New and Effective Proline Based Catalysts for Asymmetric Aldol Reaction in Water

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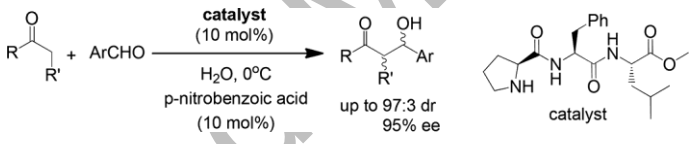
Abstract

New proline diamide organocatalysts with Pro-Phe peptide bond were synthesized and their catalytic activities in asymmetric direct aldol reactions of aliphatic ketones with aromatic aldehydes were investigated. Especially, catalyst **6a** showed good enantioselectivity at 0 ^{o}C in the presence of p-nitrobenzoic acid as co-catalyst in water.

Graphical Abstract



KEYWORDS: Aldol reaction; Proline diamide; Organocatalysis; Water medium

INTRODUCTİON

Organocatalysts are non-metal small organic compounds which have carbon, nitrogen, hydrogen, sulfur and phosphorus.[1,2] Because of their advantages such as non-toxicity, reduction in hazardous chemical waste, saving cost, time and energy, non-inert reaction conditions and easy to use[3], these pure compounds have attracted researcher's attention for asymmetric version of various reactions. Diversity and applications of asymmetric organocatalysts have been increased last decades. Proline keeps its popularity among the

asymmetric organocatalysts since the first report by List.[4] Proline has important properties expected from an asymmetric organocatayst, for example it is easily available in two enantiomeric form and cheap natural compound. But, proline have some disadvantages such as insolubility in most organic solvents, some side reactions, and low selectivity with aromatic aldehydes.[5] To overcome these disadvantages and to accomplish high enantiopurity; some bifunctional proline derivatives have been designed and investigated for various reactions.[6–20] The most important one of the reactions used proline derivatives as catalyst is aldol condensation which provides effective route to β-hydroxy carbonyl compounds which are important precursors of biologically active natural and synthetic compounds.[21-23] Several diamide derivatives of proline have been prepared and used for direct asymmetric aldol reaction successfully.[24-29] But, using of organic solvents as reaction medium is an obvious disadvantage of most of these proline derivatives from the environmental aspect. [30, 31] So, the development of new asymmetric organocatalysts which are effective in water is also important contribution to green chemistry.[32-35] But as far as we know, there are only few examples for the asymmetric direct aldol reactions in water in the literature.[36-43] In this study, we have designed, synthesized and investigated a new kind of proline based diamide asymmetric organocatalysts (Figure 1) for direct asymmetric aldol condensation. According to computational and experimental studies in the literature, double H-bonds interactions with carbonyl oxygen provide more electrophile activation and rigidity in transition state rather than single H-bonds. These interactions can increase the strength and directionality, induce the enantioselectivity and contribute the effectiveness of catalyst. [15,20,44,45] It was expected that diamide structures would show better H-bonding activity

than monoamide compounds due to two amide NH group. Besides, bulky groups were also chosen on amide moieties for steric interaction to improve the stereoselectivity. These new proline based diamide compounds are very effective organocatalysts with high enantioselectivity in water.

RESULTS AND DİSCUSSİON

The proline based diamide organocatalysts (**6a-f**) (Figure 1) were prepared by simple amidation reactions of *L*-proline. More detailed and as outlined in Scheme 1, after protection of *L*-proline, amidation with *L*-phenylalanine methyl ester, hydrolysis of ester group, second amidation with different amines and deprotection of Boc group according to literature procedure, [46] catalysts **6a-f** were successfully prepared and ^{1}H NMR, ^{13}C NMR, FTIR, LC-MS (QTOF) data were used to confirm the structure.

The catalytic activities of organocatalysts were investigated on the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone as a model reaction. To compare the catalytic activities of new diamide derivatives, the model reaction was carried out under different reaction conditions in the presence of benzoic acid co-catalyst. The reactions were investigated at room temperature or 0 ^{o}C with some typical solvents such as water, dichloromethane (DCM), THF/water or without any solvent. Promising results were obtained from the catalysts **6a**, **b**, **d** and **f** in water as shown in Table 1. Generally, benzoic acid, p-nitrobenzoic acid, TFA, acetic acid, tartaric acid have been investigated as co-catayst for this reaction via an enamine mechanism, while benzoic acid and p-nitrobenzoic acid have been found to be more effective ones in the literatures. [17, 19, 28, 46]

So, p-nitrobenzoic acid was also used as a co-catalyst. As one can see from the Table 2, considering the yield, enantioselectivity and diastereoselectivity, catalyst **6a** gave the best results (99% yield, 92% ee and 93:7 dr) and was chosen for further evaluation. This high activity may be due to the strong H-bond formation between amide N-H protons of catalyst and aldehyde (Figure 2).

To broaden the substrates of the reaction, different aliphatic ketones and aromatic aldehydes were furtherly studied in the presence of the optimal catalyst **6a** (Table 3). The aldol products are known in the literature, and their structure are in agreement with the literature data.[38, 39] The diastereomeric ratios and enantiomeric excesses were determined by chiral HPLC analysis of products by using literature methods.[30, 47, 48]

CONCLUSİON

As a result, we have designed and developed a new kind of proline based diamide organocatalysts and successfully used in the direct asymmetric aldol reaction of aliphatic ketones and aromatic aldehydes in water. Those new catalysts showed excellent catalytic activity (up to 99% yield), enantioselectivity (up to 95% ee) and good diasereoselectivity (up to 97:3). Especially, catalyst **6a**, a proline based tripeptide, as the most effective organocatalyst, gave the best results when different aliphatic ketones and aromatic aldehydes with electron withdrawing groups were used.

EXPERİMENTAL

All reagents were of commercial quality and reagent quality solvents were used without further purification. IR spectra were determined on a Perkin Elmer, Spectrum One FT-IR spectrometer and Bruker Tensor 27 spectrometer. NMR spectra were recorded on Varian-400 MHz High Resolution NMR spectrometer and Bruker Avance III 500 MHz spectrometer. Chemical shifts δ are reported in ppm with TMS as internal standart and the solvents are $CDCl_3$, CD_3OCD_3 and CD_3OD. Column chromatography was conducted on silica gel 60 (40–63 μM). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck). LC-MS (QTOF) spectra were obtained on Agilent G6530B model TOF/Q-TOF Mass Spectrometer. Optical rotations were measured with Bellingham Stanley ADP-410 Polarimeter. Chiral HPLC analysis were performed with Shimadzu HPLC (Daicel Chiralpak AD columns) equipped with SPD-20A detector and isopropanol-n-hexane mixtures as the eluent. The protection of *L*-proline[49, 50] and synthesis of compound **2**[51] and **3**[51] were carried out according to the literature procedure. Spectroscopic data of these compounds were in accordance with their structures.

Synthesis Of The Catalysts

General Procedure For Amidation Reactions

At 0^oC and with stirring, to the solution of *L*-*N*-Boc-proline (**2**) (0.92 mmol) in dry THF, HOBt (1.0 mmol) was added, and stirred for 10 min, then DCC (in the case of tyrosine methyl ester, DIC) (1.0 mmol) was added. The mixture was stirred at 0^oC for 1 h, and the amine or aminoalcohol (1.02 mmol) was added (in the case of amino acid ester hydrochloride, to the suspension of amino acid ester hydrochloride in dry THF,

triethylamine (0.5 mL) was added and stirred at room temperature for 1 h, and this solution was added to the first mixture). The reaction mixture was stirred at room temperature for 24 h, and the reaction was monitored by TLC. The formed precipitate was removed by filtration, and the filtrate was evaporated under vacuum. The residue was dissolved in 50 mL of ethyl acetate, the formed solution was washed successively with saturated aqueous solution of $NaHCO_3$ (30 ml x 3), 5% aqueous solution of $KHSO_4$ (30 ml x 3) and saturated aqueous solution of NaCl (30 ml x 3), and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated under vacuum to give the crude products which were purified by column chromatograpy on silica gel.

*(S)-tert-Butyl 2-(((S)-1-(((S)-1-methoxy-4-methyl-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidin-1-carboxylate (**5a**)*. White solid, yield 68%, mp 117-118°C; $[\alpha]_D^{20}$ -58.6 (c= 1.2, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, *J*=6.5 Hz, 3H), 0.83 (d, *J*=5.5 Hz, 3H),1.31 and 1.36 (s, 9H, rotamers), 1.44-1.54 (m, 3H), 1.64-1.67 (m, 1H), 1.75-2.06 (m, 3H), 3.00-3.39 (m, 4H), 3.63 (s, 3H), 4.11-4.16 (m, 1H) 4.45 and 4.49 (m, 1H), 4.58-4.62 (m, 1H), 6.22, 6.56 and 6.68 (brs, 2H, rotamers), 7.10-7.18 (m, 3H), 7.21-7.23 (m, 2H); 13C NMR (125 MHz, $CDCl_3$) δ 20.7, 21.7, 23.3, 23.5, 27.2, 27.9, 36.0, 39.9, 46.2, 49.8, 51.2, 52.3, 59.5, 79.6, 126.0, 127.5, 128.2, 135.4, 154.5, 169.5, 170.7, 171.7; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 490.2900. $C_{26}H_{39}N_3O_6$ requires 490.2917; IR (Atr) ν 3377, 3278, 3073, 3031, 2975, 2953, 2931, 2873, 1739, 1679, 1645, 1523 cm^{-1}.

General Procedure For Deprotection Of Boc Group

To the solution of *N*-Boc-protected compounds (**5 a-f**) (1.0 mmol) in dry CH_2Cl_2 (15 mL) at 0^oC, trifluoroacetic acid (27.0 mmol) was added dropwise over 5 min while stirring. The reaction mixture was stirred at 0 ^oC for 1 h and at room temperature for 2 h then 2M K_2CO_3 was added to adjust basic pH. The organic phase was washed with water, dried over $MgSO_4$, filtrated and evaporated to give the pure compounds.

*(S)-Methyl 4-methyl-2-((S)-3-phenyl-2-((S)-pyrrolidin-2-carboxyamido)-propanamido) pentanoate (**6a**)*. White solid, yield 68%, mp 153-154^oC; $[\alpha]_D^{20}$ -58.8 (c= 1.0, $CHCl_3$). 1H NMR (500 MHz, CD_3OD) δ 0.93 (d, *J*= 6.5 Hz, 3H), 0.97 (d, *J*= 6.0 Hz, 3H), 1.47-1.58 (m, 2H), 1.60-1.66 (m, 3H), 1.67-1.72 (m, 1H), 1.98-2.06 (m, 1H), 2.75-2.80 (m, 1H), 2.85-2.93 (m, 2H), 3.20 (dd, *J*= 13.75, 5.0 Hz, 1H), 3.59-3.62 (m, 1H), 3.72 (m, 3H), 4.48-4.51 (m, 1H), 4.69-4.72 (m, 1H), 7.20-7.29 (m, 5H); 13C NMR (125 MHz, CD_3OD) δ 21.8, 23.3, 25.9, 26.9, 31.8, 39.2, 41.4, 47.9, 52.1, 52.7, 54.9, 61.4, 127.8, 129.4, 130.4, 138.1, 173.6, 174.3, 177.3; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 390.2376. $C_{21}H_{31}N_3O_4$ requires 390.2393; IR (Atr) ν 3321, 3223, 3062, 3027, 2955, 2866, 1738, 1688, 1646, 1520 cm^{-1}.

General Procedure For Aldol Reaction

The catalyst **6a** (0.1 mmol) and p-nitrobenzoic acid (0.1 mmol) were stirred in water at 0 ^oC for 10 min. Then, aldehyde (1.0 mmol) and ketone (10.0 mmol) were added and the reaction mixture was stirred at 0 ^oC until the reaction completed. After evaporation of water, the crude products were purified by column chromatography eluted by

EtOAc/hexane. The enantioselectivity was determined by chiral HPLC with a Chiralpack AD column (UV detection set at 254 nm, i-PrOH/n-hexane as eluent).

ACKNOWLEDGEMENTS

We thank Yildiz Technical University Scientific Research Foundation (2013-01-02-KAP02) for financial support.

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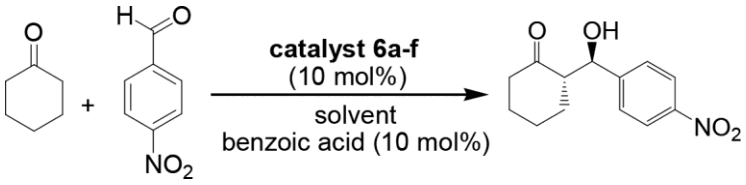
Table 1. Screening of organocatalysts for the aldol reaction with benzoic acid co-catalyst



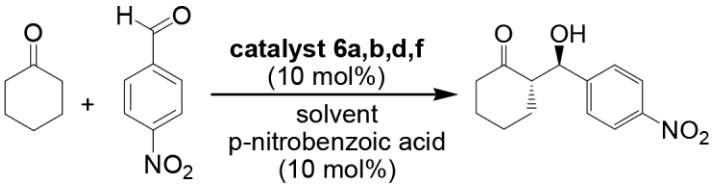
Catalyst	**Solvent**	**Temperature (^{o}C)**	**Reaction time (h)**	**dr[a] (anti/syn)**	**ee[a] (%) (anti)**	**Yield[b] (%)**
6a	CH_2Cl_2	rt	72	70:30	39	19
6a	H_2O	rt	48	63:37	84	92
6a	H_2O	0	24	74:26	88	81
6a	none	rt	48	54:46	67	95
6a	THF:H_2O (1:2)	rt	48	53:47	75	88
6b	CH_2Cl_2	rt	72	59:41	56	42
6b	H_2O	rt	48	62:38	80	85
6b	none	rt	24	82:18	67	93
6b	THF:H_2O (1:2)	rt	72	79:21	76	93
6c	CH_2Cl_2	rt	72	72:28	55	60
6c	H_2O	rt	24	61:39	60	97
6c	none	rt	24	66:34	62	97
6d	CH_2Cl_2	rt	72	69:31	60	63
6d	H_2O	rt	24	67:33	80	99
6d	H_2O	0	24	84:16	89	89
6d	none	rt	24	52:48	83	99
6d	THF:H_2O (1:2)	rt	48	77:23	80	98

6e	CH_2Cl_2	rt	72	68:32	44	65
6e	H_2O	0	24	69:31	57	90
6e	none	rt	24	67:33	63	54
6f	CH_2Cl_2	rt	72	76:24	57	51
6f	H_2O	rt	24	95:5	77	90
6f	none	rt	24	68:32	63	97
6f	THF/H_2O (1:2)	Rt	48	77:23	72	57

[a] Determined by chiral-phase HPLC analysis.

[b] Combined yields of isolated diastereomers.

Table 2. Screening of organocatalysts for the aldol reaction with p-nitrobenzoic acid co-catalyst

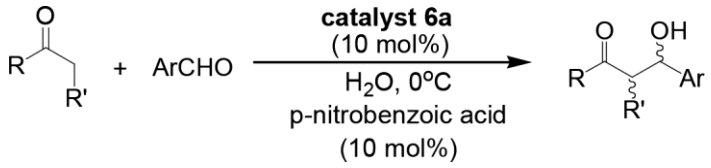


Catalyst	**Solvent**	**Temperature (^{o}C)**	**Reaction time (h)**	**dr[a] (anti/syn)**	**ee[a] (%) (anti)**	**Yield[b] (%)**
6a	H_2O	rt	24	80:20	86	71
6a	H_2O	0	48	93:7	92	99
6a	none	rt	24	74:26	70	97
6b	H_2O	rt	24	86:14	84	92
6d	H_2O	rt	24	89:11	83	98
6d	H_2O	0	72	80:20	88	96
6d	none	rt	48	55:45	82	76
6d	none	0	48	93:7	86	95
6f	H_2O	rt	24	82:18	75	95
6f	H_2O	0	24	95:5	85	99

[a] Determined by chiral-phase HPLC analysis.

[b] Combined yields of isolated diastereomers.

Table 3. The aldol reactions of **6a** with different aldehydes



Ketone	**Aldehyde**	**Reaction time (h)**	**dr**[a] **(anti/syn)**	**ee**[a] **(%) (anti)**	**Yield**[b] **(%)**
Cyclohexanone	2-Nitrobenzaldehyde	48	97:3	93	97
Cyclohexanone	3-Nitrobenzaldehyde	48	82:18	92	98
Cyclohexanone	4-Nitrobenzaldehyde	48	93:7	92	99
Cyclohexanone	4-Cyanobenzaldehyde	24	79:21	87	91
Cyclohexanone	4-Bromobenzaldehyde	48	96:4	95	98
Cyclohexanone	4-(Trifluoromethyl)benzaldehyde	48	80:20	89	94
Cyclopentanone	4-Nitrobenzaldehyde	48	32:68	65[c]	98
Acetone	4-Nitrobenzaldehyde	48	-	81	55

[a] Determined by chiral-phase HPLC analysis.

[b] Combined yields of isolated diastereomers.

[c] *syn* isomer

Scheme 1. The synthetic route of organocatalysts

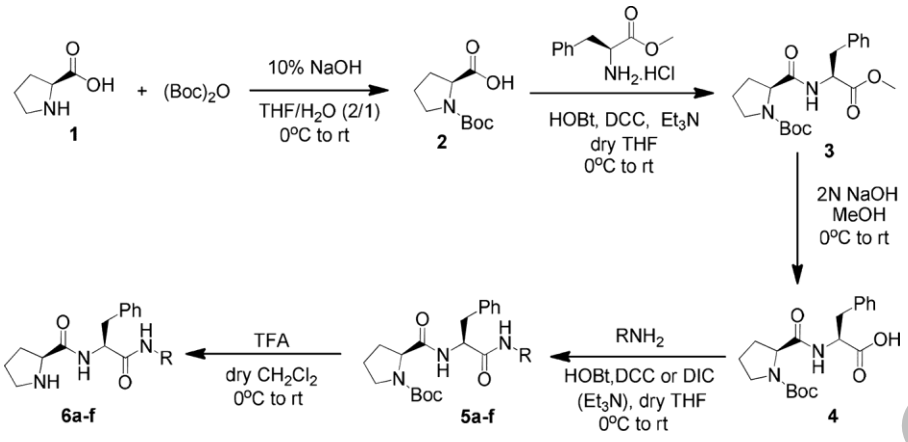


Figure 1. The structures of diamide organocatalysts (**6a**-**f**)

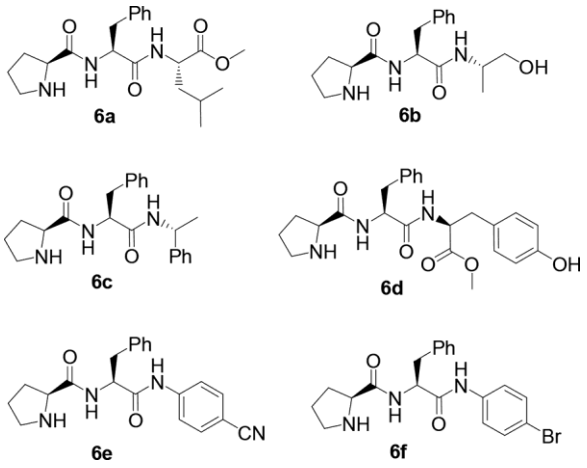


Figure 2. Proposed transition state