

Enantioselective Addition of Diethylzinc to Aryl Aldehydes Catalyzed by Novel Chiral Imino Alcohol Ligands

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The enantioselective alkylation of aryl aldehydes by diethylzinc in the presence of catalytic amounts of several novel chiral imino alcohol ligands, synthesized from the reaction of (R)-2-amino-1-butanol with aromatic aldehydes, was studied. The influence of temperature and ligand structure was investigated and enantioselectivity up to 81% was obtained.

Keywords: Imino-alcohols, Alkylation, Diethylzinc, Aryl aldehydes, Enantioselective

INTRODUCTION

The formation of C-C bonds is one of the most challenging goals in organic synthesis. Among the existing methods, the addition of dialkylzinc to aldehydes or ketones is one of the most convenient [1]. The high ligand dependence of this reaction is illustrated by the fact that aliphatic and aromatic aldehydes do not significantly react with dialkylzinc reagents in the absence of an appropriate ligand.

Since the introduction of (-)-3-exo-dimethylamino-isoborneol (DAIB) by Noyori *et al.* [2], a large variety of amino alcohol derivatives such as acyclic amine-based amino alcohols [3], cyclic amine-based amino alcohols [4], pyridyl alcohols [5], carbohydrate-based amino alcohols [6], ferrocene-based amino alcohols [7], and sulfonamide alcohols [8] have been employed in this reaction.

In contrast to the great number of chiral imino alcohol derivatives used as ligands for asymmetric catalyses [9], only few cases have so far been reported for stereoselective

addition of dialkylzinc to aldehydes (Fig. 1), most of which are rather expensive [10].

Herein we report the synthesis and utility of novel chiral imino alcohol ligands in diethylzinc addition to aromatic aldehydes and the effect of their structure and temperature on the enantioselectivity of the reactions. A substantial advantage of these ligands is that they are cheap, stable in air and can be prepared in large quantities without any special precaution.

EXPERIMENTAL

General

Melting points were obtained in open capillary tubes measured on an electrothermal 9200 apparatus and were not corrected. Mass spectra were recorded on a FINNIGAN-MAT8430 mass spectrometer operating at an ionization-potential of 70 eV. Elemental analysis was performed using a Gmbh varioEL instrument. IR spectra were recorded on KBr pellets on a Nicolet Impact 400D spectrophotometer. Conversions were determined with a Hewlett-Packard HP-5890 GC instrument equipped with a flame ionization detector

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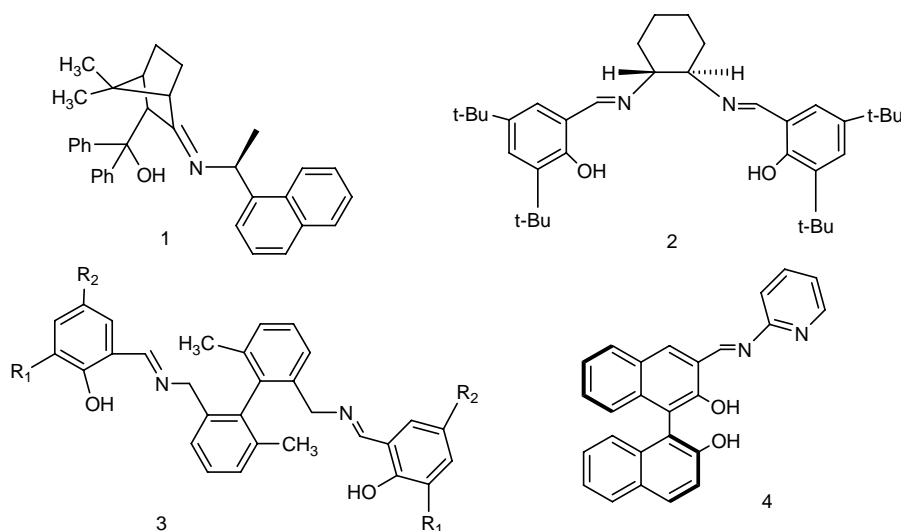


Fig. 1. Imino alcohols used as ligands in the enantioselective addition of dialkylzinc to aldehydes.

and a 30 m HP-1 capillary column, using nitrogen (2 ml min^{-1}) as carrier gas. The enantiomeric ratios were determined with the aforementioned apparatus using a 30 m WCOT fused silica capillary column (HP-chiral). ^1H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300.13 and 75.47 MHz, respectively.

Preparation of Ligands

Preparation of 2-((E-(R)-1-hydroxybutan-2-ylimino)methyl) phenol (**5e**): to a solution of (R)-2-amino-1-butanol (0.979 g, 11 mmol) in dry methanol (15 ml) was added 1.22 g (10 mmol) of salicylaldehyde. After stirring for 15 h at room temperature (TLC monitoring), the solvent was distilled off under vacuum and the residue was purified by column chromatography on silica gel (eluting with *n*-hexane-ethyl acetate mixtures) to give 1.64 g (85% yield) of the ligand **5e** as a yellow solid.

General Procedure for the Enantioselective Addition of Diethylzinc to Benzaldehyde

The ligand (0.11 mmol) was placed in a test tube and dissolved in dry toluene (2 ml). The solution was stirred for 5 min. A 1.0 M solution of diethylzinc in *n*-hexane (2.2 mmol, 2.2 ml) was then added, and after the mixture was stirred for 5 min, a solution of benzaldehyde (1.11 mmol) in dry toluene (1 ml) was added by a syringe. The mixture was stirred at the

appropriate temperature for the time reported in Table 1. Saturated aqueous NH_4Cl was added (10 ml) and the mixture was extracted with ethyl acetate ($3 \times 20 \text{ ml}$). The collected organic phases were washed with water, dried over Na_2SO_4 and analyzed by GC, after suitable dilution.

(R)-2-(4-Dimethylamino)benzylidene amino)butan-1-ol (5a). 83% Yield as colorless crystals; m.p.: $77.5\text{--}79.5 \text{ }^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = +27.5$ ($c = 1.02$, DMSO); IR (KBr) 3203, 2961, 1607, 1529, 1369, 1185, 1059, 816 cm^{-1} ; Ms (EI) 220 (M^+ , 85), 189 (100), 160 (82), 134 (70), 77 (18), 31 (33); ^1H NMR (DMSO- d_6) δ 0.77 (3H, t, $J = 7.36 \text{ Hz}$), 1.37-1.44 (1H, m), 1.57-1.64 (1H, m), 2.94 (6H, s), 2.98-3.02 (1H, m), 3.38-3.42 (1H, m), 3.46-3.51 (1H, m), 4.51 (1H, t, $J = 5.35 \text{ Hz}$), 6.71 (2H, d, $J = 8.70 \text{ Hz}$), 7.55 (2H, d, $J = 8.70 \text{ Hz}$), 8.09 (1H, s); ^{13}C NMR (DMSO- d_6) δ 160.1, 152.1 (2C), 129.6, 124.6 (2C), 111.8 (2C), 74.7, 65.5, 25.5, 11.1 (Found: C, 70.90; H, 9.35; N, 12.54; $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}$ requires: C, 70.87; H, 9.15; N, 12.72).

(R)-2-(3-Nitrobenzylideneamino)butan-1-ol (5b). 80% Yield as colorless crystals; m.p.: $114.5\text{--}116 \text{ }^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = +21.0$ ($c = 1.00$, DMSO); IR (KBr) 3218, 2980, 1646, 1524, 1340, 1059, 826, 734, 676 cm^{-1} ; Ms (EI) 223 ($\text{M}^+ + 1$, 47), 191 (100), 136 (30), 117 (45), 89 (34), 63 (22), 31 (33); ^1H NMR (DMSO- d_6) δ 0.79 (3H, t, $J = 7.35 \text{ Hz}$), 1.45-1.52 (1H, m), 1.60-1.64 (1H, m), 3.14-3.19 (1H, m), 3.38-3.58 (2H, m), 4.64 (1H, t, $J = 5.55 \text{ Hz}$), 7.73 (1H, t, $J = 7.89 \text{ Hz}$), 8.22 (1H, dd, $J = 32.4$, 7.59 Hz), 8.43 (1H, s), 8.56 (1H, S); ^{13}C NMR

(DMSO-*d*₆) δ 158.8, 148.5, 138.2, 134.7, 130.7, 125.2, 122.1, 74.5, 64.9, 25.1, 11.0 (Found: C, 59.34; H, 7.00; N, 12.32 C₁₁H₁₄N₂O₃ requires: C, 59.18; H, 6.77; N, 12.55).

4-((E)-(R)-1-Hydroxybutan-2-ylimino) methylphenol (5c). 74% yield as colorless crystals; m.p.: 163.5-165 °C; $[\alpha]_D^{25} = +28.84$ (*c* = 1.04, DMSO); IR (KBr) 3155, 2961, 1636, 1607, 1515, 1287, 1054 cm⁻¹; Ms (EI) 194 (M⁺, 65), 162 (100), 107 (55), 41 (9); ¹H NMR (DMSO-*d*₆) δ 0.76 (3H, t, *J* = 7.35 Hz), 1.34-1.44 (1H, m), 1.56-1.64 (1H, m), 3.00 (1H, m), 3.33-3.52 (2H, m), 4.52 (1H, t, *J* = 5.35 Hz), 6.80 (2H, d, *J* = 8.28), 7.57 (2H, d, *J* = 8.28), 8.13 (1H, s), 9.86 (1H, s); ¹³C NMR (DMSO-*d*₆) δ 160.0, 159, 130.0, 128.0 (2C), 115.7 (2C), 74.6, 65.3, 25.3, 11.1 (Found: C, 68.11; H, 8.10; N, 7.09 C₁₁H₁₅NO₂ requires: C, 68.37; H, 7.82; N, 7.25).

(R)-2-((Anthracen-10-yl)methyleneamino)butan-1-ol (5d). 90% Yield as green crystals; m.p.: 156-158.5 °C; $[\alpha]_D^{25} = -7.84$ (*c* = 1.02, DMSO); IR (KBr) 3194, 2932, 1646, 1073, 889, 739 cm⁻¹; Ms (EI) 277 (M⁺, 75), 246 (100), 230 (24), 204 (83), 109 (15), 31 (60); ¹H NMR (DMSO-*d*₆) δ 0.99 (3H, t, *J* = 7.39 Hz), 1.61-1.75 (2H, m), 3.45 (1H, m), 3.55-3.63 (1H, m), 3.70-3.75 (1H, m), 4.84 (1H, t, *J* = 5.28 Hz), 7.51-7.59 (4H, m), 8.10-8.13 (2H, m), 8.58-8.66 (3H, m), 9.35 (1H, s); ¹³C NMR (DMSO-*d*₆) δ 159.9, 131.2, 129.6, 129.3, 129.1, 129.0, 127.0, 125.8, 125.5, 76.3, 65.1, 25.2, 11.4 (Found: C, 82.09; H, 7.20; N, 5.02 C₁₉H₁₉NO requires: C, 82.28; H, 6.9; N, 5.05).

2-((R)-1-Hydroxybutan-2-ylimino)methylphenol (5e). 85% Yield as yellow crystals; m.p.: 52.5-55.5 °C; $[\alpha]_D^{25} = +7$ (*c* = 1.00, DMSO); IR (KBr) 3262, 2961, 1631, 1277, 1059, 758 cm⁻¹; Ms (EI) 193 (M⁺, 86), 162 (77), 145 (85), 107 (69), 77 (30), 51 (22), 31 (52); ¹H NMR (DMSO-*d*₆) δ 0.83 (3H, t, *J* = 7.39 Hz), 1.43-1.52 (1H, m), 1.61-1.67 (1H, m), 3.13-3.20 (1H, m), 3.37-3.45 (1H, m), 3.55-3.58 (1H, m), 4.80 (1H, m), 6.85-6.91 (2H, m), 7.29-7.34 (1H, m), 7.45 (1H, d, *J* = 7.44 Hz), 8.49 (1H, s); ¹³C NMR (DMSO-*d*₆) δ 165.7, 161.3, 132.5, 132.0, 119.0, 118.7, 116.9, 72.6, 64.8, 25.1, 10.8 (Found: C, 68.19; H, 8.10; N, 7.1 C₁₁H₁₅NO₂ requires: C, 68.37; H, 7.82; N, 7.25).

(R)-2-(2,6-Dichlorobenzylideneamino)butan-1-ol (5f). 98% Yield as colorless crystals; m.p.: 68.5-69.5 °C; $[\alpha]_D^{25} = +28.4$ (*c* = 1.02, DMSO); IR (KBr) 3291, 2961, 1650, 1427, 1054, 783 cm⁻¹; Ms (EI) 246 (M⁺, 16), 214 (100), 159 (70), 123 (32), 100 (17), 75 (19), 41 (81), 31 (63); ¹H NMR

(CDCl₃) δ 0.98 (3H, t, *J* = 7.38 Hz), 1.64-1.73 (2H, m), 1.86 (1H, m), 3.30-3.38 (1H, m), 3.78-3.84 (2H, m), 7.17-7.38 (3H, m), 8.47 (1H, s); ¹³C NMR (CDCl₃) δ 157.9, 134.3, 133.4, 130.3, 128.5, 75.5, 65.9, 24.5, 10.7 (Found: C, 53.59; H, 5.57; N, 5.67 C₁₃H₁₁C₁₂NO requires: C, 53.68; H, 5.32; N, 5.69).

(2R,2'R)-2,2'-{Benzene-1,4-diylbis[methylylideneamino]} dibutan-1-ol (5g). 89% Yield as colorless crystals; m.p.: 139-140.5 °C; $[\alpha]_D^{25} = -3.77$ (*c* = 1.06, DMSO); IR (KBr) 3223, 2961, 1636, 1302, 1054 cm⁻¹; Ms (EI) 277 (M⁺, 25), 245 (100), 173 (25), 146 (51), 117 (20), 91 (23), 55 (25), 31 (75); ¹H NMR (DMSO-*d*₆) δ 0.78 (3H, t, *J* = 7.05 Hz), 1.40-1.49 (1H, m), 1.61 (1H, m), 3.10 (1H, m), 3.35-3.56 (2H, m), 4.59 (1H, t, *J* = 4.75 Hz), 7.8 (4H, s), 8.31 (1H, s); ¹³C NMR (DMSO-*d*₆) δ 160.2 (2C), 138.3 (2C), 128.5 (4C), 74.7 (2C), 65.1 (2C), 25.2 (2C), 11.0 (2C) Found: C, 69.25; H, 9.05; N, 9.83 C₁₆H₂₄N₂O₂ requires: C, 69.53; H, 8.75; N, 10.14).

RESULTS AND DISCUSSION

A series of novel chiral ligands (Fig. 2) were synthesized by the reaction of R-(2)-amino-1-butanol with the appropriate aromatic aldehyde.

Imines are unreactive to dialkylzinc even at elevated temperature and it is not surprising that the same reaction fails to provide amines because of low reactivity of imines towards nucleophilic attack [11].

First, we examined the reaction of diethylzinc and benzaldehyde in the presence of catalytic amounts of chiral 2-imino-1-alcohols **5a-g** (Scheme 1). The results are summarized in Table 1. The reactions were performed using 10 mol% of the catalyst in toluene at different temperatures, and good enantioselectivity was obtained for *meta* and *para* substituted ligands. In all cases the major enantiomer of the produced 1-phenyl-propanol possessed the *S* configuration. The highest enantioselectivities were obtained with chiral ligand **5c** (Table 1, entries 8-12). By increasing the ratio of ligand **5c** to benzaldehyde, an increase in the enantioselectivity of (*S*)-1-phenyl-1-propanol was observed, and the best enantioselectivity (78% ee) was obtained, when 20 mol% of **5c** was used (Table 1, entry 12). Racemic product was obtained from the C₂-symmetry *para*-substituted ligand **5g** (Table 1, entries 23-25). Addition of titanium isopropoxide has been reported to increase the ee in many cases [12].

Table 1. Enantioselective Addition of Et₂Zn to C₆H₅CHO Catalyzed by Chiral Catalysts at Different Temperatures

Entry	Ligand	T (°C)	Time (h)	Yield (%) ^a	Ee (%) ^{b,c}
1	5a	+30	40	81	27
2	5a	+10	40	64	39
3	5a	-10	22	16	56
4	5b	+30	40	67	52
5	5b	+10	40	48	56
6	5b	-10	22	12	58
7 ^d	5b	-30	40	25	67
8	5c	+30	40	71	62
9	5c	+10	40	39	67
10	5c	-10	40	20	68
11	5c	-23	40	9	67
12 ^d	5c	-30	40	51	78
13 ^c	5c	+10	40	66	6.5
14	5d	+30	40	73	10
15	5d	+10	40	60	14
16	5d	-10	20	20	5
17	5e	+30	40	40	3
18	5e	+10	40	17	5
19	5e	-10	22	6	3
20	5f	+30	40	68	0
21	5f	+10	40	56	21
22	5f	-10	20	21	0
23	5g	+30	40	68	0
24	5g	+10	40	50	3
25	5g	-10	20	21	0
26	-	+30	40	26	0
27	-	+10	40	22	0
28	-	-10	22	5	0

^aGC yield on the mixture of the two enantiomers. ^bEe was determined by GC using a chiral capillary column (HP-Chiral). ^cAbsolute configuration of the major enantiomer was determined by comparison with authentic sample. In all cases the major product had the *S* configuration. ^dThis reaction was carried out with 20 mol% of ligand. ^eWith 120 mol% of Ti(O^{*i*}Pr)₄.

Enantioselective Addition of Diethylzinc to Aryl Aldehydes

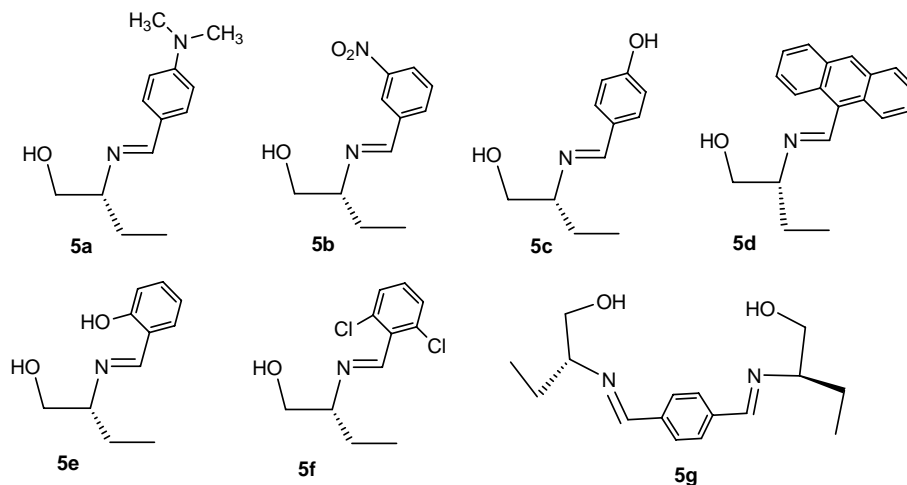
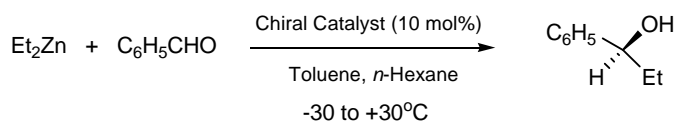


Fig. 2. Chiral ligands synthesized by the reaction of R-(2)-amino-1-butanol.



Scheme 1

However, in our experiments, treatment of **5c** with 120 mol% of titanium isopropoxide led to a significant decrease of the enantioselectivity (Table 1, entry 13).

We observed that, in the majority of cases, lower temperatures favored the enantioselectivity of the reaction, thus when the reactions were carried out at 30 °C with 10 mol% of the catalyst, lower ee values were obtained compared to 10 °C or -10 °C. The correlation of enantioselectivities with temperature for the three best ligands is depicted in Fig. 3. In addition to spectroscopic data, the spatial arrangement of groups in **5c** was established by X-ray analysis. The ORTEP of **5c** is shown in Fig. 4. As can be seen, the C=N had the E geometry in the ligand. After optimizing the best conditions for the reaction of diethylzinc with benzaldehyde, we applied the same condition to other aromatic aldehydes. According to the obtained results by **5c** (Table 1, entries 8-12) and similarity of the ees in +10 °C and -10 °C the optimized reactions were carried out at +10 °C and -30 °C. The results for the addition of diethylzinc in the presence of **5c** are summarized in Table 2. For substituted aromatic aldehydes, as shown in Table 2, fair to good selectivities were obtained. Generally, electron-

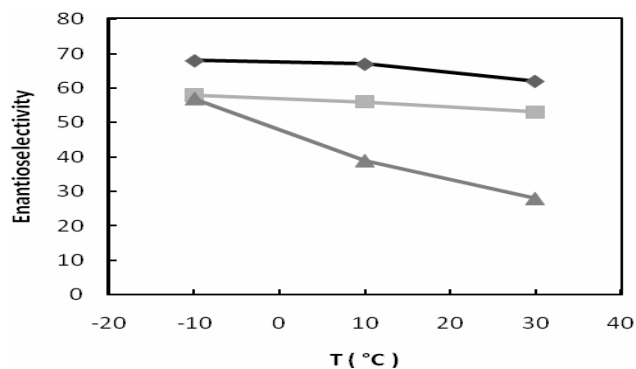


Fig. 3. Correlation of enantioselectivity with temperature for three ligands: (▲) **5a**, (■) **5b**, (◆) **5c**.

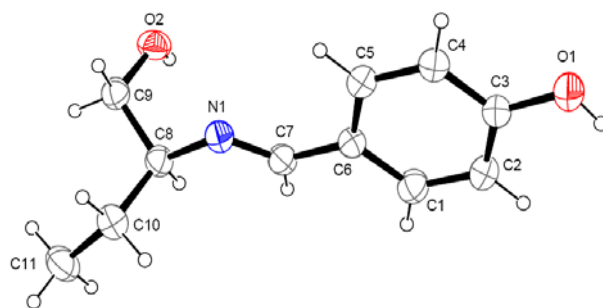


Fig. 4. The ORTEP view of **5c**.

withdrawing substituents in *para* position gave better ee values, while introduction of substituents in *ortho* position or presence of an electron-donating group on *para*, led to a slight

Table 2. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by Chiral Imino Alcohol **5c**^a

Entry	Aldehyde	Yield (%) ^b	Ee (%) ^{c,d}
1	<i>p</i> -FC ₆ H ₄ CHO	78 (70) ^e	71 (81) ^e
2	<i>p</i> -ClC ₆ H ₄ CHO	80 (61)	70 (77)
3	<i>p</i> -BrC ₆ H ₄ CHO	79 (68)	68 (70)
4	<i>p</i> -MeC ₆ H ₄ CHO	67 (60)	65 (60)
5	<i>p</i> -MeOC ₆ H ₄ CHO	46 (35)	56 (44)
6	<i>o,p</i> -(MeO) ₂ C ₆ H ₃ CHO	87 (80)	32 (51)
7	<i>o</i> -MeOC ₆ H ₄ CHO	95 (90)	48 (45)
8	<i>o</i> -ClC ₆ H ₄ CHO	90 (85)	51 (50)

^aCondition: 10 °C, 40 h and 10 mol% of **5c**. ^bMeasured as conversion% by GC.

^cDetermined by capillary chiral GC analysis using the chiral column (HP-chiral).

^dAbsolute configuration was determined by comparing the sign of specific rotation [13-16]. The major enantiomer in all cases had the *S* configuration. ^eValues in parentheses are for condition: -30 °C, 40 h and 20 mol% of **5c**.

Table 3. Enantioselective Addition of Et₂Zn to C₆H₅CHO Catalyzed by Different Chiral Imines [10]

Entry	Ligand	T (°C)	Time (h)	Yield (%)	Ee (%)
1	1	0	24	99	71
2	2	-40 to 25	25	75	70
3	3	rt	18	82	25
4	4	rt	48	57	15
5	5c	-30	40	51	78

decrease in the enantioselectivity. The best enantioselectivity up to 81% ee was obtained with *p*-fluorobenzaldehyde (Table 2, entry 1). A comparison between some previously reported methods with the present procedure has been summarized in Table 3.

CONCLUSIONS

In conclusion, we have shown that imino alcohol **5c**, which is easily prepared from (R)-2-amino-1-butanol and *p*-hydroxy benzaldehyde can be successfully used as a ligand in the enantioselective addition of diethylzinc to aryl aldehydes. The method offers the use of a cheap and stable ligand in

comparison with previous imino alcohols (Fig. 1) that have been used for this purpose.

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