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Discovery of Dipeptide-Derived Catalysts for the Enantioselective Addition of Dimethylzinc to Aldehydes

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A new class of modular chiral catalysts derived from various amino acid-L-Pro dipeptides was prepared, and the catalysts were tested for their ability to catalyze the enantioselective addition of dimethylzinc to aromatic aldehydes. Dipeptides derived from L-Asp-L-Pro were identified as effective catalysts for the addition at room temperature with up to 97:3 *er* and 95 % yield.

Introduction

Highly efficient chiral catalysts are often discovered by a stepwise, iterative process of structural modification. Therefore, a modular system comprising simple components is essential for the design of chiral catalysts. An ideal modular catalyst would be inexpensive and straightforward to synthesize and incorporate several sites of diversity. In this regard, a dipeptide catalyst is particularly attractive, as it can be prepared on a large scale by a short and simple route and easily modified by variations in the identity of two α-amino acid constituents. Dipeptide-based catalysts are making promising contributions to various asymmetric reactions in organometallic chemistry. Notable successes include cyclopropanation,[1a] alkylation of imines,[1b] vinylation of aldehydes,[1c] and the Strecker reaction.[1d]

Catalytic asymmetric addition of dialkylzinc to aldehydes is one of the most important reactions involving carbon–carbon bond formation. To date, a large number of catalysts has been developed for the preparation of chiral secondary alcohols with high enantioselectivity.[2] Most of the effective catalysts are based upon amino alcohol,[3] diol,[4] and diamine[5] derivatives. To the best of our knowledge, there have been no successful reports on peptide-based catalysts for the addition of dialkylzinc reagents to aldehydes.[6]

Enantioselective addition of dimethylzinc to aldehydes has attracted much less attention than diethylzinc additions because of its lower reactivity.[7] However, the development of an efficient method for the asymmetric addition of dimethylzinc is still a highly desirable goal in asymmetric synthesis. In this paper, we disclose enantioselective additions of dimethylzinc to aromatic aldehydes with amino acid (aa)-L-Pro dipeptide-based catalysts, whose general structure is illustrated in Figure 1. Three subunits within the dipeptide catalyst have been modified to investigate their influence on the enantioselectivity of the catalyzed reactions: the alkyl group on the N-terminus (R^1), the alkyl group on the C-terminal ester (R^2), and the amino acid side chain (R^3).

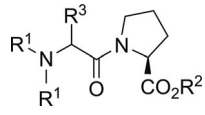

Figure 1. General structure of aa-L-Pro dipeptide catalysts.

Results and Discussion

We initiated our studies by examining the ability of the dipeptide D-Phg-L-Pro to act as a catalyst in the addition of dimethylzinc to aldehydes. First of all, the effect of *N*-alkyl substituents (R^1) on the enantioselectivity of the addition was examined with five D-Phg-L-Pro dipeptides **1**–**5**. The dipeptides were prepared by using the methodology which we have developed for the asymmetric synthesis of peptide derivatives as shown in Scheme 1.[8] Treatment of two diastereomeric mixtures (1:1) of *N*-(α-bromo-α-phenylacetyl)-L-proline methyl ester with an amine nucleophile in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA) gave D-Phg-L-Pro dipeptides **1**–**5**. The stereoselective nucleophilic substitutions with diphenylmethylamine, *N*-methylbenzylamine, piperidine, *N*-benzylphenethylamine, and dibenzylamine gave dipeptides **1**–**5** with diastereomeric ratios of 95:5, 85:15, 91:9, 99:1, and 99:1, respectively. In all cases, the diastereomerically pure *N*-alkyl-substituted D-Phg-L-Pro-OMe derivatives **1**–**5** were isolated in 91–61 % yield by flash column chromatographic separation. The functional diversity of the amino moiety was introduced through the use of various amine nucleophiles.

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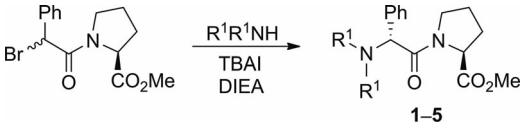
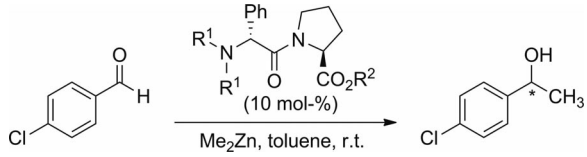


Scheme 1. Preparation of dipeptide catalysts **1**–**5**.

We then explored the asymmetric addition of dimethylzinc to 4-chlorobenzaldehyde as a preliminary evaluation of the catalytic properties of *N*-alkyl-substituted dipeptides **1**–**5** as shown in Table 1. Reactions were performed with 4 equiv. of dimethylzinc in toluene and 10 mol-% of the catalyst at room temperature for 48 h. When 4-chlorobenzaldehyde was added to the mixture of dimethylzinc and dipeptide **1**, 1-(4-chlorophenyl)-1-ethanol was obtained with poor selectivity and yield. (Table 1, Entry 1) Also, the reaction of *N*-benzyl-*N*-methyl-substituted tertiary amine catalyst **2** did not provide the improved enantioselectivity (Table 1, Entry 2). However, initial investigations with tertiary amine catalyst **2** proved promising, as the aldehyde was completely consumed, and after workup, the product was isolated in a satisfactory yield despite the low reactivity of dimethylzinc. In the reaction with cyclic amine catalyst **3**, an enantiomeric ratio of 71:29 was observed to provide (*R*)-enantiomer as a major product. (Table 1, Entry 3) When *N*-benzyl-*N*-phenethyl-substituted catalyst **4** was subjected to the same reaction conditions, a curious result was obtained. Catalyst **4** led to a reversal in the configuration of the product to afford the (*S*)-enantiomer as a major product with an enantioselectivity of 69:31 *er* (Table 1, Entry 4). Pleasingly, *N*,*N*-dibenzylated catalyst **5** was found to be more effective to give the (*S*)-enantiomer in 85% yield with 88:12 *er* (Table 1, Entry 5). The brief survey of N-substituents (R^1) indicates that subtle N-alkyl group modifications can lead to substantial variations in enantioselection. The *N*,*N*-dibenzylamino group appears to function cooperatively with the catalytic core structure of D-Phg-L-Pro and appears to be appropriate for high enantioselectivity.

In addition, the alkyl group (R^2) of the ester was varied while the R^1 position was held constant as *N*-benzyl substituents (Table 1, Entries 6–10). No substantial difference was found in the reactions of ethyl ester **6** and benzyl ester **7**, whereas lower enantioselectivities were noted for the reactions of propyl esters **8** and **9** (Table 1, Entries 6–9). Somewhat surprisingly, the larger steric bulk of *t*Bu ester **10** resulted in much lower enantioselectivity (Table 1, Entry 10). The observations suggest that the steric bulk of the C-terminal ester is an important factor in determining enantioselectivity. It is worth mentioning that *N*,*N*-dialkylated catalysts **2**–**10** do not have an O–H or N–H bond, which is known to be critical for the efficient chelation of zinc in the highly enantioselective reactions with amino alcohol, diol, and diamine based chiral catalysts.[2–4] Also, the reactivity and stereoselectivity were sensitive to temperature. Lowering the temperature of the reaction with catalyst **5** from room temperature to 0 °C resulted in a significant decrease in both reactivity and enantioselectivity (Table 1, Entry 11).

Table 1. Effects of the R^1 and R^2 groups.[a]



Entry	R^1	R^2	Catalyst	Yield [%]	*er*[b] (*S*/*R*)[c]
1	Ph_2CH, H	Me	**1**	35	53:47
2	$PhCH_2$, CH_3	Me	**2**	85	47:53
3	$-(CH_2)_5-$	Me	**3**	81	29:71
4	$PhCH_2$, $PhCH_2CH_2$	Me	**4**	84	69:31
5	$PhCH_2$, $PhCH_2$	Me	**5**	85	88:12
6	$PhCH_2$, $PhCH_2$	Et	**6**	80	88:12
7	$PhCH_2$, $PhCH_2$	Bn	**7**	77	88:12
8	$PhCH_2$, $PhCH_2$	*n*Pr	**8**	88	81:19
9	$PhCH_2$, $PhCH_2$	*i*Pr	**9**	85	74:26
10	$PhCH_2$, $PhCH_2$	*t*Bu	**10**	85	44:56
11[d]	$PhCH_2$, $PhCH_2$	Me	**5**	10	74:26
12[e]	$PhCH_2$, $PhCH_2$	Me	**5**	90	82:18

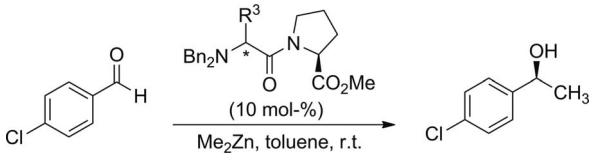
[a] Reactions run for 48 h. [b] Determined by CSP-HPLC (Chiralcel OB-H). [c] Absolute configuration assigned by comparison with known elution order according to ref.[7] [d] Reaction carried out at 0 °C. [e] Reaction carried out at 40 °C.

Increasing the temperature to 40 °C resulted in a modest decrease in enantioselectivity with a slightly higher yield (Table 1, Entry 12).

In the next stage of catalyst optimization, we examined how the amino acid side chain (R^3) of the dipeptide affected the stereoselectivity of the addition reaction while the R^1 and R^2 groups were held constant as dibenzyl and methyl, respectively[9] (Table 2). When D-Phg of **5** was changed into D-Phe or D-Ala, lower selectivities were observed in both reactions with catalysts **11** and **12** (Table 2, Entries 1 and 2). We then examined Gly-L-Pro catalyst **13** to investigate the effect of the chiral center at the α-position of the N-terminal amino acid. Interestingly, no stereoselectivity was noted for the addition with Gly-derived catalyst **13** (Table 2, Entry 3). Also, we replaced the N-terminal amino acid with the amino acid of opposite chirality. Both catalysts **14** and **15** derived from L-Phe or L-Ala gave the major product of same absolute configuration (*S*) as in the reactions with D-aa-L-Pro catalysts (Table 2, Entries 4 and 5). The results tend to indicate that the presence of the chiral center at the α-position of the N-terminal amino acid is essential for high asymmetric induction, but the absolute configuration of the product is mainly dominated by L-Pro, the C-terminal amino acid. Notably, better enantioselectivities were observed in the reactions with both L-aa-L-Pro catalysts **14** and **15** compared with D-aa-L-Pro catalysts **11** and **12** (Table 2, Entries 4 and 5).

Encouraged by the high enantioselectivity with L-Ala-L-Pro catalyst **15**, we carried out a series of reactions with several different L-aa-L-Pro catalysts. With dipeptide catalysts **16**–**20** derived from L-Trp, L-Cys(SBn), L-Glu(OBn), L-Leu, and L-Ser(OBn) amino acids, the reactions showed lower stereoselectivities compared to the reaction with L-

Table 2. Effect of the R^3 group.[a]



Entry	R^3	Catalyst	Yield [%]	*er*[b] (*S*/*R*)[c]
1	CH_2Ph (*R*)	**11** (D-Phe-L-Pro)	79	81:19
2	CH_3 (*R*)	**12** (D-Ala-L-Pro)	81	80:20
3	H	**13** (Gly-L-Pro)	82	51:49
4	CH_2Ph (*S*)	**14** (L-Phe-L-Pro)	70	83:17
5	CH_3 (*S*)	**15** (L-Ala-L-Pro)	72	92:8
6	CH_2(3-indole)	**16** (L-Trp-L-Pro)	3	56:44
7	CH_2SBn	**17** [L-Cys(SBn)-L-Pro]	8	74:26
8	$CH_2CH_2CO_2Bn$	**18** [L-Glu(OBn)-L-Pro]	89	82:18
9	$CH_2CH(CH_3)_2$	**19** (L-Leu-L-Pro)	73	86:14
10	CH_2OBn	**20** [L-Ser(OBn)-L-Pro]	95	90:10
11	CH_2CO_2Bn	**21** [L-Asp(OBn)-L-Pro]	90	94:6
12	CH_2CO_2Me	**22** [L-Asp(OMe)-L-Pro]	95	94:6

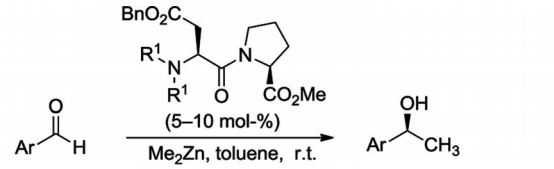
[a] Reactions run for 48 h. [b] Determined by CSP-HPLC (Chiralcel OB-H). [c] Absolute configuration assigned by comparison with known elution order according to ref.[7]

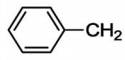
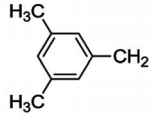
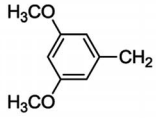
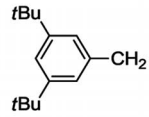
Ala-L-Pro catalyst **15** (Table 2, Entries 6–10). Particularly, much lower stereoselectivity and reactivity were observed with L-Trp-L-Pro catalyst **16** and L-Cys-L-Pro catalyst **17** (Table 2, Entries 6 and 7). In this series of catalysts, the steric factors of the side chain do not appear to play a dominant role in determining enantioselectivity. We were very pleased to observe that L-Asp(OBn)-L-Pro catalyst **21** and L-Asp(OMe)-L-Pro catalyst **22** gave the best result to produce (*S*)-ethanol with 94:6 *er* (Table 2, Entries 11 and 12).

N,*N*-Dibenzyl-L-Asp(OBn)-L-Pro catalyst **21**, which gave the highest stereoselectivity for the addition of dimethylzinc to 4-chlorobenzaldehyde was then used to explore the scope of the addition reaction with aromatic aldehydes, and the results are summarized in Table 3. Among the reactions of 4-substituted benzaldehydes, high stereoselectivities were observed in the reactions with 4-fluoro-, 4-bromo-, and 4-cyano-substituted benzaldehydes, whereas mild drops in stereoselectivity were seen with 4-trifluoromethyl-, 4-nitro-, and 4-methyl-substituted benzaldehydes (Table 3, Entries 1–6). Also, the reactions of 1-naphthaldehyde, 2-naphthaldehyde, and 3-bromobenzaldehyde gave comparable enantiomeric ratios of 94:6 and 92:8 with a lower level of reactivity (Table 3, Entries 7–9).

In an effort to improve asymmetric induction, we have attempted to modify the catalytic properties of **21** by introducing 3,5-substituents into the phenyl ring of the *N*-benzyl group (Table 3, Entries 10–29). Catalysts **23**–**25** with substituents such as methyl, methoxy, and *tert*-butyl generally gave higher enantioselectivities when compared to those obtained with catalyst **21**, regardless of the electronic character of the aldehydes. The highest enantioselectivity was observed in the reactions of 4-bromobenzaldehyde with catalyst **24** and 4-chlorobenzaldehyde with catalyst **25** to give the corresponding (*S*)-alcohols with 97:3 *er* (Table 3, Entries 16 and 22). It was also found that the catalyst loading could be decreased to 5 mol-% while still maintaining the asymmetric induction in the products with good yields (Table 3, Entries 11, 15, 16, and 24).

Table 3. Reactions of various aldehydes with L-Asp-L-Pro dipeptides.[a]



Entry	R^1	Catalyst	Ar	Yield [%]	*er*[b] (*S*/*R*)[c]
1		**21**	4-FC_6H_4	95	95:5
2		**21**	4-BrC_6H_4	90	94:6
3		**21**	4-CNC_6H_4	95	95:5
4		**21**	4-$CF_3C_6H_4$	95	91:9
5		**21**	4-$NO_2C_6H_4$	90	92:8
6		**21**	4-$CH_3C_6H_4$	85	91:9
7		**21**	1-naph	63	94:6
8		**21**	2-naph	75	94:6
9		**21**	3-BrC_6H_4	75	92:8
10		**23**	4-ClC_6H_4	94	96:4
11[d]		**23**	4-BrC_6H_4	92	95:5
12		**23**	4-CNC_6H_4	94	95:5
13		**23**	4-$CF_3C_6H_4$	91	95:5
14		**23**	1-naph	70	95:5
15[d]		**24**	4-ClC_6H_4	92	96:4
16[d]		**24**	4-BrC_6H_4	93	97:3
17		**24**	4-CNC_6H_4	95	95:5
18		**24**	4-$CF_3C_6H_4$	93	96:4
19		**24**	1-naph	67	96:4
20		**24**	2-naph	73	95:5
21		**24**	3-BrC_6H_4	91	96:4
22		**25**	4-ClC_6H_4	95	97:3
23		**25**	4-BrC_6H_4	94	96:4
24[d]		**25**	4-CNC_6H_4	91	96:4
25		**25**	4-$NO_2C_6H_4$	88	94:6
26		**25**	4-$CH_3C_6H_4$	83	96:4
27		**25**	1-naph	74	96:4
28		**25**	2-naph	65	95:5
29		**25**	3-BrC_6H_4	88	96:4

[a] Reactions run for 48 h. [b] Determined by CSP-HPLC (Chiralcel OB-H or Chiralcel OJ-H). [c] Absolute configuration assigned by comparison with known elution order according to ref.[7] [d] A catalyst loading of 5 mol-% was used.

Conclusions

We have developed a new class of dipeptide catalysts for the enantioselective addition of dimethylzinc to aromatic aldehydes. Three subunits within aa-L-Pro dipeptide were varied to increase the enantioselectivity and the optimization led us to identify L-Asp-L-Pro dipeptides **21**–**25** as effective catalysts for the addition. The simple modular structure in combination with the ready availability of L-amino acids renders the dipeptide catalysts highly attractive. This work paves the way for the synthesis and evaluation of larger libraries of dipeptide catalysts for reactions involving alkylzinc, as well as other organometallic reagents. Further studies on the improvement of enantioselectivity and on the structure of the zinc–dipeptide complex are now in progress.

Experimental Section

General Procedure: Dimethylzinc (2 M in toluene, 4.0 equiv.) was added to a solution of the dipeptide catalyst (0.1 or 0.05 equiv.) and aldehyde (1.0 equiv.) in toluene at 0 °C. The homogeneous solution was stirred at room temperature for 48 h. The reaction was quenched by the addition of 1 M HCl, and the solution was extracted with $CHCl_3$. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic separation on silica gel (hexane/EtOAc) afforded the enantioenriched ethanols in 95–93% yield, and the enantioselectivity of the products was measured by HPLC with chiral columns by using racemic material as a standard.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data including copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

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[9] Catalysts **11**–**25** shown in Tables 2 and 3 were prepared by the coupling of *N*-Boc-aa-OH and L-Pro-OMe and following *N*,*N*-dibenzylation with the corresponding benzyl bromide. See the Supporting Information for details.

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