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Asymmetric Preparation of D-Phg-L-Pro Dipeptide-derived Chiral Ligands for Enantioselective Addition of Diethylzinc to Aldehydes

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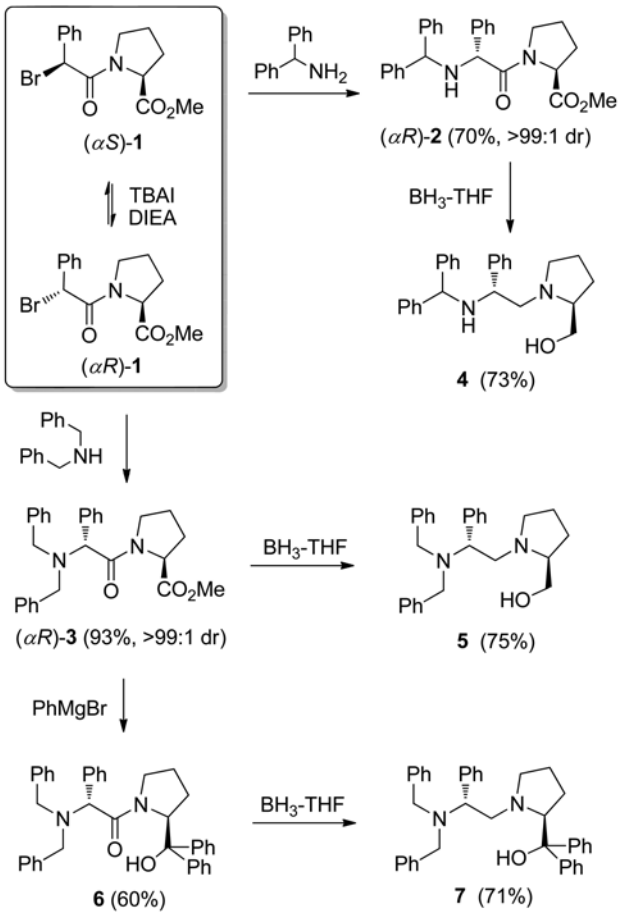
Development of dipeptide-derived ligands for enantioselective synthesis is of rapidly growing interest today.[1] We recently reported a kinetic resolution in the asymmetric dehydration of β-hydroxy esters with a prolinol ligand obtained from the reduction of D-phenylglycine-L-proline (D-Phg-L-Pro) dipeptide.[2] Since then our research has focused on the development of D-Phg-L-Pro dipeptide-derived ligands that can participate in the enantioselective carbon-carbon bond-formation involving organozinc species.[3] Herein, we describe an efficient asymmetric synthetic method for chiral ligands based on a D-Phg-L-Pro scaffold and their application to enantioselective addition of diethylzinc to aldehydes.

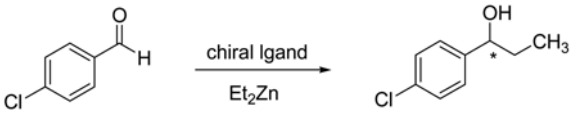


Scheme 1. Asymmetric preparation of chiral ligands **2**-**7**.

We previously developed the dynamic kinetic resolution of α-halo acetamides in nucleophilic substitution for asymmetric syntheses of di-, tri- and tetrapeptide analogues.[4] The methodology was used for asymmetric preparation of D-Phg-L-Pro dipeptide analogues **2** and **3** as shown in Scheme 1. The treatment of two diastereomeric mixture (1:1) of *N*-(α-bromo-α-phenylacetyl)-(*L*)-proline methyl ester **1** with an amine nucleophile (diphenylmethylamine or dibenzylamine) in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA) in CH_2Cl_2 gave the D-Phg-L-Pro dipeptides **2** and **3** with > 99:1 diastereomeric ratios (dr) after chromatographic purification in 70% and 93% yields, respectively. The epimerization at the α-position of **1** promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution and the (*αS*)-**1** is the faster reacting diastereomer than (*αR*)-**1**. In the asymmetric carbon-nitrogen bond formation, the chiral information of L-proline is transferred to the substitution at α-bromo carbon center *via* dynamic kinetic resolution.

First, we have explored the addition of diethylzinc to 4-chlorobenzaldehyde as a preliminary evaluation of the catalytic properties of two chiral ligands **2** and **3** which have different *N*-alkyl amino groups. 4-Chlorobenzaldehyde was added to the mixture of diethylzinc and a chiral ligand (10 mol %) at 0 °C and subsequent stirring for 12 h at room temperature provided 1-substituted propanol. *N,N*-Dibenzylated chiral ligand **3** gave a promising result to give (*S*)-propanol in 84% yield with 79:21 er, while chiral ligand **2** failed to induce noticeable enantioselectivities (Table 1, entries 1-2). In our efforts to improve asymmetric induction, we attempted to modify the catalytic properties of chiral ligands **2** and **3** by reducing two carbonyl groups of chiral ligands. The reduction of **2** and **3** using an excess of BH_3-THF (10 equiv) in THF furnished prolinols **4** and **5** in 73% and 75% isolated yields, respectively. In the addition reaction with chiral ligand **4** under the same reaction condition, we discovered that a lower level of enantioselectivity was attained although the desired propanol forms efficiently. (entry 3) Interestingly, chiral ligand **5** gave comparable enantioselectivity to the reaction with ligand **3** and led to the reversal of product configuration to afford (*R*)-enantiomer as a major product as shown in entry 4. Also, the preparation of prolinol chiral ligands **6** and **7** having two phenyl substituents was successfully achieved using PhMgBr and BH_3-

Table 1. Enantioselective addition of diethylzinc to *p*-chlorobenzaldehyde



Entry[a]	Ligand	Solvent	Temp	Er[b] (*S:R*)[c]
1	**2** (10 mol %)	toluene	rt	58:42
2	**3** (10 mol %)	toluene	rt	79:21
3	**4** (10 mol %)	toluene	rt	52:48
4	**5** (10 mol %)	toluene	rt	24:76
5	**6** (10 mol %)	toluene	rt	53:47
6	**7** (10 mol %)	toluene	rt	86:14
7	**7** (10 mol %)	toluene	–20 °C	83:17
8	**7** (10 mol %)	hexane	rt	85:15
9	**7** (3 mol %)	hexane	rt	84:16
10	**7** (3 mol %)	ether	rt	86:14
11	**7** (3 mol %)	*t*-BuOMe	rt	84:16

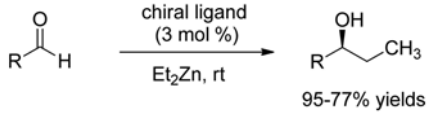
[a]Reactions run for 20 h. [b]Determined by CSP- HPLC (Chiralpak AD-H). [c]Absolute configuration assigned by comparison with known elution order according to the literature.[6]

THF reduction as shown in Scheme 1. Considerable loss of selectivity was observed in the reaction with ligand **6**, however, we were very pleased to observe that chiral ligand **7** afforded (*S*)-propanol with 86:14 er[5] (entries 5 and 6).

In order to obtain the optimized condition for the reaction with chiral ligand **7**, we have examined some experimental parameters such as reaction temperature, molar ratio of ligand and solvent. We found that the reactions below 0 °C took place slowly and lowering temperature to –20 °C abated enantioselectivity (entry 7). The reaction in *n*-hexane provided comparable enantioselectivity of 85:15 er (entry 8). The high selectivities obtained with chiral ligand **7** prompted us to test the possibility of lowering the ligand loading. As shown in entries 9-11, the selectivity did not change significantly with 3 mol % of ligand loading showing the superior reactivity of ligand **7**. However, further decreasing the ligand loading to 1 mol % of **7** was not satisfactory with lower selectivity. Among the solvents examined, diethyl ether was found to be the best for chiral ligand **7** with 3 mol % ligand loading. Thus the optimal condition for chiral ligand **7** was identified when the reactions were carried out in ether at room temperature with 3 mol % of chiral ligand.

With the optimized reaction conditions in hand, the substrate scope of enantioselective addition was examined with chiral ligand **7**. The addition of diethylzinc to a variety of aldehydes was carried at room temperature in diethyl ether using 3 mol % of chiral ligand **7**. The reaction of 4-bromobenzaldehyde provided the corresponding propanol with slightly higher enantioseletivity than the reaction with 4-chlorobenzaldehyde. (Table 2, entry 1) However, the reactions of 4-trifluoromethylbenzaldehyde, 4-methoxybenzaldehyde, 4-cyanobenzaldehyde, 4-methylbenzaldehyde, 2-metoxybenzaldehyde, 1-naphtylaldehyde, 2-naphtylaldehyde and cinnamaldehyde resulted in slightly decreased enantioselectivities, which indicate that the enantioselectivity depends on the substituent of the aldehyde.

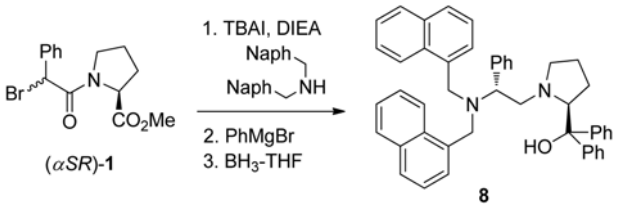
Table 2. Enantioselective addition of diethylzinc to various benzaldehydes



Entry[a]	R	Ligand	Solvent	Er[b] (*S:R*)[c]
1	4-Br-Ph	**7**	ether	88:12
2	4-CF_3-Ph	**7**	ether	76:24
3	4-MeO-Ph	**7**	ether	78:22
4	4-CN-Ph	**7**	ether	83:17
5	3-CH_3-Ph	**7**	ether	66:32
6	2-MeO-Ph	**7**	ether	82:18
7	1-Naph	**7**	ether	82:18
8	2-Naph	**7**	ether	74:26
9	PhCH=C(CH_3)-	**7**	ether	80:20
10	4-Cl-Ph	**8**	toluene	87:13
11	4-Cl-Ph	**8**	ether	84:16
12	4-Cl-Ph	**8**	*t*-BuOMe	90:10
13	4-Br-Ph	**8**	*t*-BuOMe	95:5
14	4-CF_3-Ph	**8**	*t*-BuOMe	89:11
15	4-MeO-Ph	**8**	*t*-BuOMe	90:10
16	4-CN-Ph	**8**	*t*-BuOMe	91:9
17	3-CH_3-Ph	**8**	*t*-BuOMe	86:14
18	1-Naph	**8**	*t*-BuOMe	86:14
19	2-Naph	**8**	*t*-BuOMe	86:14
20	PhCH=C(CH_3)-	**8**	*t*-BuOMe	93:7

[a]Reactions run for 20 h. [b]Determined by CSP- HPLC (Chiralpak AD-H or Chiralcel OJ-H). [c]Absolute configuration assigned by comparison with known elution order according to the literature.[6]

During our studies on *N*-substituent effect of chiral ligand **7**, we have prepared *N,N*-dinaphtylmethyl prolinol chiral ligand **8** as shown in Scheme 2. The same three step procedure as for **7** from **1** was followed with *N,N*-di(1-naphthylmethyl)amine as a nucleophile to afford **8** in 38% overall yield with > 99:1 dr. We then explored the asymmetric addition of diethylzinc to 4-chlorobenzaldehyde as a preliminary evaluation of the catalytic property of chiral ligand **8** as shown in Table 2, entries 10-12. Pleasingly, *N,N*-dinaphtylmethyl substituted ligand **8** was found to be more effective to give (*S*)-enantiomer with 90:10 er in *t*-BuOMe (entry 12). In the reactions of various aldehydes with chiral ligand **8**, much higher enantioselectivities up to 95:5 er were observed compared to the reactions with chiral ligand **7**



Scheme 2. Asymmetric preparation of chiral ligand **8**.

(entries 13-20). Simple *N*-alkyl substituent modifications of chiral ligands led to substantial increase in enantioselection. At present rational explanation about the variation of enantioselectivity is not possible due to the uncertainty on the transition structure of zinc-ligand complex.

In summary, we have developed a new class of tridentate chiral ligands for enantioselective addition of diethylzinc to aldehydes. Modification of *N*-substituents of D-Phg-L-Pro-derived chiral ligands can be achieved by simply varying the amine nucleophile in the substitution of *N*-(α-bromophenylacetyl)-L-proline ester. The optimization of ligand structure led us to identify *N,N*-dinaphtylmethyl prolinol chiral ligand **8** as an effective catalyst for the addition. Further studies on the improvement of enantioselectivity and on the structure of zinc-dipeptide complex and are now in progress.

Experimental

General Procedure for the Preparation of Chiral Ligands. ***N*-[(*R*)-α-Phenyl-*N*-(diphenylmethyl)glycinyl]-(*S*)-proline Methyl Ester (2):** To a solution of *N*-(α-bromo-α-phenylacetyl) (*S*)-proline methyl ester **1** in dry CH_2Cl_2 (0.1 M) at room temperature was added an amine (1.2 equiv), TBAI (1.0 equiv) and DIEA (1.2 equiv). The resulting reaction mixture was stirred at room temperature for 24 h. The solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel. A colorless oil was obtained in 73% yield with 99:1 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.56-7.15 (m, 15H), 4.85 (s, 1H), 4.49 (m, 1H), 4.33 (s, 1H), 3.82 (s, 3H), 3.27 (m, 1H), 3.03 (m, 1H), 2.92 (br, 1H), 2.02 (m, 1H), 1.89 (m, 2H), 1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.8, 171.6, 144.0, 143.3, 138.2, 128.9, 128.7, 128.4, 128.1, 128.0, 127.9, 127.6, 127.5, 127.3, 127.0, 64.7, 61.7, 59.1, 52.4, 46.4, 29.1, 24.6, 21.9.

***N*-[(*R*)-α-Phenyl-*N,N*-(dibenzyl)glycinyl]-(*S*)-proline Methyl Ester (3):** The same procedure as for **2** was followed with dibenzylamine to afford **3** in 93 % yield with 99:1 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43-7.20 (m, 15H), 4.62 (s, 1H), 4.58 (m, 1H), 3.94-3.80 (m, 4H), 3.85 (s, 3H), 3.03 (m, 1H), 2.82 (m, 1H), 2.11 (m, 1H), 1.90 (m, 2H), 1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 171.9, 141.1, 137.2, 129.6, 129.3, 129.0, 128.8, 128.2, 127.1, 64.1, 59.0, 54.6, 52.7, 46.8, 29.5, 25.2. Anal. calcd for $C_{23}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.98; H, 6.86; N, 6.20.

***N*-((*R*)-*N*-Diphenylmethyl-2-amino-2-phenylethyl)-(*S*)-prolinol (4):** To a solution of **2** in THF (0.5 M) was added BH_3-THF (1.0 M, 5.0 equiv), and the mixture was refluxed for 12 h. The reaction was quenched by adding MeOH (0.5 mL) under ice-water cooling, and the solvents were evaporated. Aqueous 5%-HCl (2 mL) was added to the residue, and the mixture was refluxed for 1 hour. The reaction mixture was basified with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (5 mL × 3). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Chromatographic separation on silica gel afforded ligand **4** with > 99:1 dr in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31-7.11 (m, 15H), 4.62 (s, 1H), 3.60 (m, 2H), 3.45 (dd, J = 11.0 and 4.0 Hz, 1H), 3.12 (br, 1H), 2.94 (t, J = 12.1 Hz, 1H), 2.77 (m, 1H), 2.54 (m, 1H), 2.34 (dd, J = 12.5 and 3.2 Hz, 1H), 2.04 (m, 1H), 1.80-1.63 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.5, 138.6, 129.6, 129.3, 128.7, 128.5, 127.7, 127.4, 65.4, 62.8, 61.4, 57.1, 55.1, 54.5, 28.3, 24.4; Anal. calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.77; H, 8.00; N, 7.51.

***N*-((*R*)-*N,N*-Dibenzyl-2-amino-2-phenylethyl)-(*S*)-prolinol (5):** The same procedure as for **4** was followed with **3** as starting material to afford **5** in 75% yield with > 99:1 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42-7.18 (m, 15H), 3.89 (m, 1H), 3.87 (d, J = 13.6 Hz, 2H), 3.57 (dd, J = 10.7 and 3.5 Hz, 1H), 3.40 (dd, J = 12.8 and 8.7 Hz, 1H), 3.32 (dd, J = 10.7 and 2.1 Hz, 1H), 3.15 (d, J = 13.6 Hz, 2H), 2.80 (br, 1H), 2.79 (m, 1H), 2.62 (dd, J = 12.8 and 5.5 Hz, 1H), 2.56 (m, 1H), 2.03 (q, J = 8.6 Hz, 1H), 1.81-1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.8, 144.2, 142.9, 129.0, 128.9, 128.7, 128.4, 127.9, 127.8, 127.7, 127.5, 127.1, 65.3, 64.0, 63.5, 62.9, 59.3, 54.6, 27.9, 24.2; Anal. calcd for $C_{27}H_{32}N_2O$: C, 80.96; H, 8.05; N, 6.99. Found: C, 80.83; H, 8.04; N, 6.89.

***N*-[(*R*)-α-Phenyl-*N,N*-(dibenzyl)glycinyl]-(*S*)-2-(hydroxydiphenylmethyl) pyrrolidine (6):** To a solution of **4** in THF (0.5 M) was added PhMgBr (1.0 M in THF, 3 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Chromatographic separation on silica gel afforded **6** with > 99:1 dr. A colorless oil was obtained in 60% yield with > 99:1 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.60-7.28 (m, 25H), 5.29 (m, 1H), 4.63 (s, 1H), 3.88 (q, J = 14.4 Hz, 4H), 2.74 (m, 1H), 2.62 (m, 1H), 1.92 (m, 2H), 1.15 (m, 1H), 0.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.0, 146.7, 143.7, 140.6, 136.6, 129.0, 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 127.7, 127.4, 127.3, 126.9, 81.3, 67.1, 64.5, 54.5, 47.8, 29.5, 23.0.

***N*-((*R*)-*N,N*-Dibenzyl-2-amino-2-phenylethyl)-(*S*)-2-(hydroxydiphenylmethyl) pyrrolidine (7):** The same procedure as for **3** was followed with **6** as starting material to afford **7** in 71% yield with > 99:1 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.60-6.82 (m, 25H), 5.03 (br, 1H), 3.83 (m, 1H), 3.67 (m, 1H), 3.48 (d, J = 13.6 Hz, 2H), 2.93 (m, 2H), 2.80 (d, J = 13.6 Hz, 2H), 2.19 (m, 1H), 2.04 (m, 1H), 1.78 (m, 1H), 1.63 (m, 2H), 1.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 148.6, 147.2, 140.2, 137.8, 129.1, 128.8, 128.3, 128.2, 128.1, 127.9, 127.3, 126.9, 126.3, 126.1, 125.9, 125.2, 71.3, 61.6, 58.5, 55.0, 53.8, 29.4, 24.0; $[\alpha]_D^{20}$ = −16.7° (c = 0.03, $CHCl_3$).

***N*-((*R*)-*N,N*-Dinaphtylmethyl-2-amino-2-phenylethyl)-(*S*)-2-(hydroxydiphenylmethyl) pyrrolidine (8):** The same three step procedures as for **7** from **1** was followed with *N,N*-di(1-naphthylmethyl)amine as a nucleophile to afford **8** in 38% overall yield with > 99:1 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.82-6.87 (m, 29H), 4.89 (br, 1H), 3.84 (m, 2H), 3.69 (ABq, J = 13.6 Hz, 4H), 3.14 (m, 1H), 2.84 (m, 1H), 2.34 (m, 1H), 2.03 (m, 1H), 1.78-1.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 148.5, 147.2, 135.1, 133.8, 132.3, 129.5, 128.4,

128.3, 128.1, 127.9, 127.6, 127.3, 126.3, 126.1, 125.8, 125.4, 125.2, 125.1, 124.7, 71.7, 62.3, 57.1, 55.3, 51.8, 29.3, 23.7; $[\alpha]_D^{20} = -15.5°$ ($c = 0.02$, $CHCl_3$).

General Procedure for the Addition of Diethylzinc to Aldehydes. Diethylzinc (1 M in hexanes, 2 equiv) was added to a solution of chiral ligand (0.03 equiv) and aldehyde (1.0 equiv) in *t*-BuOMe at 0 °C. The homogeneous solution was stirred at the desired temperature for 12 h. The reaction was quenched by addition of 1 M aqueous HCl and extracted with $CHCl_3$. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Chromatographic separation on silica gel afforded the enantioenriched propanols in 95-77% yields and the enantioselectivity of the products were measured by HPLC with chiral columns (Chiralpak AD-H or Chiralcel OJ-H).[6]

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