JOC Note

pubs.acs.org/joc

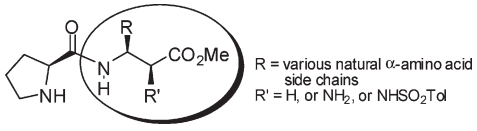
Proline−β^3-Amino-Ester Dipeptides as Efficient Catalysts for Enantioselective Direct Aldol Reaction in Aqueous Medium

Mauro De Nisco,*[,§] Silvana Pedatella,[§] Hidayat Ullah,[†] Javid H. Zaidi,[†] Daniele Naviglio,[§] Özgür Özdamar,[‡] and Romualdo Caputo[§]

[§]*Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Via Cintia, 4 Napoli 80126, Italy,* [†]*Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan, and* [‡]*Ondokuz Mayis Universitesi, Fen Edebiyat Fakültesi, Kimya Bölümü, Samsun 55200, Turkey*

denisco@unina.it

Received October 5, 2009



Dipeptide catalysts for asymmetric direct aldol reaction

Dipeptides obtained from L-proline and β^3-L-amino acids are reported to catalyze enantioselective direct aldol reaction in aqueous medium, leading to significant anti:syn diastereomeric ratios and enantiomeric excesses. The simple introduction of a polar substituent at the C-2 position of the β^3-L-amino acid was also found to enhance appreciably both diastereo- and enantioselectivity of the catalyst.

During the past decade organocatalysis, which indeed has been known for more than a century, has emerged as one of the hot topics in organic chemistry.[1−3] In this contest a great deal of attention has been paid to the catalytic power of naturally occurring amino acids,[4−8] due to both their low cost and availability in highly enantiopure form.

Recently, Singh's group have reported,[9] along the line of former reports[10] by Wu et al., some new L-proline amides having an extra chiral center at the α position of the amide nitrogen atom and a polar, bulky group at the β position. They are highly efficient organocatalysts carrying out diastereo- and enantioselective direct aldol reactions in both organic and (much better) aqueous medium.

Such new molecules aroused our attention for their amino moieties that recall C-2 substituted β^3-amino acids, whose preparation we had reported rather recently[11] as a part of our current interest in the chemistry of β^3-L-amino acids. As a matter of fact, the above-mentioned proline amides can be regarded as dipeptides of L-proline and C-2 substituted β^3-amino acids, obviously lacking the *C*-terminal carboxyl group (whose usefulness, however, will be illustrated further on).

In this view, we wanted to investigate the behavior of some real dipeptides coming from coupling of L-proline with miscellaneous β^3-L-amino acids as catalysts for enatioselective direct aldol reactions. The dipeptides tested were compounds **1a**−**f**,[12] containing simple C-2 unsubstituted β^3-L-amino acids[13] and, in addition, compounds **1g** and **1h**,[12] carrying at C-2 a polar (NH_2) group[11b] and a bulky polar[14,15] (NHTs) group,[11b] respectively (Figure 1).

The aldol addition of cyclohexanone and 4-nitrobenzaldehyde (Figure 2) was chosen as the test reaction for the catalytic activity since, from the current literature,[9] it appears to lead to the poorest results in terms of both diastereomeric ratios and enantiomeric excesses.

The reactions were carried out in three different, commonly used mediums, namely water, brine,[3a,16] and THF, and afforded quite interesting results that are shown in Tables 1−3.

(1) For an overview see: (a) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (b) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(2) Special issues on organocatalysis: (a) *Chem. Rev.* **2007**, *107*, 5413−5883. (b) *Tetrahedron* **2006**, *62*, 243−502. (c) *Acc. Chem. Res.* **2004**, *37*, 631−847. (d) *Adv. Synth. Catal.* **2004**, *346*, 1007−1249.

(3) For more on organocatalysis see: (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57. (b) Dondoni, A.; Massi, A. *Angew. Chem.* **2008**, *120*, 4716–4739. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638−4660. (c) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666–1688. (d) Longbottom, D. A.; Franckevičius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichim. Acta* **2008**, *41*, 3–11. (e) Vicario, J. L.; Bada, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092. (f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8–27. (g) List, B. *Chem. Commun.* **2006**, 819–824. (h) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584–1586. (i) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. (j) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2004**, *116*, 5248–5286. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

(4) (a) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053. (b) Peng, F.-H.; Shao, Z.-H. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1–13.

(5) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586–3588.

(6) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801–2803.

(7) Amedjkouh, M. *Tetrahedron: Asymmetry* **2007**, *18*, 390–395.

(8) Peng, Y.-Y.; Wang, Q.; He, J.-Q.; Cheng, J.-P. *Chin. J. Chem.* **2008**, *26*, 1454–1460.

(9) (a) Raj, M.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289–4297. (b) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411–9416. (c) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *13*, 2593–2595.

(10) (a) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289. (b) Tang, Z.; Cui, X.; Gong, L. Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760. (c) Tang, Z.; Jang, F.; Yu, L. T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.

(11) (a) Capone, S.; Pedatella, S.; Guaragna, A.; De Nisco, M.; Palumbo, G. *Tetrahedron* **2007**, *63*, 12202–12206. (b) Capone, S.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Tetrahedron* **2005**, *61*, 6575–6579. (c) Caputo, R.; Cecere, G.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **2002**, 3050–3054.

(12) Characterization data for all new compounds (including the intermediates of their preparations) are reported in the Supporting Information.

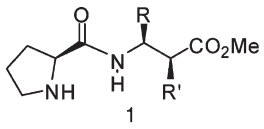
(13) Caputo, R.; Cassano, E.; Longobardo, L.; Palumbo, G. *Tetrahedron* **1995**, *51*, 12337–12350.

(14) Leo, A. B. *J. Pharm. Sci.* **2000**, *89*, 1567–1578.

(15) Jeffrey, G. A. In *An Introducdtion to Hydrogen Bonding*; Truhlar, D. G., Ed.; Oxford University Press: New York, 1997.

(16) Gryko, D.; Saletra, W. J. *Org. Biomol. Chem.* **2007**, *5*, 2148–2153.

Published on Web 11/25/2009 DOI: 10.1021/jo902106r



a) R = Ph, R' = H
b) R = Bn, R' = H
c) R = $CH_2CH(CH_3)_2$, R' = H
d) R = CH_2S(Bn), R' = H
e) R = $CH_2C_6H_4O$(Bn), R' = H
f) R = CH_2-1*H*-indole, R' = H
g) R = Ph, R' = NH_2
h) R = Ph, R' = $NHSO_2$Tol

FIGURE 1. L-Proline dipeptide catalysts for the enantioselective aldol reaction.

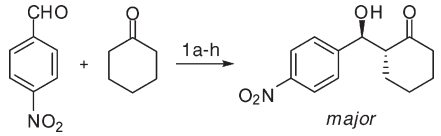


FIGURE 2. Aldol addition of cyclohexanone and 4-nitrobenzaldehyde.

TABLE 1. Cyclohexanone/4-Nitrobenzaldehyde-Catalyzed Aldol Reactions in Water (25° C, 48 h)

catalyst	mol %	yield [%][a]	dr (anti:syn)[b]	ee [%][c]
1a	10	92	81:19	45
	3	96	82:18	50
1b	10	72	93:7	83
	3	69	92:8	78
1c	10	98	91:9	84
	3	89	90:10	75
1d	10	99	94:6	87
	3	97	92:8	77
1e	10	>99	94:6	90
	3	99	93:7	85
1f	10	78	92:8	84
	3	70	91:9	81

[a]After chromatography. [b]Determined by ^{1}H NMR. [c]Determined by HPLC on chiral column.

Such results deserve some comments: it is clear that dipeptides **1b**−**f** work very well in aqueous medium (water and brine) rather than in organic solvents (anhydrous THF). Chemical yields of the catalyzed aldol reactions are satisfactorily high[3a,6,9,17] and diastereomeric ratios and enantiomeric excesses are all significant. The best results were obtained with dipeptides **1e** and **1f**, bearing the side chains of tyrosine and tryptophan, respectively. This may be accounted for by the possibility for the aromatic side chains of these compounds to form in the transition state a hydrophobic core with the other hydrophobic substrates in water.[3a,6] $\pi-\pi$ stacking interactions may also be involved[6] in the transition states of the reactions. Rather oddly, the dipeptide **1a**, which is, however, the smallest one, showed the opposite behavior, leading to reasonable results only when the reaction was carried out in THF.

Recycling of the catalysts was attempted satisfactorily in three cases (**1b**, **1e**, and **1f**): over three cycles the chemical yields decreased slowly (likely due to somewhat lower purity of the recovered catalyst) whereas diastereomeric ratios and enantiomeric excesses remained substantially at the same level.

TABLE 2. Cyclohexanone/4-Nitrobenzaldehyde-Catalyzed Aldol Reactions in Brine (25° C, 48 h)

catalyst	mol %	yield [%][a]	dr (anti:syn)[b]	ee [%][c]
1a	10	>99	77:23	54
	3	>99	80:20	56
1b	10	98	94:6	88
	3	81	94:6	88
1c	10	>99	89:11	76
	3	99	86:14	67
1d	10	>99	92:8	86
	3	>99	90:10	77
1e	10	87	93:7	89
	3	72	94:6	87
1f	10	96	93:7	90
	3	98	93:7	89

[a]After chromatography. [b]Determined by ^{1}H NMR. [c]Determined by HPLC on chiral column.

TABLE 3. Cyclohexanone/4-Nitrobenzaldehyde-Catalyzed Aldol Reactions in THF (25° C, 48 h)

catalyst	mol %	yield [%][a]	dr (anti:syn)[b]	ee [%][c]
1a	10	49	90:10	86
	3	87	91:9	85
1b	10	70	87:13	35
	3	40	86:14	38
1c	10	48	85:15	44
	3	48	85:15	49
1d	10	70	82:18	38
	3	66	87:13	48
1e	10	90	86:14	39
	3	36	86:14	42
1f	10	36	87:13	43
	3	38	84:16	44

[a]After chromatography. [b]Determined by ^{1}H NMR. [c]Determined by HPLC on chiral column.

To emphasize the role of a polar substituent β to the peptide nitrogen atom, we evaluated the effect of both a substituent like $-NH_2$ and a polar,[14,15] cumbersome substituent, like −NHTs, on the catalytic activity of our less efficient catalyst, **1a**, in aqueous medium.

The new C-2 substituted dipeptides, **1g** and **1h**, were synthesized from the already reported[11b] compound **2**, as shown in Scheme 1. Their activity was tested in both water and brine at different temperatures (25°, 4°, and, brine only, −16 °C), using two catalyst loadings (10% and 3%) for each experiment. All the reactions were duplicated and the average results are reported in Table 4.

It is worthy of note that the enantiomeric excesses obtained from **1g** were in the range 74−90% vs. the range 45−56% of **1a** that has the same skeleton, without the $-NH_2$ group at C-2. The same trend is evident in the anti:syn diastereomeric ratios that range between 80:20 and 97:3 vs. the range 77:23 to 82:18 afforded by compound **1a**.

Compound **1h** was tested under the same experimental conditions and gave on the whole poorer results in comparison with **1g** (Table 4). Only the chemical yields were somewhat higher.

The results obtained from **1g** and **1h** are congruent with the mechanism generally accepted[18] for catalyzed aldol

(17) (a) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4288–4297. (b) Giacalone, F.; Gruttadauria, M.; Lo Meo, P.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747–2760. (c) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takae, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735.

(18) (a) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *123*, 16–17. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912.

SCHEME 1. Preparation of L-Proline Dipeptide Catalysts 1g and 1h

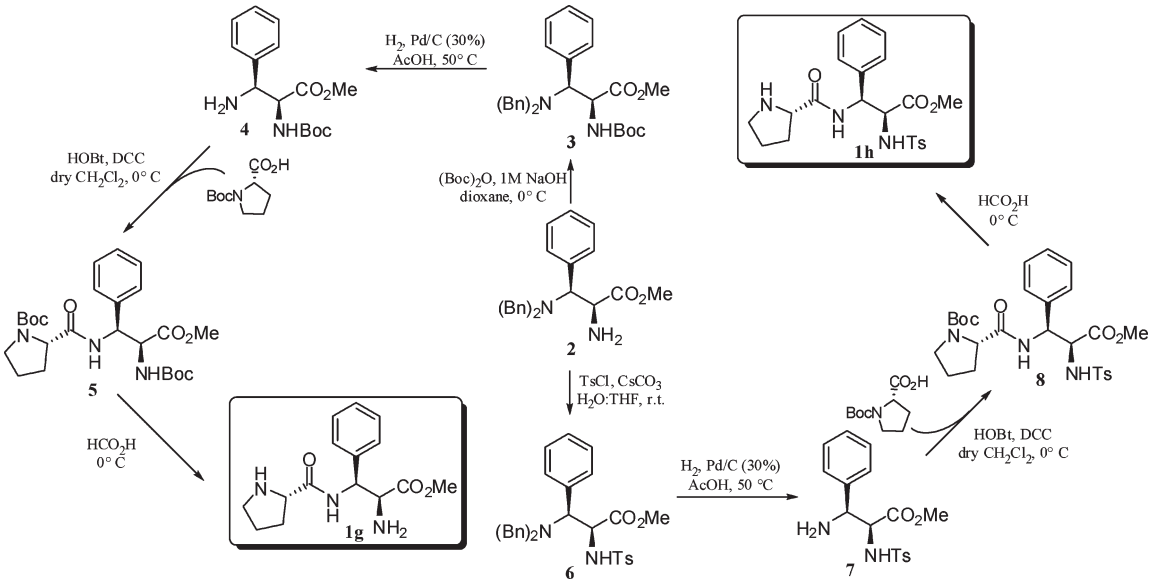


TABLE 4. Solvent and Temperature Effects on Cyclohexanone/4-Nitrobenzaldehyde Aldol Reactions (48 h) Catalyzed by Compounds 1g and 1h

catalyst	mol %	solvent	*T* [°C]	yield [%][a]	dr (anti: syn)[b]	ee [%][c]
1g	10	water	25	77	92:8	78
	3	water	25	51	91:9	75
	10	water	4	78	89:11	74
	3	water	4	62	80:20	74
	10	brine	25	96	92:8	81
	3	brine	25	52	92:8	82
	10	brine	4	81	87:13	81
	3	brine	4	79	92:8	78
	10	brine	−16	45	97:3	90
	3	brine	−16	34	96:4	86
1h	10	water	25	99	75:25	56
	3	water	25	>99	77:23	67
	10	water	4	75	90:10	65
	3	water	4	80	88:12	67
	10	brine	25	>99	72:28	66
	3	brine	25	>99	78:22	50
	10	brine	4	96	88:12	75
	3	brine	4	97	88:12	71
	10	brine	−16	80	91:9	86
	3	brine	−16	70	90:10	77

[a]After chromatography. [b]Determined by ^{1}H NMR. [c]Determined by HPLC on chiral column.

reactions: as a matter of fact, the polar $-NH_2$ substituent in **1g** enables the formation of a hydrogen bond with the aldehyde carbonyl oxygen whereas the bulky −NHTs group does not favor the formation of such a bond for both electronic and stereochemical reasons.[14,15] As a consequence, **1g** leads to higher enantioselectivity of the nucleophile attack onto the aldehyde carbonyl group.

These results are in rather good agreement with those of Singh et al.,[9b] where sulfonamides are shown to be favored catalysts in aqueous medium. In fact, the introduction of the −NHTs group at C-2 of the dipeptide **1a** increases significantly the enatioselectivity of the addition (cf. Table 1 and the bottom of Table 4).

At present, a full comparison of the results appears to be untimely since our compound **1g** (or its analogues) is unprecedented in catalyzed aldol additions. Its better results, in comparison with **1h**, seem to suggest that in the transition state the ability of the substituent to afford a hydrogen bond prevails on steric effects.

Brine, in principle, seems to be more effective than water, although at this stage the results are difficult to rationalize and still appear somewhat random.

In conclusion, L-Pro-β^3-L-Aaa-OMe dipeptides have been shown to be promising water-friendly organocatalysts that present interesting features such as the following: (i) easy preparation from *N*-protected L-proline and α-L-amino acids[13] that are both commercially available in enantiomerically pure form and (ii) modulation of the catalytic activity through insertion, at C-2 of the starting β^3-L-amino acid methyl ester, of substituents that can be either polar or nonpolar, and bulky as well.

In the near future we intend to hydrolyze[19] the protected carboxyl group of our dipeptides and anchor them to a polymeric support, perhaps through a suitable spacer to ensure rotational freedom of the catalyst species. Work is already in progress in our lab to improve the performance of the above more promising catalysts (e.g., **1e** and **1f**, having Tyr and Trp side chains, respectively) by playing with different substituents at the C-2 position of the starting β^3-L-amino acid methyl ester.

Experimental Section

General Procedure for Cyclohexanone/4-Nitrobenzaldehyde Aldol Reaction Catalyzed by Compounds 1a−h. In a 10 mL round-bottomed flask, equipped with a Teflon-coated stir bar and some small glass beads, cyclohexanone (2 mmol) was poured together with the proper solvent (water/brine/dry THF, 1 mL). 4-Nitrobenzaldehyde (0.5 mmol) and catalyst (0.05 mmol) were then added in sequence under stirring and the mixture was gently stirred in the stoppered flask at room temperature for 48 h. Independently of the solvent used, the reaction was quenched by addition of 20% aq NH_4Cl (5 mL) and extraction with EtOAc (3 × 5 mL). The organic layers were

(19) (a) Wu, X.-A.; Ying, P.; Liu, J.-Y.; Shen, H.-S.; Chen, Y.; He, L. *Synth. Commun.* **2009**, *39*, 3459–3470. (b) Walton, E.; Rodin, J. O.; Stammer, C. H.; Holly, F. W. *J. Org. Chem.* **1962**, *27*, 2255–2257.

washed with brine and dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. The crude residue was adsorbed on a preparative layer plate and eluted twice with hexane:EtOAc (7:3) to separate anti and syn couples. The residue on the plate was then recovered and flash chromatographed ($CHCl_3$) to get back the catalyst. The ee values were determined by HPLC on a chiral column.

The same procedure was followed for the reactions with use of 0.017 mmol catalyst (3 mmol % loading). Under such circumstances, the recovery of catalyst turned out to be unreliable.

All the experiments were duplicated.

Acknowledgment. ^{1}H and ^{13}C NMR spectra were performed at Centro Interdipartimentale di Metodologie Chimico-Fisiche, Università di Napoli Federico II. The 500 MHz NMR instrument is the property of Consorzio Interuniversitario Nazionale la Chimica per l'Ambiente (INCA).

Supporting Information Available: Experimental procedures and characterization data of 21 new compounds, ^{1}H and ^{13}C NMR, and HPLC area graphs. This material is available free of charge via the Internet at http://pubs.acs.org.