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Dipeptide-catalyzed direct asymmetric aldol reactions in the presence of water

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Abstract—The L-proline-based dipeptide has been discovered and developed as an efficient catalyst for the direct asymmetric aldol reactions of unmodified ketones with various aldehydes including aromatic, aliphatic, heteroaromatic, and unsaturated aldehydes in the presence of water at 0 °C. The resulted methodology and optimal conditions led to the corresponding aldol products with high yields (up to 94%) and good enantioselectivities (up to 97% ee).

1. Introduction

The aldol reaction is one of the most powerful methods for the formation of C–C bonds in organic synthesis.[1] In recent years, organocatalytic asymmetric direct aldol reactions have received great attention, and various organocatalysts have been developed in order to achieve high diastereomeric and enantiomeric selectivities.[2] However, these reactions were typically performed in organic solvents, such as DMSO, DMF, or chloroform.[3] Although addition of a small amount of water often accelerates reactions and/or improves enantioselectivities,[4] large amount of water or aqueous buffer typically resulted in low yield with low or no enantioselectivity.[5] Water as a preferred reaction solvent offers a series of advantages over organic solvents, such as safety, convenience, economy, and environmental benign, etc. Therefore, utilizing water as reaction solvent for the development of enantioselective aldol reactions is urgently needed, especially for the discovery of new small organic molecule catalysts to catalyze this critical reaction. Recently, while our research is in progress, Hayashi,[6] Barbas,[7] Zhao,[8] Pericas,[9] and Gong[10] reported the direct asymmetric aldol reactions catalyzed by some proline derivatives with high diastereomeric and enantioselectivities in the presence of water or in water. Therefore, we are prompted to disclose our discovery in this important area. Herein, we report a new dipeptide-based organocatalyst that efficiently catalyzed direct asymmetric aldol reaction in the presence of water with high yields (up to 94%) and good enantioselectivities (up to 97% ee).

2. Results and discussion

2.1. Design and preparation of catalysts

We have previously reported that a combination of Pro–Phe (**1**) with *N*-methyl morpholine (NMM) as a base and PEG400 as a surfactant (Pro–Phe/NMM/PEG400) efficiently catalyzed the asymmetric aldol reactions in DMSO.[11] Recently, Gong,[12] Kudo,[13] Tsogoeva,[14] Córdova,[15] and Lu[16]also examined the aldol reactions catalyzed by some amino acids and small dipeptides in different reactive systems including organic solvents, organic solvents/H_2O mixture or aqueous media. Though the catalysts used in these reports were easily synthesized, there were still no very successful examples on the use of this kind of catalysts in direct asymmetric aldol reactions for a broad scope of new substrates and desired results in water. Inspired by aldolase enzymes and antibodies catalyzed asymmetric biochemical aldol reactions in water[17] and based on our previous work,[11] we applied our catalytic system in the aldol reaction of cyclohexanone (**6a**) with 4-pyridinecarbaldehyde (**7a**) in the presence of water. It is interesting to find that the reaction proceeded very smoothly under emulsion conditions with good yield and enantioselectivity (Table 1, entry 1, 91%, 73% ee). We were encouraged by this result and four new dipeptides (Fig. 1, **2**–**5**) were designed by replacing the benzyl in Pro–Phe (**1**) with various

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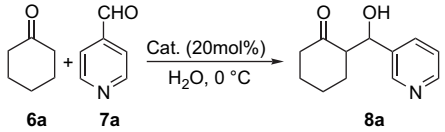
Table 1. Screening of reaction conditions in the direct asymmetric aldol reaction of cyclohexanone (**6a**) with 4-pyridinecarbaldehyde (**7a**) in the presence of water[a]



6a **7a** **8a**

Entry	Catalyst	Time (h)	*T* (°C)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[c] (%)
1	Pro–Phe (**1**)	3.5	0	91	72:28	73
2	Pro–Leu (**2**)	3.5	0	90	58:42	69
3	Pro–Ile (**3**)	3	0	92	67:33	75
4	Pro–Tyr (**4**)	2.5	0	94	68:32	77
5	Pro–Trp (**5**)	2.5	0	92	78:22	85
6	Pro–Trp (**5**)	2	10	93	69:31	78
7	Pro–Trp (**5**)	2	20	94	60:40	77
8[d]	Pro–Trp (**5**)	6	0	88	63:37	75
9[e]	Pro–Trp (**5**)	2.5	0	93	76:24	85

[a] Reaction was performed in a solution of 1 mmol scale of aldehyde and 6 equiv of ketone with 0.2 mmol catalyst, 0.2 mmol NMM, 0.05 mmol PEG400, and 1.5 mL water at 0 °C.
[b] Isolated yield of the corresponding product.
[c] Determined by chiral-phase HPLC.
[d] Donor **6a** (2 mmol, 2 equiv) was used.
[e] Donor **6a** (4 mmol, 4 equiv) was used.

larger side chains to further improve the diastereo- and enantioselectivities of the aldol reactions. The design of new catalysts was based on the following two principles: (1) keeping the proline unit and the hydrogen atom connected with the nitrogen of amide unit in the catalyst is necessary, which has been demonstrated in our previous work;[11] (2) a small organic catalyst with appropriate hydrophobic groups should assemble with hydrophobic reactants in water and sequester the transition state from water, which was hypothesized and demonstrated by Barbas.[8]

Dipeptides **1–5** were synthesized from the condensation of Boc-Pro-OH with the corresponding amino acid methyl ester hydrochlorides, following deprotection with NaOH and trifluoroacetic acid in sequence according to the general method for the preparation of dipeptides.[18]

2.2. Screening of catalysts and optimization of reaction conditions

The catalytic efficiency of dipeptides **1–5** was examined by the direct asymmetric aldol reaction of cyclohexanone with 4-pyridylaldehyde in the presence of water, and the results are listed in Table 1.

It can be seen from Table 1 that all the dipeptides utilized gave excellent yields (>90%), however, the enantioselectivities varied (range from 69% to 85% ee). Size of the side chains in dipeptides significantly influenced the catalytic efficiency. For example, the catalyst **5** containing the largest side chain gave the best result with 85% ee and 78:22 dr (entry 5), and the catalyst **2** containing the smallest side chain showed the lowest catalytic selectivity (entry 2, 69% ee and 58:42 dr). Raising the temperature slightly accelerated the reaction, but the ee and dr values decreased in some extent (entries 5–7). Entries 8 and 9 showed the effects of the ratios of donor **6a** to acceptor **7a** on the reaction rate and the selectivity. The decrease of their ratio from 4:1 to 2:1 led to slightly lower yield and selectivity (entry 8), and the increase of their ratio from 4:1 to 6:1 did not improve the yield and selectivity (entry 9). Therefore, the ratio of 4:1 was most suitable and adopted for further studies.

We further investigated the critical roles and effects of bases and surfactants on the asymmetric aldol reaction. In order to get more accurate results, 4-nitrobenzaldehyde (**7b**) was selected as the acceptor to react with **6a** in the presence of catalyst **5** due to its lower activity and longer reaction time than **7a**. As shown in Table 2, in the absence of both base and surfactant, only trace of product was detected by TLC even after 20 h (entry 1). However, when the base NMM or the surfactant polyethylene glycol 400 (PEG400) was used separately in the reaction, the aldol reaction products were obtained in yields of 90% and 60%, *anti*:*syn* ratios of 87:13 and 97:3, ee values of 77% and 90%, respectively (entries 2 and 3). Further, the yield and enantioselectivity are all excellent in the presence of both base and surfactant PEG400 (entry 4, yield of 92% and 92% ee). Therefore, the presence of base and surfactant is definitely essential for the success of this reaction. According to the phenomenon of the experiment, most of the catalyst was excluded from the reaction system as a form of solid in the absence of base (entry 3), and contrastively, the emulsion reaction system was formed in the presence of the base (entry 4), we presumed that the equivalent of catalyst and base might form the carboxylate of Pro–Trp under the reaction conditions. As a comparison, we also carried out the reaction in DMSO (entry 5) and obtained the aldol product in yield of 84% with 85% ee, which are obviously

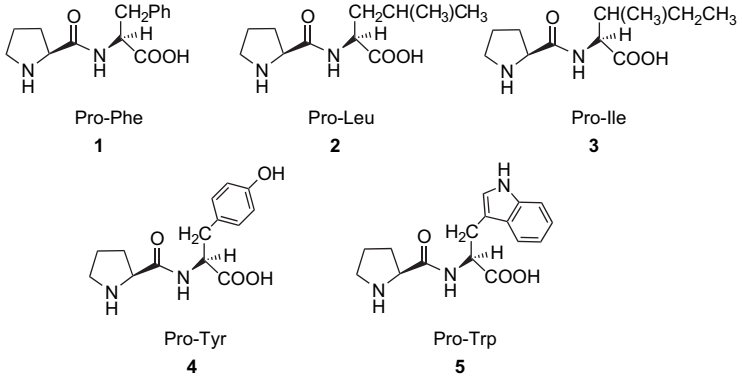
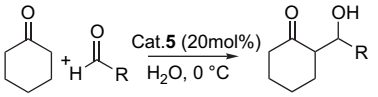


Figure 1. The structure of dipeptides **1–5**.

Table 2. Efficiency of different additives for the direct asymmetric intermolecular aldol reaction between **6a** and **7a** or **7b** in the presence of water[a]



6a **7a-b**

8a: R=4-pyridyl
8b: R=4-nitrophenyl

Entry	Product	Base[b]	Surfactant	Time (h)	Yield[c] (%)	dr[d] *anti*:*syn*	ee[d] *anti* (%)
1	**8b**	—	—	20	Trace	—	—
2	**8b**	NMM	—	18	90	87:13	77
3	**8b**	—	PEG400	20	60	91:9	90
4	**8b**	NMM	PEG400	16	92	81:19	92
5[e]	**8b**	NMM	PEG400	8	84	90:10	85
6	**8a**	NMM	PEG400	2.5	93	76:24	85
7	**8a**	DMAP	PEG400	3	92	83:17	79
8	**8a**	Pyridine	PEG400	4	90	83:17	80
9	**8a**	Triethylamine	PEG400	2	93	80:20	78
10	**8a**	*N*,*N*-Diisopropyl ethylamine	PEG400	2.5	92	80:20	79
11	**8a**	HMTA	PEG400	3.5	91	78:22	84
12	**8a**	*N*-Methyl piperidine	PEG400	2.5	92	85:15	80
13	**8a**	Hexamethyl disilylamine	PEG400	2.5	91	80:20	81
14	**8a**	1-Methyl pyrrolidine	PEG400	2.5	93	78:22	80
15	**8a**	DABCO	PEG400	2.5	93	77:23	86
16	**8a**	NMM	PGME5000	2.5	92	75:25	81
17	**8a**	DABCO	PGME5000	2.5	93	77:23	80
18	**8a**	NMM	TBAB	2.5	92	50:50	82
19	**8a**	DABCO	TBAB	2.5	92	50:50	82
20	**8a**	NMM	SDS	2.5	93	75:25	86
21	**8a**	DABCO	SDS	2.5	92	82:18	80

[a] Reaction was performed at 1 mmol scale of the aldehyde and 4 equiv of ketone with catalyst **5** (0.2 mmol), base (0.2 mmol), and surfactant (0.05 mmol) in 1.5 mL water.
[b] NMM: *N*-methylmorpholine; DMAP: 4-(dimethylamino)pyridine; HMTA: hexamethylenetetramine; DABCO: 1,4-diazabicyclo[2.2.2]octane; PEG400: polyethylene glycol 400; TBAB: tetrabutylammonium bromide; SDS: sodium dodecyl sulfate; PGME5000: propylene glycol methyl ether.
[c] Isolated yield of the corresponding product.
[d] Determined by chiral-phase HPLC.
[e] DMSO as solvent.

lower than that in the presence of water (entry 4). So water is essential for this reaction.

Subsequently, the influence of different amines with highly steric hindrance on the reaction by using catalyst **5** (20 mol %) and PEG400 (5 mol %) was further studied. The reaction of **7a** with **6a** was used as a model reaction (entries 6–15). The results showed that all the amines provided excellent yields (90–93%), whereas the enantioselectivities were different. Among the screened amines, both NMM and 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the best enantioselectivities of 85% ee (entry 6) and 86% ee (entry 15), respectively.

To further optimize the reaction conditions, we then turned our attention to explore the best surfactant and the combination of base with surfactant in the presence of NMM or DABCO (entries 16–21). When tetrabutyl ammonium bromide (TBAB) was used as a surfactant, good enantioselectivity was observed, however, there was no diastereoselectivity (entries 18 and 19); combination of DABCO with sodium dodecyl sulfate (SDS) significantly increased the diastereoselectivity (*anti*:*syn*, 82:18), but the enantioselectivity slightly decreased; the combination of NMM with SDS (entry 20, *anti*:*syn* 75:25 and 86% ee) gave the similar result as DABCO/PEG400 (entry 15, *anti*:*syn* 77:23 and 86% ee). Thus, the combination systems of NMM/SDS (A) and DABCO/PEG400 (B) were superior to the others.

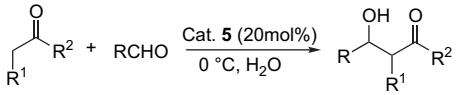
Based on our extensive screening results, we concluded that the optimal reaction conditions were to utilize Pro–Trp (**5**) as a catalyst, NMM/SDS (A) or DABCO/PEG400 (B) as an additive, and H_2O as solvent at 0 °C. In the reaction system, the base might form the carboxylate with catalyst, which could increase the solubility in water; the surfactant could increase the interfacial areas of water and organic reagent. Therefore, it should be the cooperation of catalyst, base, and surfactant, which led to the effective catalytic activity of our reaction system.

2.3. Substrate generality

Under our optimized reaction conditions, the application of dipeptide **5** in direct asymmetric intermolecular aldol reaction between different acceptors and donors was further explored. A series of aldehyde acceptors, including aromatic, aliphatic, heteroaromatic, and unsaturated aldehydes, were examined. Subsequently, some ketone donors were investigated. The data are summarized in Table 3.

It can easily be seen from Table 3 that all studied aldol reactions catalyzed by Pro–Trp **5** in the presence of water afforded high yields (up to 94%) and splendid selectivities (up to 99:1 dr and 97% ee). The most noticeable advantage of our discovery is that the reaction can be applied to a variety of acceptors and donors. Especially, when **6a** was used as a donor, the reactions with a series of aldehydes, including aromatic, aliphatic, heteroaromatic, and unsaturated

Table 3. Reactions of aliphatic and cyclic ketones (**6a–d**) with various aldehydes (**7a–l**) catalyzed by catalyst **5** in the presence of water[a]



Entry	R^1, R^2	R	Product	Additive[b]	Time (h)	Yield[c] (%)	dr[d] *anti*:*syn*	ee[d] *anti*:*syn* (%)
1	$-(CH_2)_4-$ (**6a**)	Pyridin-4-yl (**7a**)	**8a**	B	2.5	93	77:23	86:-
2	$-(CH_2)_4-$ (**6a**)	4-Nitrophenyl (**7b**)	**8b**	A	16 (20)[e]	94 (48)[e]	83:17 (90:10)[e]	92:- (70:-)[e]
3	$-(CH_2)_4-$ (**6a**)	4-Nitrophenyl (**7b**)	**8b**	B	16	93	90:10	97:-
4	$-(CH_2)_4-$ (**6a**)	2-Nitrophenyl (**7c**)	**8c**	B	26	88	>99:1	89:-
5	$-(CH_2)_4-$ (**6a**)	3-Nitrophenyl (**7d**)	**8d**	A	20	89	90:10	80:-
6	$-(CH_2)_4-$ (**6a**)	4-Cyanophenyl (**7e**)	**8e**	A	28	94	93:7	85:-
7	$-(CH_2)_4-$ (**6a**)	Phenyl (**7f**)	**8f**	B	208	72	98:2	88:-
8	$-(CH_2)_4-$ (**6a**)	6-Nitro-1,3-dihydroisobenzofuran-5-yl (**7g**)	**8g**	A	230	70	89:11	93:-
9	$-(CH_2)_4-$ (**6a**)	6-Nitro-1,3-dihydroisobenzofuran-5-yl (**7g**)	**8g**	B	260	68	>99:1	95:-
10	$-(CH_2)_4-$ (**6a**)	4-Methyloxyphenyl (**7h**)	**8h**	A	210	67	95:5	83:-
11	$-(CH_2)_4-$ (**6a**)	2-Chlorophenyl (**7i**)	**8i**	A	160	73	99:1	90:-
12	$-(CH_2)_4-$ (**6a**)	5-Nitrofuran-2-yl (**7j**)	**8j**	A	12	90	53:47	85:83
13	$-(CH_2)_4-$ (**6a**)	Styryl (**7k**)	**8k**	A	32	81	76:24	72:-
14	$-(CH_2)_3-$ (**6b**)	2-Nitrophenyl (**7c**)	**8l**	B	8	82	41:59	88:40
15	$-(CH_2)_3-$ (**6b**)	3-Nitrophenyl (**7d**)	**8m**	B	18	80	40:60	81:72
16	$-(CH_2)_3-$ (**6b**)	4-Nitrophenyl (**7b**)	**8n**	B	8	85	35:65	79:62
17	H, CH_3 (**6c**)	4-Nitrophenyl (**7b**)	**8o**	A	3	94	—	58
18	H, CH_3 (**6c**)	2-Propyl (**7l**)	**8p**	A	70	81	—	67
19	2-Propyl, CH_3 (**6d**)	4-Nitrophenyl (**7b**)	**8q**	A	180	67	95:5	83:-

[a] Reaction was performed at 1 mmol scale of aldehyde and 4 equiv of ketone in 1.5 mL water at 0 °C.
[b] A catalyst/NMM/SDS=0.2:0.2:0.05 (mmol); B catalyst/DABCO/PEG400=0.2:0.2:0.05 (mmol).
[c] Isolated yield of the corresponding product.
[d] Determined by chiral-phase HPLC.
[e] The dipeptide Val–Val as the catalyst.

aldehydes, were completed smoothly and excellently (from entry 1 to 13). It can be concluded from the results that the aromatic aldehydes with substituents at 2-position generally gave excellent diastereoselectivities (entries 4, 9, and 11; *anti*:*syn*≥99:1). In terms of enantioselectivity, the aromatic aldehydes with electron-withdrawing groups usually afforded higher enantioselectivity as compared to other aldehydes. Such as, **7b** and 6-nitro-1,3-dihydroisobenzofuran-5-carbaldehyde (**7g**) provided the highest ee values in both A and B additive systems (entries 2, 3 and entries 8, 9; >92% ee). During our studying progress, Córdova[15] reported aldol reaction catalyzed by dipeptide Val–Val in water, so we compared the Val–Val with Pro–Trp in the optimal reaction conditions. The dipeptide Pro–Trp exhibited the better catalytic activities and the results are shown in Table 3. When 2-nitrobenzaldehyde (**7c**) and 3-nitrobenzaldehyde (**7d**) were utilized as acceptors, the enantioselectivities reached 89% ee and 80% ee, respectively. Besides, both heteroaromatic aldehydes, the **7a** and 5-nitrofuran-2-carbaldehyde (**7j**), were also good substrates to be used in the aldol reactions (entry 1, 86% ee; entry 12, 85% ee). Particularly, the cinnamaldehyde (**7k**) was used as acceptor with good yield and moderate enantioselectivity for the first time (entry 13, 81% yield and 72% ee). Compared with **6a**, cyclopentanone (**6b**) and 4-methyl-2-pentanone (**6d**) as donors also afforded good enantioselectivities (entries 14–16 and 19, 79–88% ee). Moreover, the donor acetone (**6c**) exhibited moderate enantioselectivities (entry 17, 58% ee; entry 18, 67% ee).

Though the catalytic effects in enantioselectivities were good in most cases, the reaction times were greatly different (from 2.5 h to 260 h), and the yields of the products varied. When **6a** was selected as the donor, electron-poor aromatic aldehydes (from entry 2 to 6 and entry 12) were favorable to the reaction. Therefore, the reactions typically completed much faster than those of the aromatic aldehydes with an electron-donating group on the phenyl rings (entries 9 and 10). When the same acceptor was utilized, **6b** and **6c** reacted faster than **6a** (compare: entry 4 and entry 14; entry 5 and entry 15; entry 3 and entry 17; etc.). In contrast, **6d** required longer time to complete the reaction and also gave moderate yield (entry 19, 180 h, 67%).

3. Conclusions

We have developed and firstly utilized dipeptide Pro–Trp as an effective organocatalyst. Extensive studies indicated that this catalyst efficiently catalyzed the direct asymmetric intermolecular aldol reaction in the presence of water at 0 °C. The methodology and reaction conditions can be broadly utilized to a variety of cyclic or acyclic ketones and various aldehydes, including aromatic, aliphatic, heteroaromatic, and unsaturated aldehydes. The favorable additives were discovered to improve the catalytic effects. And in all cases, the corresponding catalytic aldol products were obtained in high yields (up to 94%) and good enantioselectivities (up to 97% ee).

4. Experimental section

4.1. General remarks

THF were dried with P_2O_5 for four days and refluxed over diphenylketone and sodium, and then distilled onto 4 Å

molecular sieves after the reagent became blue. Some reagents were re-distilled before use. The common solvents were used directly without further purification. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} glass backed plates. Melting points were measured on an X_4-type micro-melting point apparatus and were uncorrected. Mass spectrometric analyses were performed on a ZAB-2F spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury-300 spectrometer in needful D-reagents with tetramethylsilane (TMS) as an internal standard. The maximum wavelength values were recorded with a TU-1901-type UV-spectrophotometer. Enantiomeric excess values of aldol products were determined by analytical HPLC using Daicel Chiralpak AD or AS analytical columns with 2-propanol in hexanes as the eluent.

4.2. Preparation of catalysts 1–5

The synthesis of catalysts **1–5** were carried out according to the standard method of dipeptide preparation.[18]

4.2.1. Pro–Phe (1). White powder; mp 236–237 °C; $[\alpha]_D^{25}$ −50 (*c* 2, HCl aq); ^{1}H NMR (300 MHz, D_2O): δ 7.11–7.23 (m, 5H), 4.26–4.30 (q, *J*=5.1 Hz, 1H), 4.05–4.08 (m, 1H), 3.17–3.22 (m, 2H), 3.04 (q, *J*=5.1 Hz, 1H), 2.79 (q, *J*=9.0 Hz, 1H), 2.15–2.28 (m, 1H), 1.82–1.88 (m, 3H); ESI-MS *m*/*z* 263.2 (M^++1).

4.2.2. Pro–Leu (2). White powder; mp 235–237 °C; $[\alpha]_D^{25}$ −55 (*c* 0.4, HCl aq); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.01–8.04 (m, 1H), 5.76 (s, 1H), 3.58–3.64 (m, 1H), 1.17–1.88 (m, 7H), 1.09 (t, *J*=7.2 Hz, 2H), 0.82–0.87 (m, 6H); ESI-MS *m*/*z* 229.2 (M^++1).

4.2.3. Pro–Ile (3). White powder; mp 231–232 °C; $[\alpha]_D^{25}$ −44 (*c* 2, HCl aq); ^{1}H NMR (300 MHz, CD_3OD): δ 4.23–4.27 (m, 2H), 2.37–2.44 (m, 2H), 1.89–2.14 (m, 4H), 1.51–1.59 (m, 1H), 1.12–1.22 (m, 1H), 0.89–0.96 (m, 6H); ESI-MS *m*/*z* 229.2 (M^++1).

4.2.4. Pro–Tyr (4). White powder; mp 232–234 °C; $[\alpha]_D^{25}$ −26 (*c* 2, HCl aq); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.20 (s, 1H), 8.12 (s, 1H), 6.92 (d, *J*=8.4 Hz, 2H), 6.62 (d, *J*=8.4 Hz, 2H), 4.31 (s, 1H), 3.59–3.63 (m, 1H), 2.82–2.98 (m, 3H), 2.67–2.75 (m, 1H), 1.92–1.98 (m, 1H), 1.51–1.66 (m, 3H); ESI-MS *m*/*z* 278.2 (M).

4.2.5. Pro–Trp (5). White powder; mp 183–184 °C; $[\alpha]_D^{25}$ −32 (*c* 1, HCl aq); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.36 (d, *J*=7.2 Hz, 1H), 7.51 (d, *J*=7.8 Hz, 1H), 7.32 (d, *J*=7.8 Hz, 1H), 6.94–7.10 (m, 3H), 4.48 (q, *J*=5.4 Hz, 1H), 3.77 (q, *J*=5.7 Hz, 1H), 3.06–3.24 (m, 2H), 2.87–2.95 (m, 1H), 2.75–2.83 (m, 1H), 1.99–2.11 (m, 1H), 1.57–1.73 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.1, 171.4, 136.0, 127.3, 123.6, 120.9, 118.3, 111.3, 109.6, 59.4, 53.0, 48.6, 46.1, 29.9, 27.1, 24.7; ESI-MS *m*/*z* 301.1 (M).

4.3. General procedure for aldol reactions

To a solution of aldehyde acceptor (1 mmol) and ketone donor (4 mmol) in 1.5 mL of H_2O were added the catalyst (20 mol %), base (20 mol %), and surfactant (5 mol %). The resulting reaction mixture was stirred at 0 °C for needful time. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated. The residue was subjected directly to flash silica gel chromatographic column using petroleum–ethyl acetate as the eluent to afford the corresponding pure aldol adducts.

4.3.1. 2-[Hydroxyl(pyridin-4-yl)methyl]cyclohexanone (8a). White powder; mp 108–109 °C; 93% yield; 86% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 254 nm; t_R (*anti*)=29.79 min (major) and 27.10 min, t_R (*syn*)=22.81 min and 19.68 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55–8.59 (m, 2H), 7.24–7.27 (m, 2H), 4.77–5.39 (dd, 1H), 2.31–2.64 (m, 3H), 2.09–2.14 (m, 1H), 1.82–1.86 (m, 1H), 1.59–1.76 (m, 3H), 1.34–1.56 (m, 1H); HRMS for $C_{12}H_{15}NO_2$ (M+H): calcd 206.11756, obsd 206.11784.

4.3.2. 2-[Hydroxyl(4-nitrophenyl)methyl]cyclohexanone (8b).[19,20] White powder; mp 129–130 °C; 93% yield; 97% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 268 nm; t_R (*anti*)=45.64 min (major) and 42.01 min, t_R (*syn*)=37.83 min and 26.57 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.24 (m, 2H), 7.48–7.54 (m, 2H), 4.90 (d, *J*=8.1 Hz, 1H), 4.09 (s, 1H), 2.32–2.64 (m, 3H), 2.08–2.16 (m, 1H), 1.82–1.86 (m, 1H), 1.35–1.73 (m, 4H).

4.3.3. 2-[Hydroxyl(2-nitrophenyl)methyl]cyclohexanone (8c).[20] Yellow powder; mp 116–118 °C; 88% yield; 89% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 209 nm; t_R (*anti*)=27.55 min and 25.38 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J*=7.8 Hz, 1H), 7.77 (d, *J*=7.8 Hz, 1H), 7.64 (t, *J*=7.2 Hz, 1H), 7.40–7.46 (m, 1H), 5.44 (d, *J*=7.2 Hz, 1H), 4.11 (br, 1H), 2.73–2.81 (m, 1H), 2.29–2.48 (m, 2H), 2.04–2.14 (m, 1H), 1.55–1.86 (m, 5H).

4.3.4. 2-[Hydroxyl(3-nitrophenyl)methyl]cyclohexanone (8d).[20] White powder; mp 69–71 °C; 89% yield; 80% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 263 nm; t_R (*anti*)=31.87 min and 24.65 min (major), t_R (*syn*)=21.82 min (major) and 19.65 min]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–8.22 (m, 2H), 7.67 (d, *J*=7.5 Hz, 1H), 7.53 (t, *J*=7.8 Hz, 1H), 4.90 (d, *J*=8.4 Hz, 1H), 4.14 (d, *J*=2.4, 1H), 2.58–2.67 (m, 1H), 2.32–2.54 (m, 2H), 2.09–2.16 (m, 1H), 1.82–1.86 (m, 1H), 1.36–1.71 (m, 4H).

4.3.5. 2-[Hydroxyl(4-cyanophenyl)methyl]cyclohexanone (8e).[20] White powder; mp 82–83 °C; 94% yield; 85% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 267 nm; t_R (*anti*)=32.54 min (major) and 26.75 min, t_R (*syn*)=23.80 min and 20.80 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=8.1 Hz, 2H), 7.43 (d, *J*=8.1 Hz, 2H), 4.84 (d, *J*=8.4 Hz, 1H), 4.07 (s, 1H), 2.47–2.62 (m, 2H), 2.31–2.41 (m, 1H), 2.08–2.15 (m, 1H), 1.81–1.83 (m, 1H), 1.49–1.73 (m, 3H), 1.32–1.41 (m, 1H).

4.3.6. 2-[Hydroxyl(phenyl)methyl]cyclohexanone (8f).[20,21] Light yellow powder; mp 99–101 °C; 72% yield;

88% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 215 nm; t_R (*anti*)=28.44 min and 24.63 min (major), t_R (*syn*)=22.81 min and 19.43 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.35 (m, 5H), 4.77 (d, J=9.0 Hz, 1H), 3.95 (br, 1H), 2.57–2.66 (m, 1H), 2.05–2.51 (m, 2H), 1.56–1.58 (m, 1H), 1.48–1.53 (m, 4H), 1.27–1.32 (m, 1H).

4.3.7. 2-[Hydroxy(6-nitro-1,3-dihydroisobenzofuran-5-yl)methyl]cyclohexanone (8g). Light yellow powder; mp 165–166 °C; 68% yield; 95% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 214 nm; t_R (*anti*)=58.83 min and 37.32 min (major), t_R (*syn*)=33.22 min (major) and 30.14 min]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.26 (s, 1H), 6.22 (s, 2H), 5.69 (d, J=7.5 Hz, 1H), 5.57 (dd, 1H), 2.39–2.51 (m, 2H), 2.17–2.26 (m, 1H), 1.92–2.09 (m, 4H); HRMS for $C_{14}H_{15}NO_6$ (M+Na): calcd 316.07916, obsd 316.07943.

4.3.8. 2-[Hydroxyl(4-methoxyphenyl)methyl]cyclohexanone (8h).[21] White powder; mp 74–76 °C; 67% yield; 83% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 218 nm; t_R (*anti*)=28.10 min (major) and 27.35 min, t_R (*syn*)=18.64 min and 15.94 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.26 (m, 2H), 6.86–6.90 (m, 2H), 4.74 (d, J=8.7 Hz, 1H), 3.92 (s, 1H), 3.80 (s, 3H), 2.31–2.64 (m, 3H), 2.05–2.13 (m, 1H), 1.48–1.81 (m, 4H), 1.19–1.33 (m, 1H).

4.3.9. 2-[Hydroxyl(2-chlorophenyl)methyl]cyclohexanone (8i).[20] White powder; mp 89–91 °C; 73% yield; 90% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 210 nm; t_R (*anti*)=15.63 min and 13.64 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.56 (m, 4H), 5.34 (dd, J=8.1 Hz, 1H), 4.10 (br, 1H), 1.53–2.69 (m, 9H).

4.3.10. 2-[Hydroxyl(5-nitrofuran-2-yl)methyl]cyclohexanone (8j). Yellow oil; 90% yield; 85% ee (*anti*); 83% ee (*syn*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 316 nm; t_R (*anti*)=27.31 min and 22.83 min (major), t_R (*syn*)=17.48 min and 18.88 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (q, J=3.9 Hz, 1H), 6.59–6.61 (m, 1H), 4.81–5.37 (dd, 1H), 2.92–3.02 (m, 1H), 2.40–2.46 (m, 2H), 2.12–2.16 (m, 1H), 1.60–1.94 (m, 5H); HRMS for $C_{11}H_{13}NO_5$ (M+H): calcd 2240.08665, obsd 240.08710.

4.3.11. (*E*)-2-(1-Hydroxy-3-phenylallyl)cyclohexanone (8k).[22] White powder; mp 119–121 °C; 81% yield; 72% ee (*anti*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 255 nm; t_R (*anti*)=21.63 min and 18.64 min (major), t_R (*syn*)=17.65 min and 15.01 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, 2H), 7.31 (t, J=7.8 Hz, 2H), 7.20–7.26 (m, 1H), 6.58–6.66 (m, 1H), 6.15–6.25 (m, 1H), 4.43 (t, J=4.8 Hz, 1H), 2.31–2.59 (m, 3H), 2.07–2.13 (m, 2H), 1.87–1.94 (m, 1H), 1.63–1.78 (m, 3H).

4.3.12. 2-[Hydroxyl(2-nitrophenyl)methyl]cyclopentanone (8l).[23] Yellow oil; 82% yield; 88% ee (*anti*); 40% ee (*syn*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 209 nm; t_R (*anti*)=25.03 min and 23.46 min (major), t_R (*syn*)=20.00 min and 17.13 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J=8.1 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.75 (t, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 5.68 (d, J=4.8 Hz, 1H), 5.55 (s, 1H), 1.93–2.43 (m, 5H), 1.62–1.68 (m, 2H).

4.3.13. 2-[Hydroxyl(3-nitrophenyl)methyl]cyclopentanone (8m).[23] White powder; mp 72–74 °C; 80% yield; 81% ee (*anti*), 72% ee (*syn*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 269 nm; t_R (*anti*)=34.55 min and 23.91 min (major), t_R (*syn*)=19.85 min and 17.64 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.11–8.19 (m, 1H), 7.69 (t, J=7.8 Hz, 1H), 7.50–7.57 (m, 1H), 4.82–5.43 (dd, J=3.3 Hz, 1H), 2.71 (s, 1H), 1.91–2.53 (m, 5H), 1.70–1.80 (m, 2H).

4.3.14. 2-[Hydroxyl(4-nitrophenyl)methyl]cyclopentanone (8n).[23] Light yellow powder; mp 88–90 °C; 85% yield; 79% ee (*anti*), 62% ee (*syn*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 251 nm; t_R (*anti*)=26.20 min (major) and 25.20 min, t_R (*syn*)=19.36 min and 14.40 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.24 (m, 2H), 7.51–7.56 (m, 2H), 4.78–5.43 (m, 1H), 1.52–2.62 (m, 7H).

4.3.15. 4-(4-Nitrophenyl)-4-hydroxy-2-butanone (8o).[20] White powder; mp 59–61 °C; 94% yield; 58% ee [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 254 nm; t_R=43.72 min (major) and 42.09 min]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H), 5.25–5.29 (m, 1H), 3.57 (d, J=3.3 Hz, 1H), 2.84–2.87 (m, 2H), 2.22 (s, 3H).

4.3.16. 4-Hydroxy-5-methylhexan-2-one (8p).[24] Yellow oil; 81% yield; 67% ee [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 280 nm; t_R=11.4 min and 10.4 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79–3.85 (m, 1H), 2.45–2.66 (m, 3H), 2.20 (s, 3H), 1.63–1.74 (m, 1H), 0.93 (t, 6H).

4.3.17. 1-(4-Nitrophenyl)-5-methyl-1-hydroxy-3-hexanone (8q). Light yellow powder; mp 70–72 °C; 67% yield; 83% ee (*anti*), 76% ee (*syn*) [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol=92:8, 1.0 mL/min, 269 nm; t_R (*anti*)=46.48 min (major) and 34.41 min, t_R (*syn*)=31.08 min and 25.42 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.23 (m, 2H), 7.50–7.53 (m, 2H), 4.90 (d, J=8.4 Hz, 2H), 4.09 (s, 1H), 2.48–2.64 (m, 2H), 2.32–2.42 (m, 1H), 2.09–2.15 (m, 1H), 1.82–1.85 (m, 1H), 1.26–1.71 (m, 6H); HRMS for $C_{13}H_{17}NO_4$ (M+H): calcd 252.12358, obsd 252.12399.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.077.

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