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Cadmium-proline catalyzed direct asymmetric Michael and Aldol reactions in water

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The cadmium-proline complex has been used in direct asymmetric Michael and aldol reactions in water at room temperature. The chiral catalyst has been easily prepared from commercially available L-proline. Moreover, the catalyst has been readily recovered and reused for at least five times without a significant loss of catalytic activity or stereoselectivity.

Keywords: Aldol reaction, cadmium-proline, ketones, Michael addition, nitrostyrene

The design and the development of efficient chiral catalysts for enantioselective asymmetric synthesis in aqueous media is one of the most challenging areas of organic chemical research[1]. Another obvious consequence of the aqueous media is that hydroxyl functional groups do not require protection at the carbon-carbon bond formation step. This is particularly useful in the area of carbohydrate chemistry since the water-soluble carbohydrate molecules can react directly without the tedious protection-deprotection processes. Specially, organometallic reactions in aqueous media have attracted considerable interest in organic synthesis due to a number of advantages[2]. Successful design of a simple and highly effective chiral catalyst which could be easily recovered and recycled for a diverse range of organic reactions is still a challenging task. Also the additions of organometallic nucleophiles constitute an important class of carbon-carbon bond forming reactions, and substantial effort has been dedicated towards the discovery of enantioselective Michael and Aldol reactions.

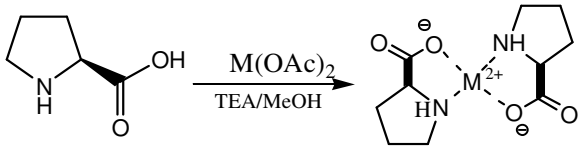
After the first organocatalytic asymmetric Michael addition of aldehydes to nitrostyrenes was reported by Betancourt and Barbas[3b], extraordinary progress has been sought in order to find more selective and efficient catalytic systems for these Michael reactions. List[3a], Barbas[3b], and Enders[4] independently reported the first organocatalytic addition of ketones to *trans*-β-nitrostyrene using L-proline as catalyst with good yields but very low enantioselectivities. Since then, over the past few years, various proline-based organocatalysts, such as pyrrolidine-triazole[5], pyrrolidine-tetrazole[6], pyrrolidine-thiourea[7], pyrrolidine-sulphonamide[8], pyrrolidine-pyridine[9], pyrrolidine-imidazolium[10], 2, 2-bipyrrolidine[11], have been successively employed for asymmetric Michael additions with diverse range of stereoselectivities. However, these proline-derived or pyrrolidine-based catalytic systems are generally more complex and, therefore, have to be prepared by a multistep synthesis. Moreover, most of them cannot be easily recovered and recycled. Being interested in the development of mild and convenient methodologies of asymmetric reactions using water soluble Lewis acids having unprotected amino acids as chiral ligands and to investigate their activities as catalysts, we herein report metal-proline complexes as catalysts for achieving high stereoselectivity in the asymmetric Michael addition of unmodified ketones to nitrostyrenes.

Results and Discussion

A series of metal-proline complexes **1-4** were prepared from the "chiral pool" using L-proline as the starting material (**Scheme I**)[12]. Complexes were characterised by ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. Initially, these chiral metal-proline complexes were used for the direct asymmetric Michael addition of acetone to β-nitrostyrene to afford the Michael adducts using water as reaction medium[13]. The reactions using L-proline **5**[3a] and L-β-homoproline **6** as the catalysts were also carried out for comparison. All the reactions were performed at

RT (25°C) for 36 hr in the presence of 7.5 mol% of the catalyst. The results were summarized in **Table I**. As shown in **Table I**, all the catalysts exhibited good catalytic activity with the corresponding products, which were obtained in good to excellent chemical yields (entries 1-6). It was found that cadmium-proline complex, **2** promoted the Michael addition reaction with higher yield (94%) and enantio-selectivity (89% *ee*) (entry 2). Since the catalyst **2** provided the best result, we decided to use the catalyst for further examination.

Catalyst **2** was used as the catalyst of choice and evaluated in different protic and aprotic solvents. The influence of solvent was investigated in Michael addition reaction of *trans*-β-nitrostyrene and acetone at RT (25°C) in the presence of 7.5 mol% of the catalyst. The results were summarized in **Table II**. The yields and enantioselectivities of the products differed significantly. In aprotic solvents with low polarity such as DCM, 1, 4-dioxane and THF, the reactions were very slow due to the low solubility of the catalyst **2** in the organic solvents (entries 1-3). When polar aprotic solvents such as MeCN and DMF were used, the reactions provided the adduct **7** in higher yields with moderate enantioselectivities (entries 5 and 6). The highest yield (94%), and highest enantioselectivity (89% *ee*) of **7** was obtained when H_2O was used as a solvent (entry 8). On the other hand, protic solvent such as DMSO also gave higher yield and higher enantioselectivity of **7** (entry 4). When the medium was changed from organic to aqueous, the enantio-selectivity was high (89% *ee*) (entry 8). A combination of organic solvent and water gave poor enantio-selectivities but with moderate yields (entries 9-10).

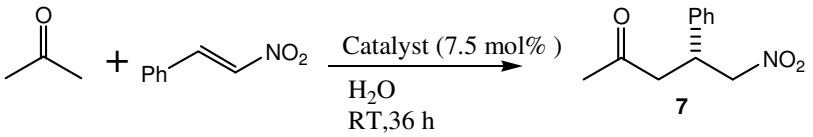


1, M=Zn; **2**, M=Cd; **3**, M=Hg; **4**, M=Pb

Scheme I — Synthesis of Metal-Proline complexes

The influence of reaction temperature was examined in the Michael addition reaction of acetone and *trans*-β-nitrostyrene in presence of 7.5 mol% of catalyst **2** in water. It was observed that the reactions at 35°C yielded the adduct **7a** in 78% yield with 85% *ee*. When the reaction was carried out at RT (25°C), the adduct **7a** was obtained in 94% yield with a higher enantioselectivity (89% *ee*). However, lowering in the reaction temperature at 15°C resulted in a considerable decrease in yield 65% and enantioselectivity (45% *ee*). Thus, these results indicated that H_2O is the most suitable solvent and RT is the most suitable reaction temperature for asymmetric Michael addition reaction of acetone to *trans*-β-nitrostyrene using the catalyst **2**. Having established the standard reaction conditions for the Michael addition of acetone to nitrostyrene, we then examined the reactions of other ketones to establish a general scope of these asymmetric transformations. Thus, on the basis of solvent and temperature effects, all reactions were carried out in water at RT in presence of 7.5 mol% of **2**. The results were summarized in **Table III**.

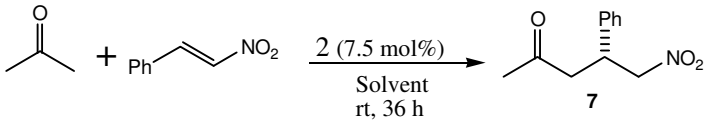
Table I — The asymmetric Michael addition reaction of acetone to *trans*-β-nitrostyrene in H_2O in presence of various catalysts



Entry	Catalyst	Yield[a] (%)	*ee* of 7[b] (%)
1	1	76	86
2	2	94	89
3	3	58	13
4	4	62	78
5	L-Proline, 5	97	11
6	L-β-Homoproline, 6	73	28

[a]Isolated yields
[b]Determined by HPLC using chiral column

Table II — Effect of solvent and reaction temperature on the asymmetric Michael addition reaction of acetone and *trans*-β-nitrostyrene in presence of catalyst **2**[a]



Entry	Solvent	Yield[b] (%)	*ee* of **7**[c] (%)
1	DCM	11	n.d.[d]
2	THF	15	n.d.[d]
3	1,4-Dioxane	9	n.d.[d]
4	DMSO	68	56
5	DMF	62	47
6	MeCN	75	38
7	MeOH	85	45
8	water	94	89
9	DMSO/water	66	42
10	MeCN/water	73	36

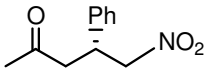
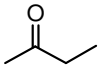
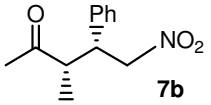
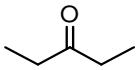
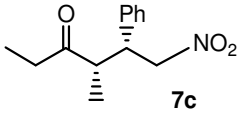
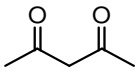
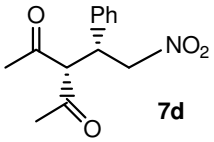
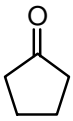
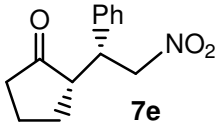
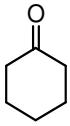
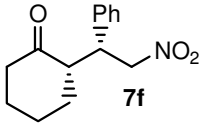
[a]Nitrostyrene (2 mmol), acetone (excess), catalyst **2** (7.5 mol %) and solvent (2mL) at RT for 36 hr
[b]Isolated yields
[c]Determined by HPLC using chiral column
[d]Not determined

Acetone with a catalytic amount of Cd-proline complex gave the desired γ-nitroketone (**7a**) in an excellent yield (94%) with *ee* 89% (entry 1). The catalytic Michael addition of 2-butanone afforded **7b** in moderate yield (68%) with *ee* 78% (entry 2). When 3-pentanone was used as a Michael donor, the reaction proceeded slowly, giving the corresponding product **7c** in 12% yield after 72 hr, although the diastereoselectivity and enantioselectivity were both high (d.r. 92:8, 88% *ee* of syn isomer) (entry 3). The reaction of acetyl acetone with *trans*-β-nitrostyrene afforded the product **7d** in 56% yield (entry 4). In the case of cyclic ketones, the ring size of the ketones strongly influenced the reactivities (entries 5 and 6). The reaction rate of cyclopentanone with *trans*-β-nitrostyrene was very slow, only 11% yield of the Michael adduct **7e** (84% *ee*) with moderate diastereoselectivity (d.r. 85:15) was obtained after 72 hr. However, the reaction of cyclohexanone gave **7f** in a remarkably high yield (92%) with diastereoselectivity (d.r. 95:5) and enantioselectivity (81%).

The reusability of the Cd-proline complex, **2** was also examined by treating acetone and nitrostyrene in water at room temperature for five consecutive reactions respectively (**Table IV**). When the reaction was completed, ethyl acetate was added into the system, organic materials were extracted out and the aqueous phase of the recovered Cd-complex could be recycled up to five times without showing appreciable decrease in the catalytic activity. In each case, the catalyst retained its high activity and high levels of enantioselectivities (86-89% *ee*) despite some degree loss of the yields observed (recycles 3-5).

To extend the present methodology, another important carbon-carbon bond forming reaction–aldol reaction was examined[14]. The methods utilizing Lewis acids rely on the catalysis of metal complexes bearing chiral ligands, such as the heterobimetallic $LaLi_3$ tris(binaphthoxide) and the Zn-BINOL homo-bimetallic catalysts developed by Shibasaki[14] as well as Trost's Zn-semi crown ether[15]. The reactions described above were carried out under anhydrous conditions in organic solvents and the metal complexes were reported to be water sensitive. Darbre and Machuqueiro reported[16] the aldol reaction of acetone and p-nitrobenzaldehyde catalyzed by a zinc-proline complex in the presence of water. The catalytic ability of Zn-complexes bearing other amino acids was also reported. The exploration of water soluble Zn $(proline)_2$-complex in effecting various asymmetric aldol type transformations as chiral catalyst was thoroughly studied by Darbre's group[17].

Table III — Asymmetric Michael addition reaction of various ketones to *trans*-β-nitro styrene using catalyst **2**[a]

Entry	Ketone	Product	Time (hr)	Yield[b] (%)	d.r.[b] (syn/anti)	*ee*[c] (%)
1		 **7a**	36	94	___	89
2		 **7b**	50	68	95:5	78
3		 **7c**	72	12	92:8	88
4		 **7d**	46	56	___	85
5		 **7e**	72	11	85:15	84
6		 **7f**	48	92	95:5	81

[a]All reactions were carried out at RT in H_2O in presence of 7.5 mol% of **2**
[b]Isolated yields
[c]Determined by HPLC using chiral column

Table IV — Recycling study of Michael addition reaction of various ketones to *trans*-β-nitrostyrene using catalyst **2**[a]

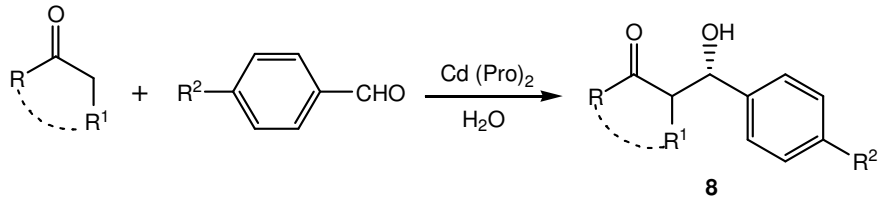
Recycle	Yield[b] (%)	*ee* of **7a**[c] (%)
1	94	89
2	94	89
3	88	87
4	82	86
5	82	86

[a]All reactions were carried out at RT for 36 hr in H_2O in the presence of 7.5 mol% of **2**
[b]Isolated yields
[c]Determined by HPLC using chiral column

Herein, aldol reactions of unmodified ketones with aldehydes catalyzed by Cd-proline complex in the presence of water at room temperature are reported. The results for the enantioselective direct aldol condensation of the unmodified ketones and various aldehydes catalyzed by Cd-proline complex in the presence of water are presented in **Table V**.

When a solution of Cd-proline catalyst (73 μmol) in water (10 mL) was added to a mixture of 4-nitrobenzaldehyde (1 mmol) in acetone (5 mL) and stirred at RT for 24 hr, the adduct was obtained in quantitative yield and 78% *ee* (entry 1, **Table V**). The Cd-proline catalyzed direct enantioselective aldol condensation of 2-butanone with 4-nitrobenzaldehyde also proceeds in quantitative yield and the product was obtained in up to 83% *ee* (entry 3, **Table V**). The aldol products of 4-chlorobenzaldehyde (entries 2, 4 and 7) with different ketones were found to be obtained in 82-98% yields but lower enantioselectivities (50-72% *ee*) as compared to that of 4-nitrobenzaldehyde (except entry 8). The aldol reaction of benzaldehyde (entry 9) with acetone obtained the product in 83% yield and 78% *ee* which were found to be of better reaction as compared with the literature[10]. The yield and enantioselectivity were improved by using the Cd-proline complex for the asymmetric aldol reaction of *p*-anisaldehyde with

Table V — Asymmetric direct Aldol condensation of ketones with aldehydes catalyzed by **2** in water



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Entry	Product	Reaction time[a] (hr)	Yield[b] (%)	*ee*[c]
1	**8a**; R=CH_3, R^1=H, R^2=NO_2	24	100	78
2	**8b**; R=CH_3, R^1=H, R^2=Cl	24	98	65
3	**8c**; R=CH_3, R^1=CH_3, R^2=NO_2	26	100	83
4	**8d**; R=CH_3, R^1=CH_3, R^2=Cl	28	97	72
5	**8e**; R=R^1=$(CH_2)_4$, R^2=NO_2	40	75	56
6	**8f**; R=CH_3,R^1=CH_3CO,R^2=NO_2	24	85	58
7	**8g**; R=CH_3,R^1=CH_3CO, R^2=Cl	27	82	50
8	**8h**; R=CH_3,R^1=PhCO,R^2=NO_2	30	92	48
9	**8i**; R=CH_3, R^1=R^2=H	24	83	78
10	**8j**; R=CH_3, R^1=H, R^2=OCH_3	32	88	65
11	**8k**; R=CH_3, R^1=H, R^2=Br	96	72	63
12	**8l**; R=CH_3, R^1=H, R^2=F	70	92	72

[a]After full conversion of product;
[b]Isolated yields;
[c]Determined by HPLC using Chiral column.

acetone (entry 9) compared to results obtained by using ionic liquid[15]. However, the enantioselectivity of the aldol products could not be improved (entries 7 and 8), although the yields are relatively high. Thus, a variety of substituted benzaldehydes and unmodified ketones were employed and aldol products were in good yields (72-100%) and reasonable enantio-selectivities (48-83% *ee*). It was demonstrated that the Cd-proline complex is found to be more suitable organocatalyst for asymmetric aldol reactions as compared to other systems[16,18].

Experimental Section

All chemicals were used without further purification and all the aldehydes, ketones and metal acetates were obtained from Merck and Aldrich. Infrared (IR) spectra were recorded on Shimadzu FT-IR spectrophotometer in the range of 200 to 4000 cm^{-1}. All the samples were run on a sodium chloride plate as a liquid film. Absorption maxima were recorded in wave numbers (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy was used to determine the formation of synthesized compounds. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker-ACF-300 (300 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker-ACF-300 (75 MHz). All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS), reference to the chemical shifts of residual solvent resonances (^{1}H and ^{13}C NMR). Coupling constants are given in Hz. All samples are run in deutero-chloroform ($CDCl_3$) and DMSO. The FAB mass spectra were recorded–6000 Mass Spectrometer data systems using Argon/Xenon (6KV, 10mA) as the FAB gas.

Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) using chiral column by using LichroCart 250-4 ChiraDex. Detection was done by UV at 254nm and data was processed using an HP-3D Dos chem. station.

General experimental procedure for the preparation of metal-proline complexes

Triethyl amine (0.7 mL) was added to a mixture of L-proline (0.58g, 5mmol) in methanol (10 mL), then

after 10 min respective metal acetate (2.5 mmol) was added. After stirring for 45 min, a white precipitate was collected by filtration.

Cadmium-proline complex 2: White amorphous solid; Yield 100%; m.p., decomposed at 240°C; IR (KBr): 3269, 3202, 2964, 1575, 1389 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 1.66 (m, br, 3H), 2.12 (m, br, 1H), 2.76 (s, br, 1H), 3.03 (m, br, 1H), 3.70 (m, br, 1H); ^{13}C NMR (75 MHz, D_2O): δ 25.7(CH_2-C), 30.1(CH_2-NH), 47.8 (CH_2-C), 60.7(CH-CO); MS (D_2O): *m/z* 358[M+H_2O]; Anal Calcd for $C_{10}H_{16}CdN_2O_4$: C, 35.26; H, 4.73; N, 8.22. Found: C, 35.19; H, 4.69; N, 8.20%.

Mercury-proline complex 3: White amorphous solid; Yield 100%; m.p., decomposed at 250°C; IR (KBr): 3543, 3231, 2974, 1615, 1424, 1070 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 1.56 (m, br, 3H), 1.96 (m, br, 1H), 2.79 (m, br, 1H), 3.06 (s, br, 1H), 3.72 (m, br, 1H); ^{13}C NMR (75 MHz,D_2O): δ 24.7(-CH_2-C), 29.2(-CH_2-NH), 51.7(-CH_2-C), 61.9(-CH-CO), 178.6(-CO); MS (D_2O): *m/z*, 428[M^+], 429[M+H], 447[M+H_2O], 467[M+K]; Anal Calcd for $C_{10}H_{16}HgN_2O_4$: C, 28.01; H, 3.76; N, 6.53. Found: C, 27.95; H, 3.70; N, 6.48%.

Lead-proline complex 4: White amorphous solid; Yield 100%; m.p. decomposed at 210°C; IR (KBr): 3236, 2981, 2868, 1653, 1571, 1377 $cm^{-1;}$ ^1H NMR (300 MHz, D_2O): 1.93 (m, br, 3H), 2.23 (m, br, 1H), 3.14(m, br, 1H), 3.23 (m, br, 1H), 3.91(m, br, 1H); ^{13}C NMR (75 MHz, D_2O): δ 178.3(-CO), 62.4(-CH-C), 49.1(-CH_2-C), 47.1(-CH_2-NH), 30.6(-CH_2-C); Anal Calcd for $C_{10}H_{16}N_2O_4Pb$: C, 27.58, H, 3.70; N, 6.43. Found: C, 27.53, H, 3.62; N, 6.39%.

General procedure for Cadmium-proline catalyzed Michael reaction of nitrostyrene with various unmodified ketones

To a mixture of Cd-proline complex (150 μmol, 0.051 g) in water (2.0 mL), the corresponding ketone (2 mmol)/acetone (excess) was added at RT. After 15 min, β-nitrostyrene (2 mmol, 0.298 g) was added at RT and the mixture was further stirred at RT. until TLC indicated complete reaction. The reaction was quenched at 0°C with 1 M HCl (10.0 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed successively with sat. aq. $NaHCO_3$ solution (3 x 10.0 mL), water (3 x 10.0 mL) and brine (3 × 10.0 mL), dried over $MgSO_4$, filtered and volatile organic materials were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel/ petroleum ether). Compounds **7a** (Ref 19), **7b** (Ref 3a, 20), **7c** (Ref 20b, 21), **7e** (Ref 20b, 22), **7f** (Ref 3a, 20b, 23) are known compounds**.**

3-Acyl-5-nitro-4-phenyl-pentane-2-one, 7d: Yield 56%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.31(m, 3H), 7.23-718 (m, 2H), 4.65 (dd, *J* = 6.9, 12.3 Hz, 1H, CH_2NO_2), 4.62 (dd, *J* = 7.6, 12.3 Hz, 1H, CH_2NO_2), 4.37 (d, *J* = 7.0 Hz, 1H, CH_2COCH_3), 4.25 (m, 1H, PhCH), 2.30 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8 (CO), 201.0 (CO), 136.0 (Ar), 129.3 (Ar), 128.6 (Ar), 128.5 (Ar), 127.9 (Ar), 127.9 (Ar), 78.2 (CH_2), 70.7 (CH), 42.8 (CH), 30.5 (CH_3), 29.6 (CH_3); MS ($CDCl_3$): *m/z*, 249 [M^+], 272 [M+Na], 288 [M+K]. HRMS calcd for $C_{13}H_{15}NO_4$: 249.1001 found 249.1052; *ee*=85%, determined by Chiral HPLC analysis of the crude product (Chiradex, Hexane/*i*-propanol 80:20), 1.0 mL min^{-1}, UV 220 nm, t_{major} = 20.523 min, t_{minor} = 16.712 min.).

General procedure for Cd-proline catalyzed direct asymmetric Aldol reaction in water

A solution of Cd-proline complex (73 μmol, 0.025 g) in water (10 mL) was added to a mixture of benzaldehyde (1 mmol) in ketone (5 mL). The reaction mixture was stirred at RT for several hours until TLC indicated the complete reaction. The solvent was evaporated the residue was extracted with chloroform (3 × 20 mL). The chloroform extract was concentrated and the residue was purified by flash column chromatography. Compounds **8a**, **8b**, **8c**, **8d**, **8e**, **8i**, **8j**, **8k**, **8l** are reported already and verify the results compared with the reported structures[24].

4-Hydroxy-3-acetyl-(4-nitrophenyl)-butan-2-one, 8f: White amorphous solid compound. Yield 85 %. IR (KBr): 3500 (-OH), 2974 (aromatic –CH), 1695 (-OH), 1348-798 cm^{-1} (-NO_2); ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.48 (d, *J* = 7.0 Hz, 2H, Ar-H), 4.30-4.13 (m, 1H, CH-Ph), 3.34-3.26 (m, 1H, -OH), 2.85-2.77 (d, *J* = 7.0 Hz, 1H, -CH-CO), 1.75 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4(-CO), 151.9(-Ar), 128.9(-Ar),124.4(-Ar), 69.2(-CH), 63.2(-CH-OH), 27.9(-CH_3), 27.1(-CH_3); MS ($CDCl_3$): *m/z* 274[M+Na]; Anal Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.31; H, 5.18; N, 5.52%; *ee* = 58%. The enantiomeric excess was determined by HPLC using chiral column–197 Lichro Cart 250-4, Chira Dex. (Methanol/Water, 40:60, λ = 254 nm, flow rate=0.8 mL/min), t_R= 4.23 min (major) associated with a very small negligible peak for minor.

4-Hydroxy-3-acetyl-(4-chlorophenyl)-butan-2-one, 8g: White amorphous solid compound. Yield 82%. IR (KBr): 3412 (-OH), 2972 (aromatic –CH), 1718(-CO), 1695 cm^{-1} (-CO); ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.24(m, 3H, Ar-H); 7.18 (dd, *J* = 6.3 Hz, 1H, Ar-H); δ 7.09 (dd, *J* = 6.3 Hz, 1H, Ar-H), 4.09-3.86 (m, 1H, -CH-Ph), 3.45 (s, 1H, -OH), 2.8-2.43 (m, 1H, -CHCO), 1.67 (m, 3H, CH_3), 1.39 (m, 3H, CH_3): ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.5 (-CO), 203.6(-CO), 136.9(-Ar),133.8 (-Ar),133.0 (-Ar), 129.5(-Ar), 129.2 (-Ar), 73.9(-CH), 63.4(-CH-OH), 28.4(-CH_3),27.8 (-CH_3); MS ($CDCl_3$): *m/z* 221[M-H-H_2O], 244[M-H-H_2O+Na]; Anal Calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44. Found: C, 59.80; H, 5.38; *ee*=50%. The enantiomeric excess was determined by HPLC using chiral column–Lichro Cart 250-4, Chira Dex. (Methanol/Water, 40:60, λ_{max} 254 nm, flow rate = 0.8 mL/min), t_R = 2.23 min (major) and t_R= 4.01 min (minor).

4-Hydroxy-3-benzoyl-(4-nitrophenyl)-butan-2-one, 8h: White amorphous solid compound. Yield 92%. IR (KBr): 3439, 3049, 1678, 1659, 1234-914 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J*= 6.3 Hz, 2H, Ar-H), 7.90 (dd, *J* = 5.7 Hz, 2H, Ar-H), δ 7.59-7.45 (m, 5H, Ar-H), δ 2.41 (s, 3H, CH_3), δ1.61 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9(-CO), 195.1(-CO), 148.2(-Ar), 142.7(-Ar),139.2(-Ar), 137.7(-Ar), 135.4(-Ar), 134.8(-Ar), 130.7(-Ar), 129.2(-Ar), 129.2(-Ar), 123.9(-Ar), 27.7(-CH_3); MS ($CDCl_3$): *m/z* (%) 394[M-H-H_2O]; Anal Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.14; H, 4.78; N, 4.43; *ee*=48 %. The enantiomeric excess was determined by HPLC using chiral column–197 Lichro Cart 250-4, Chira Dex. (Methanol/Water, 40:60, λ = 254 nm, flow rate=0.8 mL/min), t_R= 3.98 min (major) associated with a very small negligible peak for minor.

Conclusion

In summary, the metal-proline complexes (**1**-**4**) have been designed and prepared and it has been found for the first time that the catalyst **2** could be used in the Michael addition reaction of unmodified ketones to nitrostyrene to provide high yields and high enantioselectivities of the corresponding Michael adducts. It was also shown that the aldol reactions of unmodified ketones with aldehydes catalyzed by Cd-proline complex in water were found to give high yields (upto quantitative yield) and high *ee* (up to 83%). Moreover, the catalyst was readily recovered and reused for at least five times without a significant loss of catalytic activity or stereoselectivity.

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