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L-Valine Dipeptide Organocatalysts with Two Amide Units for the Direct Asymmetric Aldol Reaction in Brine

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Abstract A series of valine dipeptide organocatalysts containing a primary amine group and two amide units have been developed and evaluated in the direct asymmetric intermolecular aldol reaction of 4-nitrobenzaldehyde and cyclohexanone. When 2,4-dinitrophenol (DNP) was used as an acidic additive, the catalyzed reactions of various aldehydes and ketones gave the corresponding aldol products with moderate to high enantioselectivities (up to 95%) and diastereoselectivities (up to >99/1, anti/syn) in the presence of **3c** in brine.

Keywords Valine · Dipeptide · Aldol reaction · Brine

1 Introduction

The asymmetric aldol reaction is one of the most useful carbon–carbon bond-forming reactions [1–5] and plays an important role in organic synthesis. Since the pioneering work by List et al. [6–8] in asymmetric organocatalysis, development of simple small moleculars as efficient organocatalysts for this reaction has attracted a great deal of attention [9–13]. On the other hand, the development of stereoselective reactions using water as reaction medium is another attractive research field [14, 15], mainly due to the low cost, safety and environmentally benign nature of water. Therefore, a great deal of emphasis has been devoted to the development of water-tolerant organocatalyst for direct asymmetric aldol reaction, and some groups have reported organocatalytic direct asymmetric aldol in water without using any organic co-solvent [16–19].

Most of the reported peptide organocatalysts for the direct asymmetric aldol reaction are *N*-terminal prolyl dipeptides [20–29]. Córdova et al. showed that amino acids [30, 31] and small di- to tetra-peptides [32, 33] with a primary amino functionality are able to catalyze the asymmetric intermolecular aldol reaction with high stereoselectivity. In addition, the small peptides can catalyze the aldol reaction in water and aqueous media with high asymmetric induction [33]. Since these findings, linear amino acids and their derivatives are used more often as catalysts for highly enantioselective intermolecular aldol reactions [34–37]. However, the reports about dipeptides of *N*-terminal primary amine catalyzed asymmetric aldol reaction in aqueous medium are limited [33].

Herein we report a series of *N*-primary-amine terminal valine dipeptide organocatalysts which containing a primary amine group and two amide units for the asymmetric aldol reaction in brine. These catalysts were synthesized from *N*-*t*-butyloxycarbonyl protected valine and arylamines. The catalyst properties can be readily tuned by varying the stereo and electronic effects of the terminal amide to affect the ability of hydrogen bonding formation between the catalysts and the substrate. Strong electron-withdrawing nitro group was introduced to enhancing the amide NH acidity in the hope of improving stereocontrol [38–41].

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2 Experimental

2.1 Materials and Instruments

Arylamines and *N*-*t*-butyloxycarbonyl protected valine were purchased from commercial suppliers. ^{1}H NMR spectra were recorded on a 300 MHz FT-NMR Mercury-300B (Varian) spectrometer with tetramethylsilane as an internal reference. Solvent for NMR is $CDCl_3$. ^{13}C NMR were recorded on 75 MHz. Elemental analysis (C, H, and N) were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD-H (4.6 mm × 250 mm), OD-H (4.6 mm × 250 mm) and AS-H (4.6 mm × 250 mm) column. Diastereoselectivities were determined by ^{1}H NMR analysis of the aldol product.

2.2 Catalyst Preparation

Organocatalyst **3a**–**3d** was prepared from *N*-*t*-butyloxycarbonyl protected L-valine and arylamines as shown in Scheme 1.

N-*t*-butyloxycarbonyl-L-valine (10 mmol) and arylamine (10 mmol) were dissolved in 30 mL dry pyridine [42]. Then the clear yellowish solution was cooled to −15 °C and phosphorus oxychloride (1.0 mL, 11 mmol) was added dropwise with vigorous stirring over 15 min. The reaction mixture was stirred until the reaction was completed (monitored by TLC). Quenched with crushed ice/water, and extracted with ethyl acetate (30 mL × 4). Combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel [eluent, *V*(chloroform)/*V*(ethyl acetate) = 5:1] to afford compound **1**.

Compound **1** was dissolved in 8 mL dichloromethane, to which 2 mL TFA was added. The solution was stirred for 4 h at room temperature. Then the reaction was quenched with concentrated ammonia solution and extracted with chloroform (3 × 15 mL). The organic layer was washed with brine (2 × 15 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated to give compound **2**.

N-*t*-butyloxycarbonyl-L-valine and DCC (1.0 equiv) were dissolved in 20 mL dichloromethane. Then the solution was cooled to 0 °C and stirred for 0.5 h. After that, compound **2** was added and the reaction mixture was warmed to room temperature and stirred for another 5 h. After filtration and the removal of solvent under reduced pressure, the residue was purified through chromatography on silica gel column [eluent, *V*(chloroform)/*V*(ethyl acetate) = 2:1] to afford the *N*-*t*-butyloxycarbonyl protected L-valine dipeptide.

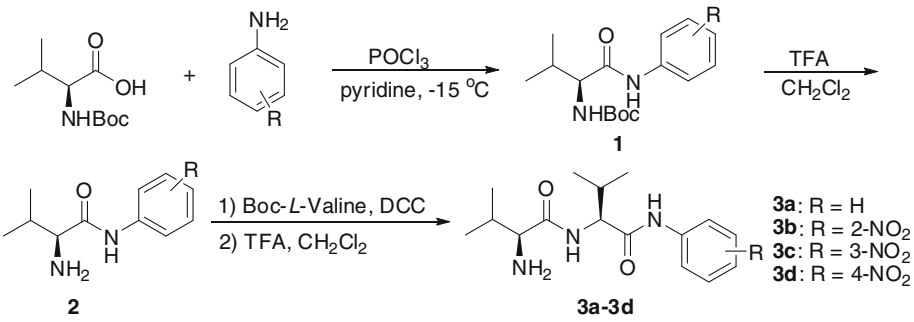
N-*t*-butyloxycarbonyl protected L-valine dipeptide was dissolved in 10 mL dichloromethane, to which 2 mL TFA was added. The solution was stirred for 5 h at room temperature. Then the reaction was quenched with concentrated ammonia solution and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel (eluent, *V*(chloroform)/*V*(methanol) = 5:1) to afford compound **3**.

2.2.1 Catalyst *3a*

White solid, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.85 (d, J = 6.9 Hz, 3H), 1.00–1.05 (m, 9H), 1.61 (br, 2H), 2.22–2.39 (m, 2H), 3.33 (d, J = 2.4 Hz, 1H), 4.43 (t, J = 8.2 Hz, 1H), 7.07 (t, J = 7.3 Hz, 1H), 7.25–7.30 (m, 2H), 7.53 (d, J = 7.8 Hz, 2H), 8.14 (d, J = 8.1 Hz, 1H), 8.84 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.64, 18.09, 18.82, 19.18, 30.43, 30.77, 58.38, 59.70, 119.41, 123.37, 128.09, 137.64, 169.82, 174.52; (EI) *m/z* 291 (rel intensity) ($M^+ + 1$); Analysis calculated for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 66.12; H, 8.74; N, 14.31.

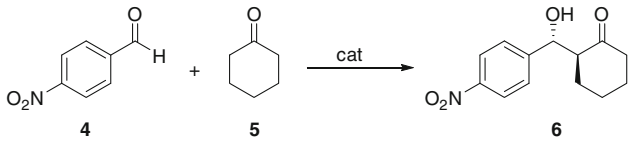
2.2.2 Catalyst *3b*

Yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.87 (d, J = 6.9 Hz 3H), 0.97 (d, J = 6.9 Hz 3H), 1.03–1.07 (m, 6H), 1.58 (br, 2H), 2.39–2.45 (m, 1H), 2.50–2.62 (m, 1H), 3.52 (d, J = 6.9 Hz 1H), 4.52–4.56 (m, 1H), 7.16–7.22



Scheme 1 Preparation of organocatalysts

Table 1 Aldol reaction of cyclohexanone and 4-nitrobenzaldehyde under various conditions



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Entry	Solvent	Additive	Catalyst	Time (h)	Yield (%)[a]	Anti/syn[b]	ee for anti (%)[c]
1	CH_2Cl_2	None	**3a**	75	65	91:9	42
2	$CHCl_3$	None	**3a**	77	73	94:6	55
3	Toluene	None	**3a**	92	58	93:7	53
4	DMF	None	**3a**	72	25	83:17	38
5	Water	None	**3a**	52	77	94:6	80
6	Brine	None	**3a**	42	79	95:5	81
7[d]	Brine	None	**3a**	48	76	97:3	82
8[e]	Brine	None	**3a**	68	67	94:6	81
9	Brine	PhCOOH	**3a**	14	81	97:3	86
10	Brine	3,5-Dinitrobenzoic acid	**3a**	12	73	95:5	83
11	Brine	2-Nitrobenzoic acid	**3a**	9	75	94:6	83
12	Brine	TFA	**3a**	7.5	65	92:8	82
13	Brine	DNP	**3a**	33	82	99:1	88
14	Brine	DNP	**3a**	29	79	94:6	92
15	Brine	DNP	**3c**	26	84	98:2	95
16	Brine	DNP	**3d**	24	83	99:1	93

Conditions: aldehyde (0.25 mmol), cyclohexanone (2.5 mmol), catalyst (10 mol%), 1.0 mL brine, rt

[a] Isolated yield

[b] Determined by ^{1}H NMR

[c] Determined by chiral HPLC

[d] Reaction temperature 5 °C

[e] 5 mol % of catalyst used

(m,1H), 7.63–7.69 (m, 1H), 8.21–8.24 (m, 1H), 8.30 (d, $J = 8.7$ Hz, 1H), 8.87–8.90 (m, 1H), 11.01 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.89, 17.10, 19.58, 19.62, 29.53, 30.35, 59.18, 59.87, 121.63, 123.31, 125.66, 134.38, 136.02, 170.74, 175.28; (EI) *m/z* 336 (rel intensity) ($M^+ + 1$); Analysis calculated for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.28; H, 7.33; N, 16.52.

2.2.3 Catalyst *3c*

White solid, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.89 (d, $J = 6.9$ Hz, 3H), 1.04–1.08 (m, 9H), 1.51 (br, 2H), 2.19–2.30 (m, 1H), 2.37–2.43 (m, 1H), 3.48 (d, $J = 3.3$ Hz, 1H), 4.595 (t, $J = 8.2$ Hz, 1H), 7.36 (t, $J = 8.2$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 8.35, (m, 2H), 9.98 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 16.07, 18.55, 19.22, 19.58, 30.95, 31.31, 58.91, 60.11, 114.22, 118.09, 125.11, 129.37, 139.46, 148.11, 170.69, 175.47; (EI) *m/z* 336 (rel intensity) ($M^+ + 1$); Analysis calculated for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.26; H, 7.30; N, 16.48.

2.2.4 Catalyst *3d*

White solid· ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.86 (d, $J = 6.9$ Hz, 3H), 1.03–1.07 (m, 9H), 1.49 (br, 2H), 2.23–2.46 (m, 2H), 3.38 (d, $J = 3.3$ Hz, 1H), 4.41 (t, $J = 8.2$ Hz,1H), 7.67 (d, $J = 9.0$ Hz, 2H), 8.10 (d, $J = 9.3$ Hz, 2H), 8.26 (d, $J = 8.1$ Hz, 1H), 9.78 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 16.04, 18.47, 19.28, 19.63, 30.86, 30.91, 59.22, 60.09, 118.96, 124.53, 142.94, 144.15, 170.89, 175.60; (EI) *m/z* 336 (rel intensity) ($M^+ + 1$); Analysis calculated for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.18; H, 7.26; N, 16.51.

2.3 General Procedure for the Catalytic Direct Asymmetric Aldol Reaction

All solvents were refined according to standard methods. Aldehyde, ketone (freshly distilled), catalyst and 1.0 mL solvent were added to a 5 mL glass reactor. The reaction mixture was stirred until all the aldehyde has been consumed (monitored by TLC). Quenched with saturated

ammonium chloride solution (5 mL), and extracted with ethyl acetate (10 mL × 3). Combined organic layer was washed with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel [eluent, *V*(ethyl acetate)/*V*(petroleum ether) = 1:3] to afford pure aldol product.

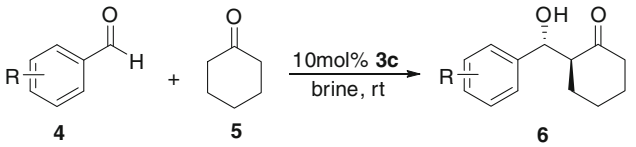
3 Results and Discussion

As shown in Scheme 1, dipeptide organocatalysts **3a**–**3d** was prepared from Boc-L-valine and arylamines in four steps. The catalytic activity of these new catalysts was then evaluated in the direct asymmetric intermolecular aldol reaction of 4-nitrobenzaldehyde and cyclohexanone. Results were summarized in Table 1. Initially, various solvents were screened with **3a** at room temperature. It was found that brine [43–46] was the more suitable reaction medium (entry 6). Higher stereoselectivity and diastereoselectivity were obtained in brine compared to organic solvent (entry 1–5). Decreasing the reaction temperature did not increase the enantioselectivity as indicated in entry 7. Influence of catalyst loading was also examined. Reducing the amount of catalyst (entry 8) from 10 to 5 mol% did not cause the drop of enantioselectivity but led to a prolonged reaction time. Considering the effect of acid additives on increasing the yield and enantioselectivity [29, 46], a series of acidic additives were tested in the same reaction. As expected, the acidic additives increased the enantioselectivity and abbreviated the reaction time. The increase of the enantioselectivities caused by strong acidic additives such as 2-nitrobenzoic acid and TFA was founded to be slightly (entry 9–12). When DNP (2,4-dinitrophenol) was added as an additive, both the higher enantioselectivity and diastereoselectivity were obtained. Hence DNP was chose as the additive for this reaction. The influence of the ratio of ketone and aldehyde on the reaction was also determined. Increasing the ratio of ketone and aldehyde from 10:1 to 20:1 did not cause the improved enantioselectivity. Decreasing the ratio of ketone and aldehyde from 10:1 to 5:1 caused the drop in enantioselectivity (from 88 to 84% ee). Next, the catalytic activity of catalysts **3b**–**3c** was evaluated under the optimized condition. As can be seen from the results summarized in Table 1, catalysts **3b**, **3c** and **3d** which bearing an electron-withdrawing nitro group on the benzene ring gave the desired product in high enantioselectivity and diastereoselectivity, **3c** gave the best result (ee up to 95%, dr up to 98:2). Catalyst **1a** which having no electron-withdrawing group on the benzene ring gave lower enantioselectivity and diastereoselectivity. The resluts indicated that NH acidity plays a pivotal role in stereocontrol, and the steric factors also influenced the enantioselectivity.

To further explore the scope of the reaction, the direct asymmetric aldol reactions of various aldehydes and cyclohexanone in the presence of **3c** were examined as shown in Table 2. The benzaldehydes substituted by strong electron-withdrawing nitro and canyo groups were converted to the corresponding aldol products in good yields, with moderate to high enantioselectivities (86–95% ee) and high diastereoselectivities (dr up to >99:1). Enantioselectivity was influenced by the electron-withdrawing ability of the substituent on the benzene ring. The aldol reactions of cyclohexanone and benzaldehydes which bearing chloro and fluoro substituents on the benzene ring (entrys 7–10) were very sluggish, giving the corresponding aldol product in moderate yields with moderate enantioselectivities (68–82%) and high diastereoselectivities (up to 99:1). Under the same condition, reaction of less reactive benzaldehyde with cyclohexanone afforded trace product.

The direct asymmetric aldol reactions between various ketones and aldehydes were also examined as shown in Table 3. The aldol reactions of cyclopentanone with 4-nitrobenzaldehyde and 3-nitrobenzaldehyde gave the corresponding aldol product in high yield but with low enantioselectivity and diastereoselectivity. The reaction of

Table 2 Aldol reaction of various aldehydes and cyclohexanone in the presence of **3c**



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Entry	R	Product	Time (h)	Yield (%)[a]	Anti/syn[b]	ee for anti (%)[c]
1	4-NO_2	**6a**	26	84	98:2	95
2	3-NO_2	**6b**	29	79	99:1	93
3	2-NO_2	**6c**	38	76	>99:1	94
4	4-CN	**6d**	43	77	98:2	87
5	3-CN	**6e**	72	73	96:4	86
6	2-CN	**6f**	72	69	>99:1	87
7	3-Cl	**6g**	96	45	92:8	72
8	2-Cl	**6h**	96	43	98:2	68
9	3-F	**6i**	96	51	99:1	82
10	2-F	**6j**	96	48	99:1	83
11	H	**6k**	72	Trace	–	–

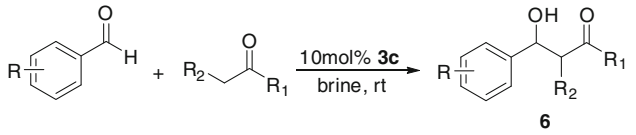
Conditions: aldehyde (0.25 mmol), cyclohexanone (2.5 mmol), catalyst (10 mol%), 2,4-dinitrophenol (10 mol%), 1.0 mL brine, rt

[a] Isolated yield

[b] Determined by ^{1}H NMR

[c] Determined by chiral HPLC

Table 3 Aldol reaction of aldehydes and various ketones in the presence of **3c**



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Entry	R	R^1	R^2	Product	Time (h)	Yield (%)[a]	anti/syn[b]	ee (%)[c]
1	4-NO_2	$-(CH_2)_3-$		**6l**	34	92	22:78	89
2	3-NO_2	$-(CH_2)_3-$		**6m**	45	89	37:66	86
3	4-NO_2	CH_3-	H	**6n**	32	63		29

Conditions: aldehyde (0.25 mmol), ketone (2.5 mmol), catalyst (10 mol%), 2,4-dinitrophenol (10 mol%), 1.0 mL brine, rt

[a] Isolated yield

[b] Determined by ^{1}H NMR

[c] Determined by chiral HPLC

acetone and 4-nitrobenzaldehyde afforded the aldol product in moderate yield with low enantioselectivity.

4 Conclusions

In summary, a series of valine dipeptide organocatalysts containing a primary amine group and two amide units have been developed and applied to the asymmetric direct aldol reactions in brine with the addition of DNP as cocatalyst. Aldol products were obtained in mederate yields with moderate to high enantioselectivities (up to 95%) and diastereoselectivities (up to >99:1).

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