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L-Alanine-derived Chiral Ligands for Asymmetric Addition of Diethylzinc to Aldehydes

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Great efforts have been devoted to the development of efficient chiral ligands for catalytic asymmetric addition of dialkylzinc.[1] Among the various types of chiral ligands explored several β-amino alcohols have proven to be especially efficient ligands for the additions.[2] However, the development of stable and easily accessible β-amino alcohol ligands is still desirable for practical applications. It is convenient that β-amino alcohols can be prepared through simple synthetic pathways from easily accessible starting materials such as chiral natural products. Herein, we will outline our efforts to develop a new class of enantiomerically pure β-dialkylamino alcohol ligands derived from natural L-amino acids.

The β-dialkylamino alcohol ligands studied in this paper have some structural modules, that have been varied in a systematic fashion to study the influence of each module in performing the reaction of diethylzinc with aldehyde. As shown in Figure 1, three subunits such as substituents at the hydroxyl carbon (R^1), the substituent at the amino carbon (R^2), and the aromatic group of *N*-benzyl substituent (Ar) were varied to optimize the ligand structure for high enantioselectivity.

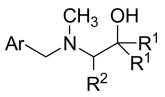
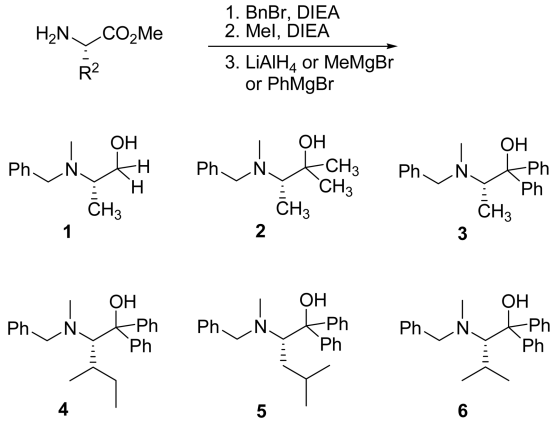


Figure 1

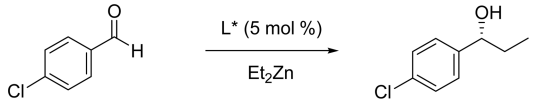
The synthesis of *N*-benzyl-*N*-methyl substituted β-amino alcohols was performed with L-alanine, L-isoleucine, L-leucine and L-valine methyl esters as illustrated in Scheme 1. Two successive *N*-alkylations with benzyl bromide and methyl iodide were efficiently carried out in DMF using diisopropylethylamine (DIEA) as a base. Following treatment with excess $LiAlH_4$ or corresponding alkylmagnsium bromide completed the synthesis of β-dialkylamino alcohols **1-6** in 49-35% overall yields.

First, we have explored the addition of diethylzinc to 4-chlorobenzaldehyde as a preliminary evaluation of three L-alanine-derived chiral ligands **1-3** which have different substituents at the hydroxyl carbon. Diethylzinc was added to the mixture of 4-chloroaldehyde and a chiral ligand (5 mol %) in toluene at 0 °C and subsequent stirring for 10 h at room temperature provided 1-substituted propanol. Chiral



Scheme 1

Table 1.



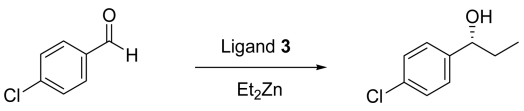
Entry[a]	Ligand	Conversion[b]	Er[c] (*R*:*S*)[d]
1	**1**	54	56:44
2	**2**	53	75:25
3	**3**	99	94:6
4	**4**	85	82:18
5	**5**	67	76:24
6	**6**	82	86:14

[a]Reactions run for 10 h in toluene at room temperature. [b]Determined by ^{1}H NMR analysis of reaction mixture. [c]Determined by CSP-HPLC (Chiralcel OB-H). [d]Absolute configuration assigned by comparison with known elution order according to the literature.[2]

ligand **3** having two phenyl substituents gave a best result to give (*R*)-propanol with 94:6 er, while chiral ligands **1** and **2** failed to induce a high enantioselectivity[3] (Table 1, entries 1-3).

Next, the effect of the substituent at the amino carbon on enantioselectivity of the addition was examined with three chiral ligands **4-6** derived from L-isoluecine, L-leucine and L-valine, respectively. In the addition reactions of chiral ligands **4-6** under the same reaction condition, we discovered that a lower level of enantioselectivity compared to the reaction with chiral ligand **3** was attained although the

Table 2.



Entry[a]	Solvent	Temp.	Mol %	Conversion[b]	Er[c] (*R*:*S*)
1	MTBE	rt	5	99	93:7
2	ether	rt	5	87	86:14
3	THF	rt	5	19	76:24
4	xylene	rt	5	69	87:13
5	*n*-hexane	rt	5	99	95:5
6	*n*-hexane	0 °C	5	92	95:5
7	*n*-hexane	−20 °C	5	81	83:17
8	*n*-hexane	rt	3	99	92:8

[a]Reactions run for 10 h. [b]Determined by ^{1}H NMR analysis of reaction mixture. [c]Determined by CSP-HPLC (Chiralcel OB-H).

desired propanol forms efficiently (entries 4-6).

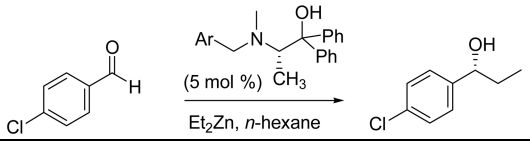
In order to obtain the optimized condition for the reaction of L-alanine-derived chiral ligand **3**, we have examined some experimental parameters such as solvent, reaction temperature, and molar ratio of ligand as shown in Table 2. Among the solvents examined, *n*-hexane was found to be the best for chiral ligand **3** with 5 mol % ligand loading (entry 5). We found that the reactions below 0 °C took place slowly and lowering temperature to 20 °C abated enantioselectivity. (entries 6-7) As shown in entry 8, decreasing the ligand loading to 3 mol % was not satisfactory to give a lower enantiomeric ratio of 92:8. Thus the optimal condition for chiral ligand **3** was identified when the reactions were carried out in *n*-hexane at room temperature with 5 mol % of chiral ligand.

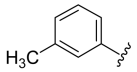
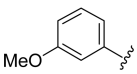
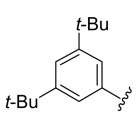
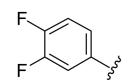
In an effort to improve asymmetric induction, we have attempted to modify the catalytic properties of chiral ligand **3** by introducing substituents into the phenyl ring of *N*-benzyl group as shown in Table 3. Chiral ligands **7**-**10** with substituents such as methyl, methoxy, *tert*-butyl, and fluoro groups generally gave similar enantioselectivities when compared to ligand **3**. Difluoro substituted ligand **10** was highly comparable to ligand **3** in the reaction of 4-chlorobenzaldehyde to give the corresponding (*R*)-alcohol with 95:5 er (entry 4).

Chiral ligands **3** and **10**, which gave the highest stereoselectivity for the addition of diethylzinc to 4-chlorobenzaldehyde was then used to explore the scope of the addition reaction with aldehydes, and the results are summarized in Table 4. Among the reactions of 4-substituted benzaldehydes, the high stereoselectivity was observed in the reactions with 4-bromo substituted benzaldehyde, whereas noticeable drops in stereoselectivity were seen with 4-fluorobenzaldehyde, 4-methylbenzaldehyde and 4-methoxybenzaldehyde. (entries 1-6) Also, the reactions of 3-bromobenzaldehyde, 2-bromobenzaldehyde and 2-naphthaldehyde gave comparable enantioselectivities of 93:7, 85:15 and 90:10 ers, respectively (entries 7-9). The reaction of an aliphatic aldehyde, dihydrocinnamaldehyde, provided the corresponding alcohol with a slightly lower enantioseletivity than the reactions of aromatic aldehydes (entry 10). Difluoro substituted chiral ligand **10** gave slightly better enantioselectivities in the reactions of dihydrocinnamaldehyde and 4-fluorobenzaldehyde compared to the reaction with ligand **3** (entries 11-12). Pleasingly, significantly improved ers (91:9 and 93:7) were observed in the reactions of 4-methylbenzaldehyde and 4-methoxybenzaldehyde with chiral ligand **10** (entries 13-14).

In summary, we have developed a new class of L-amino acid-derived chiral ligands for enantioselective addition of

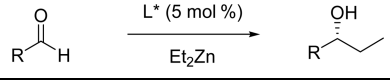
Table 3.



Entry	Ar	Ligand	Conversion[b]	Er[c] (*R*:*S*)
1		**7**	99	94:6
2		**8**	99	92:8
3		**9**	99	93:7
4		**10**	99	95:5

[a]Reactions run for 10 h. [b]Determined by ^{1}H NMR analysis of reaction mixture. [c]Determined by CSP-HPLC (Chiralcel OB-H).

Table 4.



Entry	R	Ligand	Conversion[b]	Er[c] (*R*:*S*)[d]
1	4-Br-Ph	**3**	99	95:5
2	4-CN-Ph	**3**	96	91:9
3	4-CF_3-Ph	**3**	99	91:9
4	4-F-Ph	**3**	99	85:15
5	4-Me-Ph	**3**	86	85:15
6	4-MeO-Ph	**3**	95	74:26
7	3-Br-Ph	**3**	97	93:7
8	2-Br-Ph	**3**	93	85:15
9	2-Naph	**3**	98	90:10
10	$PhCH_2CH_2$	**3**	90	84:16
11	$PhCH_2CH_2$	**10**	84	85:15
12	4-F-Ph	**10**	100	88:12
13	4-Me-Ph	**10**	97	91:9
14	4-MeO-Ph	**10**	73	93:7

[a]Reactions run for 10 h. [b]Determined by ^{1}H NMR analysis of reaction mixture. [c]Determined by CSP-HPLC (Chiralcel OB-H or OJ-H or OD). [d]Absolute configurations assigned by comparison with known elution order according to the literature.[2]

diethylzinc to aldehydes. Three subunits of the chiral ligands were varied to increase enantioselectivity and the optimization led us to identify L-alanine-derived chiral ligands **3** and **10** as effective chiral ligands for the addition. Further studies on the modification of ligand structure for the improvement of enantioselectivity is now in progress.

Experimental

General Procedure for the Preparation of Chiral Ligands 1-10. To a solution of methyl L-amino ester in DMF at room temperature, benzyl bromide (1.0 equiv) and DIEA (1.2 equiv) were added slowly. The resulting reaction mixture was stirred at room temperature for 24 h. After the mixture was concentrated, the crude product was dissolved in DMF. Methyl iodide (2.0 equiv) and DIEA (1.2 equiv) were added at 0 °C and the resulting reaction mixture was stirred at room temperature for 24 h. The concentrated crude product was purified by column chromatography on silica gel to afford *N,N*-dialkylated products in 68-46% yields. To a solution of the product in anhydrous THF was added a solution of the corresponding alkylmagnesium bromide (or $LiAlH_4$). The reaction was then allowed to proceed at room temperature for 36 h. The reaction was quenched by the addition of 1 M aqueous HCl and extracted with EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Chromatographic separation on silica gel afforded the chiral ligands **1-10** in 72-38% yields. (49-35% overall yields) To examine the possibility of racemization during the above synthetic procedure, the optical purity of ligand **3** was measured by HPLC with chiral columns using racemic material as a standard and determined to be > 99% ee. Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min; 217 nm UV detector; 11.1 min (*S* enantiomer), 13.1 min (*R* enantiomer).

2-[Benzyl(methyl)amino]propan-1-ol (1): 38% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.14 (m, 5H), 3.58 (d, *J* = 13.2 Hz, 1H), 3.37-3.26 (m, 3H), 2.86 (m, 1H), 2.05 (s, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 128.9, 128.4, 127.1, 62.9, 58.7, 57.8, 35.4, 8.5.

2-[Benzyl(methyl)amino]-1,1-dimethylpropan-1-ol (2): 36% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.20 (m, 5H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 2.64 (q, *J* = 7.2 Hz, 1H), 2.18 (s, 3H), 1.17 (s, 6H), 1.04 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.4, 128.7, 128.4, 127.1, 71.6, 67.2, 60.4, 39.4, 28.5, 24.8, 7.8.

2-[Benzyl(methyl)amino]-1,1-diphenylpropan-1-ol (3): 41% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47-7.16 (m, 15H), 3.75 (q, *J* = 7.2 Hz, 1H), 3.45 (d, *J* = 13.2 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 1.97 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.6, 144.7, 139.0, 128.8, 128.5, 128.1, 127.9, 127.5, 127.3, 127.0, 126.9, 78.5, 65.6, 60.1, 38.9, 9.8.

2-[Benzyl(methyl)amino]-3-methyl-1,1-diphenylpentan-1-ol (4): 44% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.14 (m, 15H), 5.66 (br, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 9.2 Hz, 1H), 2.06 (s, 3H), 1.72 (m, 1H), 1.21 (m, 1H), 0.87 (m, 3H), 0.71 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.2, 143.8, 139.7, 128.8, 128.6, 128.4, 127.8, 127.7, 127.3, 127.1, 126.8, 79.7, 78.4, 62.5, 38.6, 36.2, 27.8, 19.0, 11.4.

2-[Benzyl(methyl)amino]-4-methyl-1,1-diphenylpentan-1-ol (5) 49% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.22 (m, 15H), 3.85-3.62 (m, 3H), 2.04 (s, 3H), 1.76-1.44 (m, 3H), 0.87 (m, 3H), 1.10 (d, *J* = 6.4 Hz, 1H), 0.92 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.1, 144.6, 139.5, 128.6, 128.5, 128.2, 128.0, 127.5, 127.3, 127.2, 127.0, 126.6, 78.8, 68.8, 61.9, 38.4, 37.7, 26.3, 24.3, 21.3.

2-[Benzyl(methyl)amino]-3-methyl-1,1-diphenylbutan-1-ol (6): 40% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69-7.16 (m, 15H), 5.93 (br, 1H), 3.83 (d, *J* = 13.6 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.35 (d, *J* = 9.6 Hz, 1H), 2.38 (m, 1H), 2.01 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 1H), 0.68 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7, 143.4, 139.6, 128.8, 128.7, 128.5, 128.1, 127.8, 127.6, 127.4, 127.2, 126.9, 80.5, 79.2, 62.3, 38.4, 29.8, 23.6, 23.4.

2-[3-Methylphenylmethyl(methyl)amino]-1,1-diphenylpropan-1-ol (7): 45% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.02 (m, 14H), 6.02 (br, 1H), 3.76 (q, *J* = 6.8 Hz, 1H), 3.44 (d, *J* = 12.8 Hz, 1H), 3.38 (d, *J* = 12.8 Hz, 1H), 2.32 (s, 3H), 1.97 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.6, 144.7, 139.0, 138.0, 129.6, 128.3, 128.0, 127.9, 127.8, 127.4, 127.2, 127.0, 126.6, 125.8, 78.5, 65.6, 60.2, 38.8, 21.5, 9.8.

2-[3-Methoxyphenylmethyl(methyl)amino]-1,1-diphenylpropan-1-ol (8): 37% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44-6.77 (m, 14H), 5.92 (br, 1H), 3.79-3.74 (m, 4H), 3.46 (d, *J* = 13.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H), 2.01 (s, 3H), 1.19 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 146.5, 144.7, 140.8, 129.5, 128.1, 127.7, 127.5, 127.2, 127.0, 126.7, 121.1, 114.0, 112.9, 78.7, 65.5, 60.0, 55.2, 39.1, 9.7.

2-[3,5-Di-*t*-butylphenylmethyl(methyl)amino]-1,1-diphenylpropan-1-ol (9): 35% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53-7.08 (m, 13H), 3.76 (q, *J* = 6.8 Hz, 1H), 3.47 (d, *J* = 12.8 Hz, 1H), 3.37 (d, *J* = 12.8 Hz, 1H), 2.02 (s, 3H), 1.32 (s, 18H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8, 143.5, 128.0, 127.8, 127.4, 127.2, 126.9, 126.6, 123.2, 121.0, 78.4, 65.4, 60.9, 39.0, 34.8, 31.5, 9.6.

2-[3,4-Difluorophenylmethyl(methyl)amino]-1,1-diphenylpropan-1-ol (10): 41% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44-6.86 (m, 13H), 5.20 (br, 1H), 3.76 (q, *J* = 6.4 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 3.31 (d, *J* = 13.2 Hz, 1H), 2.04 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.1 (dd), 148.7 (dd), 146.3, 144.7, 136.4, 128.1, 127.9, 127.7, 127.3, 127.0, 126.8, 124.3, 117.3 (d), 117.0 (d), 79.3, 65.5, 58.8, 39.2, 9.3.

General Procedure for the Addition of Diethylzinc to Aldehydes. Diethylzinc (1 M in hexanes, 2 equiv) was added to a solution of chiral ligand (0.006 mmol, 0.05 equiv) and aldehyde (0.12 mmol, 1.0 equiv) in *n*-hexane (2 mL) at 0 °C. The homogeneous solution was stirred at room temperature for 10 h. The reaction was quenched by addition of 1 M aqueous HCl and extracted with $CHCl_3$. The com-

bined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Chromatographic separation on silica gel afforded the enantioenriched propanols and the enantioselectivity of the products were measured by HPLC with chiral columns (2-propanol in hexane; 0.5 mL/min, 217 nm UV detector). The absolute configuration of all the products was found to be *R* by comparing their optical rotation values and HPLC data with the literature results.[2]

(*R*)-1-(4-Chlorophenyl)-1-propanol: 95:5 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 18.8 min (minor), 21.0 min (major).

(*R*)-1-(4-Bromophenyl)-1-propanol: 95:5 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 21.6 min (minor), 24.5 min (major).

(*R*)-1-(4-Cyanophenyl)-1-propanol: 91:9 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 32.4 min (minor), 34.8 min (major).

(*R*)-1-(4-Trifluoromethylphenyl)-1-propanol: 91:9 er (Chiralcel OJ-H column; 2% 2-propanol in hexane) 18.3 min (minor), 19.6 min (major).

(*R*)-1-(4-Fluorophenyl)-1-propanol: 85:15 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 18.8 min (minor), 20.2 min (major).

(*R*)-1-(4-Methylphenyl)-1-propanol: 91:9 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 19.2 min (minor), 24.8 min (major).

(*R*)-1-(4-Methoxyphenyl)-1-propanol: 93:7 er (Chiralcel OD column; 5% 2-propanol in hexane) 22.0 min (minor), 24.5 min (major).

(*R*)-1-(3-Bromophenyl)-1-propanol: 93:7 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 15.0 min (minor), 17.6 min (major).

(*R*)-1-(2-Bromophenyl)-1-propanol: 85:15 er (Chiralcel OB-H column; 2% 2-propanol in hexane) 15.7 min (minor), 18.5 min (major).

(*R*)-1-(2-Naphthyl)-1-propanol: 90:10 er (Chiralcel OD column; 5% 2-propanol in hexane) 29.1 min (minor), 33.2 min (major).

(*R*)-1-Phenyl-3-pentanol: 85:15 er (Chiralcel OD column; 5% 2-propanol in hexane) 25.2 min (minor), 17.3 min (major).

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