, 86.42; H, 6.39; N, 3.20%. MS (*m*/*z*): 443 (M^+, 0.35), 260 (15), 191 (100), 77 (6).

3.1.3. Preparation of 1d. Prepared by a similar method to the literature,[12] yield 80%, white solid, $[\alpha]_D^{20}=+41.0$ (*c* 1.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.6–1.8 (4H, m), 1.7 (3H, s) 2.4 (1H, m), 3.1 (1H, m), 3.5 (1H, m), 4.8 (1H, br s), 6.9–7.6 (8H, m). ^{19}F NMR (300 MHz, $CDCl_3$): δ –40.2 (1F, s), –39.8 (1F, s). IR (KBr): 3315, 1601, 1502, 1373, 1156 cm^{-1}. Anal. calcd for $C_{18}H_{19}F_2NO$: C, 71.27; H, 6.31; N, 4.62. Found: C, 71.22; H, 6.36; N, 4.60%. MS (*m*/*z*): 304 (M^++1, 14), 286 (10), 201 (1), 123 (6), 84 (100).

3.1.4. Preparation of 1f. Similar to the preparation of **1b**, yield 72%, colourless oil, $[\alpha]_D^{20}=-3.0$ (*c* 1.40, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.1 (3H, s), 1.2 (3H, s), 1.6–1.9 (4H, m), 2.2 (3H, s), 2.4 (6H, s), 2.4–2.7 (4H, m), 3.7, 3.9 (2H, AB-system, $J=12.5$ Hz), 6.8 (2H, s). IR (KBr): 3457, 1614, 1579, 1463, 1375 cm^{-1}. Anal. calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.92; H, 10.60; N, 5.22%. MS (*m*/*z*): 260 (M^+–1, 34), 244 (5), 202 (79), 133 (100), 59 (7).

3.1.5. Preparation of 1g. A solution of (*S*)-1-(2,4,6-trimethyl)benzenemethyl-proline ethyl ester (2 mmol) in THF (4 mL) was dropped carefully into a mixture

of $LiAlH_4$ (2.5 mmol) in THF (4 mL) at room temperature. After addition, the mixture was stirred under reflux until the reaction was complete, then cooled to 0°C. Ethyl acetate (2 mL) and water (2 mL) were added to the mixture slowly. The mixture was extracted with ether (3×3 mL). The combined organic layer was dried and evaporated. The residue was purified by flash chromatography to provide **1g** as a white solid (350 mg, 75%): $[\alpha]_D^{20} = -12.3$ (c 1.68, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.5–2.1 (4H, m), 2.2 (3H, s), 2.3 (6H, s), 2.4–2.6 (2H, m), 2.7 (1H, m), 2.9 (1H, m), 3.4, 3.9 (2H, AB-system, $J = 11.6$ Hz), 3.55 (2H, m), 6.85 (2H, s); IR (KBr): 3431, 1612, 1578, 1461, 1374 cm^{-1}. Anal. calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.00; H, 10.04; N, 5.81%. MS (m/z): 233 (M^+, 0.35), 202 (35), 133 (100), 117 (7), 91 (6).

3.2. Typical procedure for asymmetric addition of Ph_2Zn to aldehyde

To a solution of chiral ligand **1a** (0.15 mmol) in toluene (7.5 mL) was added dropwise a solution of Ph_2Zn (0.5 M in toluene, 4 mL) at −30°C. After stirring for 1 h, *p*-chlorobenzaldehyde (140.5 mg, 1 mmol) in toluene (2 mL) was added at a rate of 5 mL/h by syringe pump at −30°C. The reaction was monitored by TLC. When the reaction was complete, the mixture was quenched by addition of 1N aqueous HCl and the mixture was extracted with ethyl acetate (3×3 mL), the combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography to give (*p*-chlorophenyl)phenylmethanol (210 mg, 96%) as a white solid. The e.e. was 92.6% (chiral AD column, 10% 2-propanol in hexane as eluent). Catalyst was recovered (36.4 mg, 91%).

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