



REGULAR ARTICLE

Diastereoselective Mannich reaction with prolinated MWCNTs as a heterogeneous organo-nanocatalyst

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Abstract. We intended to convert proline as a homogeneous catalyst to a heterogeneous catalyst by proline of MWCNTs to improve proline efficiency as a catalyst by the ease of separating, catalytic economy, reusability, etc. To reach these goals, we sketched Pro-MWCNT catalyst and characterized it by different analyses such as FT-IR, SEM, EDX, CHNS. The efficiency of this heterogeneous catalyst was investigated and compared with proline homogeneous catalyst in Mannich reaction. The results hold out improvements in stereoselectivity, ease of separating and reusability.

Keywords. Multiwall Carbon Nanotubes; L-proline; Diastereoselective; Mannich reaction; Heterogeneous Catalyst.

1. Introduction

Organocatalysis is a substoichiometric amount of an organic compound, which is considered to be the promotion and acceleration of chemical reactions.¹ Although the use of organic molecules as catalysts turns to the beginnings of chemistry, their application as enantioselective catalysts has only emerged as a major concept in organic chemistry in the last few years.^{2–4} Recently, enantioselective organocatalysis has found a key role in the production of chiral molecules⁵ due to environmental friendliness.^{6–8}

Chiral secondary amine catalysts with ketones or aldehydes can form iminium ions as intermediates react by imine–enamine tautomerism or a related mechanism to form a nucleophilic enamine species, which can be trapped conveniently by an activated p electrophile, for example, an aldehyde, ketone or azidocarboxylate.

Proline has a higher pK_a value and enhanced nucleophilicity relative to other amino acids because it is the only natural amino acid with secondary amine functionality. Proline can, therefore, react as a

nucleophile with carbonyl groups or Michael acceptors to form iminium ions or enamines. Furthermore, as the carboxylic acid functionality of the amino acid acts as a Bronsted acid in these reactions, proline can be considered as a bifunctional catalyst.¹

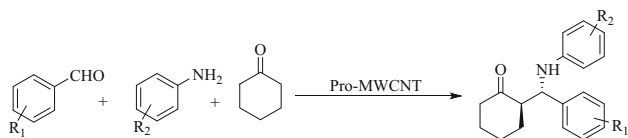
In this context, proline and its structural analogues have been intensively investigated in organocatalytic reactions⁹ and found to be very effective in enamine-based direct catalytic asymmetric Aldol,¹⁰ Mannich,¹¹ Diels–Alder,¹² α -amination reaction,¹³ Knoevenagel-type reactions,¹⁴ unsymmetric Biginelli reaction,¹⁵ and some domino reactions.¹⁶

Nowadays, interest in organocatalysts has been increased due to low toxicity, commercial availability, operational simplicity and efficiency, compared to traditional metal-based catalysts.¹⁷ However, some limitation factors such as high catalyst cost, high catalyst loadings requirement, and difficulties in catalyst recovery and reusability have restricted its practical applications. To avoid these limitations,¹⁸ an alternative strategy is to design recyclable and subsequently reusable versions of organocatalysts¹⁹ by immobilization of organocatalysts onto solid supports²⁰ such as polymers,²¹ mesoporous materials,²² or magnetic nanoparticles.²³

Accordingly, we decided to design a new heterogeneous organo-nanocatalyst by decorating MWCNTs

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This article is dedicated to the memory of, Professor Mehdi Bakavoli, who recently passed away.



Scheme 1. Mannich reaction of aldehyde, amine and cyclohexanone in presence of Pro-MWCNT.

with L-proline amino acid. The increase of knowledge on the synthesis and understanding of nanocarbon materials resulted in more rational bases to be used as advanced catalysts. MWCNTs are still the main type of nanocarbon material studied for catalytic applications and also that commercialized for over 95% of global nanocarbon production.²⁴ However, insolubility of pristine CNTs in water or organic solvents is the main drawbacks in their use.²⁵ We hope that the decoration of MWCNTs with proline increases their solubility in solvents or stability of their colloid. The efficiency of this catalyst was investigated in Mannich reaction of aldehyde, amine and cyclohexanone and other ketones (Scheme 1).

The Mannich reaction is one of the most important methods for the construction of carbon-carbon bonds to build β -amino carbonyl compound.²⁶ β -amino carbonyl compounds are important synthetic intermediates for the synthesis of various pharmaceuticals and natural products.²⁷

2. Experimental

2.1 Materials

MWCNTs (>95%, OD: 20-30) were obtained from US Research Nanomaterials, Inc. 3302 Twig Leaf Lane, Houston, TX 77084, USA. $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, H_2O_2 , L-proline, aryl aldehydes, arylamines, cyclohexanone, EtOH and other solvents were obtained from Merck and used without further purification except for aniline, which was distilled prior to use.

2.2 Apparatus

Ultrasonication was performed using a PARSONIC 15S (PARS NAHAND ENGG. CO., Iran) sonicator. Filtration was done by using PTFE MEMBRANES 0.22 μm (MF047PT022 filtraTECH, France). Centrifugation was done with UNIVERSAL 320 centrifuge from (POLE IDEAL TAJHIZ Co., Iran). Melting points were recorded with a Thermo Scientific IA9200 (Electrothermal Engineering) melting point apparatus. Fourier transforms infrared (FT-IR) spectra were obtained using a Nicolet Fourier spectrophotometer (USA) as KBr discs. Morphology studies of the prepared samples were carried out using a Leo 912

AB microscope (Germany) scanning electron microscope (SEM). Energy Dispersive X-ray (EDX) was performed to detect the element compositions using a Leo 912 AB microscope (Germany) instrument. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-300 AVANCE spectrometer, respectively at 300 and 75 MHz with tetramethylsilane (TMS) as internal reference ($\delta_{\text{H}} = 7.26$ for CDCl_3 , $\delta_{\text{C}} = 77$ for CDCl_3). Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and examined under ultraviolet (UV) light. Elemental analysis was done by using FLASH EA 1112 SERIES from thermos Finnigan Co.

2.3 Synthesis of hydroxylated MWCNTs (MWCNT-OH)

In order to remove residual catalyst nanoparticles originating from the CNT growth, as-received CNTs were washed with diluted HCl. Hydroxylation using the Fenton reaction was carried out as follows:

MWCNT (3 g) and toluene (340 mL) were mixed using an ultrasonic bath for 1 h. The resulting suspension was filtered and washed with toluene, then n-hexane and then dried under vacuum at 80 $^\circ\text{C}$ for 24 h. After that, 1 g of these MWCNTs were added to H_2O (300 mL) and dispersed using an ultrasonic bath for 30 min. To the suspension was then added $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.5 g) and 30% H_2O_2 (300 mL). After stirring for 24 h, the suspension was thoroughly washed with H_2O then EtOH, and dried under vacuum at 80 $^\circ\text{C}$.

2.4 Functionalization of MWCNT-OH with L-proline

MWCNT-OH (0.1 g) and of L-proline (0.2 g) in CH_2Cl_2 (20 mL) were mixed and sonicated for 30 min. The mixture was then stirred for 2 h. Functionalized MWCNTs centrifuged and washed several times with water and ethanol then filtrated with PTFE filters and dried at 50 $^\circ\text{C}$.

2.5 General procedure for synthesis of β -amino carbonyls

2.5a General procedure for synthesis of β -amino carbonyls in presence of Pro-MWCNT: In a typical experiment, a mixture of aromatic aldehyde (3 mmol), aromatic amine (3mmol), cyclohexanone or other ketones (3 mmol) and Pro-MWCNT (0.005 g \sim 0.1% mole L-proline) in deionized H_2O (1 mL) was sonicated for 2 min and the suspension was stirred at room temperature for about 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, CHCl_3 was added and Pro-MWCNT was easily separated by centrifugation,

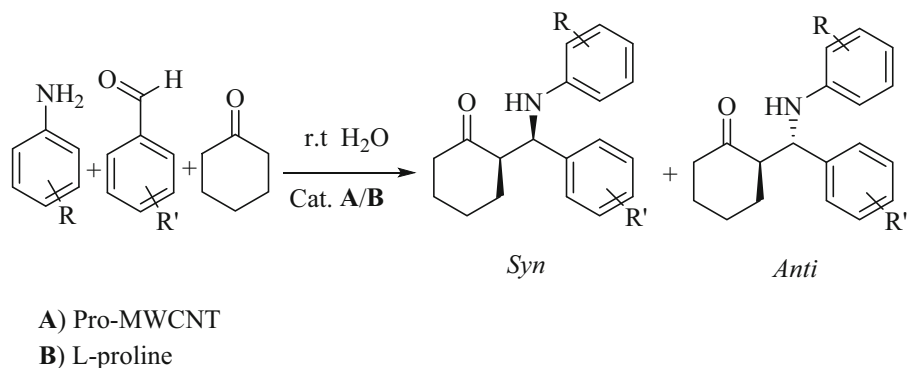
the product was purified by plate chromatography and recrystallization from EtOH.

2.5b General procedure for synthesis of β -amino carbonyls in presence of L-proline: In a typical experiment, a mixture of aromatic aldehyde (3 mmol), aromatic amine (3 mmol), cyclohexanone (3 mmol) and L-proline (0.0035 g \sim 1% mole) in deionized H₂O (1 mL) was stirred at room temperature for about 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, CHCl₃ was added organic materials were extracted and the aqueous solution which contained L-proline was evaporated for recovery of catalyst. The extract was dried over anhydrous Na₂SO₄ then evaporated to dryness. Further purification of the residue was done by

recrystallization from EtOH. The products were identified by comparing their melting points and spectroscopic data (FT-IR, ¹H NMR, ¹³C NMR) with those reported in the literature.^{28–36}

2.5c Enantiomeric excess determination by means of chiral (1S)-(+)-Camphor-10-sulphonic acid: In order to determine the enantiomeric excess (ee) of β -amino carbonyl compounds, a mixture of β -aminocarbonyl (1 mmol) and a chiral compound ((1S)-(+)-Camphor-10-sulphonic acid) (1 mmol) were dissolved in DMSO-d₆. After about 20 h the ¹H NMR spectra of the mixture was recorded. The ee of the compounds was computed based on the splitting spectra of the enantiomeric C-H, chemical shift and it is integral at δ ppm: (4.5–6). The ee (%) of some of

Table 1. One-pot, three-component asymmetric Mannich reaction^a.



Entry	R	R'	Cat.	Anti ^b (%)	Syn ^b (%)	Yield (%)
1	H	H	A *	100	0	96
2	H	H	B **	100	0	94
3	4-Cl	H	A (A')	>99 (79)	<1 (21)	81 (78)
4	4-Cl	H	B (B')	90 (86)	10 (14)	76 (28)
5	4-Br	H	A	93	7	85
6	4-Br	H	B	89	11	82
7	H	4-Cl	A	65	35	89
8	H	4-Cl	B	60	40	82
9	4-Me	4-Cl	A	67	33	86
10	4-Me	4-Cl	B	67	33	76
11	4-Cl	4-Cl	A	68	32	87
12	4-Cl	4-Cl	B	64	36	79
13	H	4-NO ₂	A	73	27	83
14	H	4-NO ₂	B	62	38	79
15	H	4-Me	A	88	12	75
16	H	4-Me	B	78	22	71

a) 3 mmol Amin, 3 mmol Aldehyde, 3 mmol cyclohexanone, 1 ml H₂O (Deionized water).

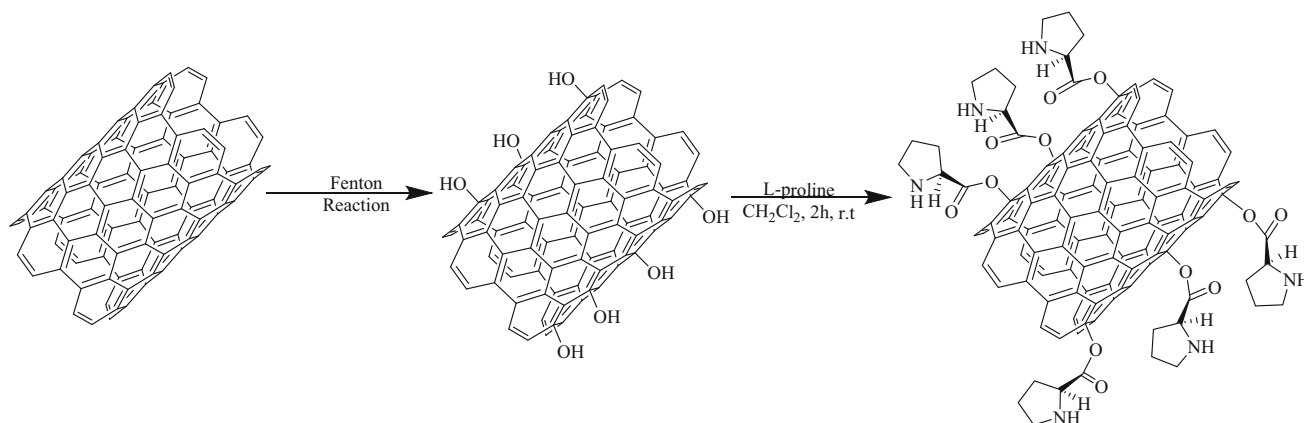
b) *Syn*(%) and *Anti*(%) of the products was determined by crystal clear peak of benzylic C-H bond in ¹H NMR spectrum.

*) **A**: Pro-MWCNT (0.005 g, include \sim 0.1 mol% L-proline).

) **B: L-proline (\sim 0.004 g \sim 1 mol%).

A') Pro-MWCNT (0.05 g, include \sim 1 mol% L-proline).

B') L-proline (\sim 0.0004 g \sim 0.1 mol%).



Scheme 2. Preparation of Pro-MWCNTs.

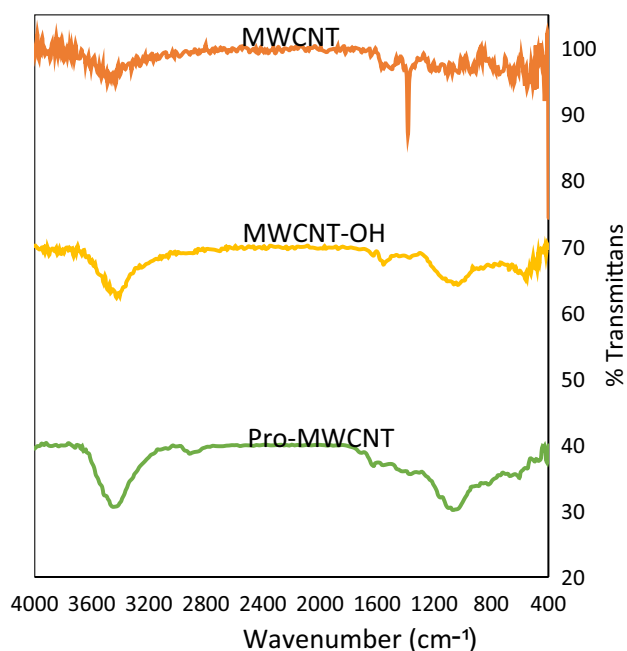


Figure 1. Comparative FT-IR spectra of MWCNTs (top), MWCNT-OH (middle) and Pro-MWCNT (bottom).

the β -amino carbonyl derivatives have been reported in Table 3.

2.5d *Spectral data for some selected β -amino carbonyls:* 2-

(Phenyl(phenylamino)methyl)cyclohexanone (Table 1, Entry 1) White solid, M.p. 140–140.8 °C; IR (KBr) ν_{\max} : 3329, 3031, 2934, 2864, 1701, 1601, 1497, 1278 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ ppm: 1.62–2.02 (m, 6H, $3 \times \text{CH}_2$), 2.29–2.62 (m, 2H, CH_2), 2.75–2.82 (m, 1H, CH), 4.64–4.66 (d, $J = 6.9$ Hz, *anti* isomer 1H), 4.74 (s, 1H, NH), 6.55–6.57 (d, $J = 7.8$ Hz, 2H, Ar-H), 6.65 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.09 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.26–7.29 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.33 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.41 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 23.6, 27.9, 31.3, 41.7, 57.5, 57.9, 113.5, 117.5, 127.1, 127.2, 128.4, 129.0, 141.7, 147.2, 212.9.

2-(Phenyl(4-Chlorophenylamino)methyl)cyclohexanone (Table 1, Entry 3) Yellow solid, M.p. 139.9–140.8 °C; IR (KBr) ν_{\max} : 3411, 3348, 2953, 2846, 1700, 1594, 1491, 1290, 821, 748 cm^{-1} . ^1H NMR (300MHz, CDCl_3) δ ppm: 1.68–1.79(m, 2H, CH_2), 1.89–1.98 (m, 4H, $2 \times \text{CH}_2$), 2.36–

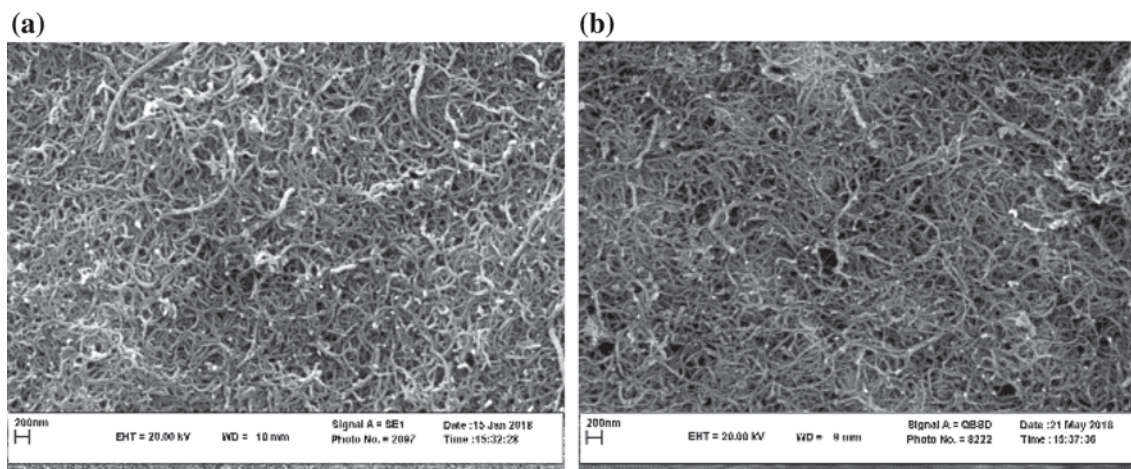


Figure 2. Representative of (a) raw MWCNT, (b) pro-MWCNT.

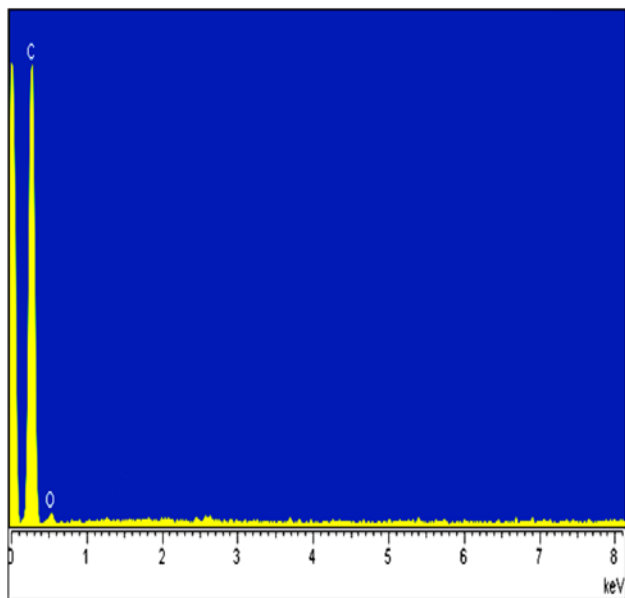


Figure 3. EDX spectrum of pro-MWCNT.

Table 2. Effect of water solvent on diastereoselectivity.

Entry	R	R'	Cat.	Solvent	<i>Anti</i> ^a (%)	<i>Syn</i> ^a (%)
1	H	H	A *	n-hexane	85	15
2	H	H	A	H ₂ O ^b	100	0
3	H	H	B **	EtOH	94	6
4	H	H	B	H ₂ O	100	0
5	4-Br	H	B	EtOH	88	12
6	4-Br	H	B	–	89	11
7	4-Br	H	B	H ₂ O	89	11
8	H	4-Cl	B	EtOH	56	44
9	H	4-Cl	B	H ₂ O	60	40

a) *Syn* (%) and *Anti* (%) of the products was determined by crystal clear peak of benzylic C-H bond in ¹H NMR spectrum.

b) Deionized water.

*) **A** Pro-MWCNT.

***) **B** L-proline.

2.48 (m, 2H, CH₂), 2.71–2.81 (m, 1H, CH), 4.57–4.59 (d, *J* = 6.6 Hz, *anti* isomer, 1H, CH), 4.94 (s, 1H, NH), 6.48–6.51 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.02–7.05 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.23–7.28 (m, 1H, Ar-H), 7.29–7.39 (m, 4H, Ar).

2-(Phenyl(4-bromophenylamino)methyl)cyclohexanone (Table 1, Entry 5) White solid, M.p. 121–122 °C; IR (KBr) ν_{\max} : 3404, 3343, 2944, 2859, 1701, 1591, 1493, 1294, 701, 547 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ ppm: 1.74–1.98 (m, 6H, 3×CH₂), 2.32–2.48 (m, 2H, 2CH), 2.77–2.81 (m, 1H, CH), 4.57–4.59 (d, *J* = 6.9 Hz, *anti* isomer, 1H, CH), 4.96 (Broad, 1H, NH), 6.44–6.47 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.16–7.18 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.23–7.29 (m, 1H, Ar-H), 7.31–7.4 (m, 4H, Ar-H).

1,3-diphenyl-3-(phenylamino)propanone (Table 5, Entry 1) White crystal, IR (KBr) ν_{\max} : 3424, 3055, 2925, 1727, 1665, 1604, 1448, 1384, 748, 692 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ ppm: 3.46 (dd, *J*₁ = 16.05 Hz, *J*₂ = 7.8 Hz, 1H, CH), 3.56 (dd, *J*₁ = 16.05, *J*₂ = 5.4 Hz, 1H, CH), 5.06 (dd, *J*₁ = 7.35 Hz, *J*₂ = 5.4 Hz, 1H, CH), 7.26–7.31 (m, 9H, Ar-H), 7.94–7.98 (m, 3H, Ar-H), 8.51 (s, 1H, NH).

3. Results and Discussion

3.1 Synthesis and characterization of prolinatad MWCNTs

One of the most useful methods among different strategies to increase the hydrophilicity of CNTs is the surface modification of them with hydroxyl groups. Hydroxylation results in further conjugation of CNTs with other molecules.³⁷ Hydroxylation of MWCNTs using the well-known Fenton reaction was carried under sonication condition (Scheme 2).

Well-washed prolinatad MWCNTs (Pro-MWCNTs) characterized as follows.

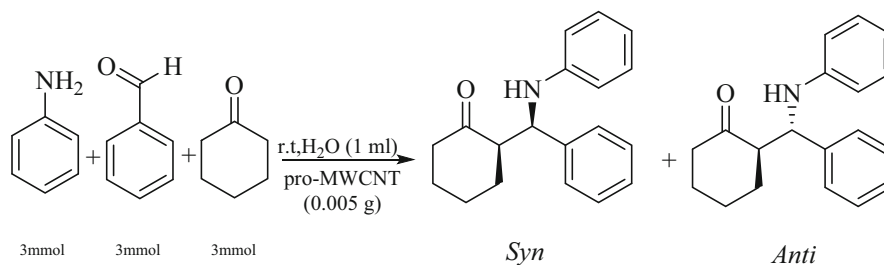
Table 3. The enantioselectivity of the new established heterogeneous Pro-MWCNT catalyst in asymmetric Mannich reaction^a.

Entry	R	R'	<i>Anti</i> ^b (%)	<i>Syn</i> ^b (%)	ee ^c (% <i>Anti</i>)	Yield (%)
1	4-Cl	H	>99	<1	79	81
2	4-Br	H	93	7	86	85
3	H	4-NO ₂	73	27	74	83
4	H	4-Me	88	12	67	75

a) 3 mmol Amin, 3 mmol Aldehyde, 3 mmol cyclohexanone, Pro-MWCNT (0.005 g, include ~0.1 mol% L-proline), 1ml H₂O (Deionized water).

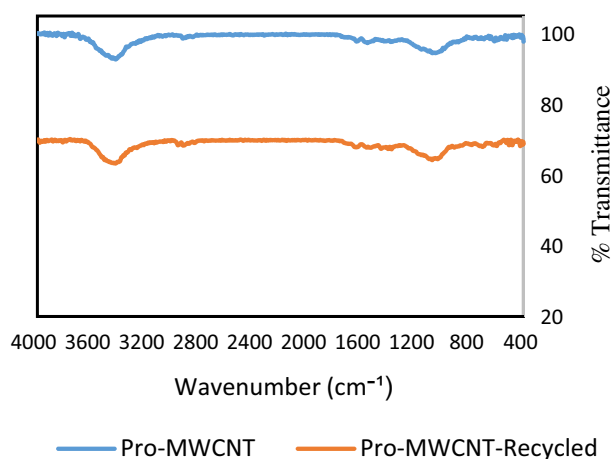
b) *Syn* (%) and *Anti* (%) of the products was determined by crystal clear peak of benzylic C-H bond in ¹H NMR spectrum.

c) ee (%) of the products was determined by ¹H NMR spectrum *via* the addition of chiral (1S)-(+)-Camphor-10-sulfonic acid.

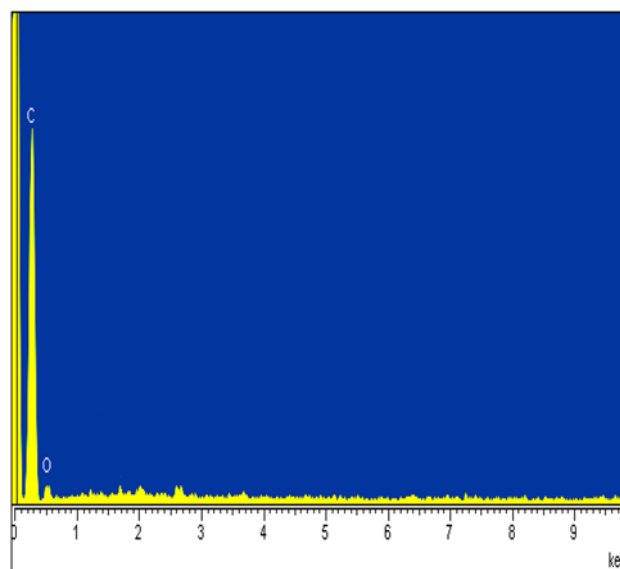
Table 4. Reusability of pro-MWCNT.

Entry	Yield (%)	<i>Anti</i> ^a (%)	<i>Syn</i> ^a (%)
1	96	100	0
2	95	<99	>1
3	92	98	2
4	92	97	3
5	81	70	30

a) *Syn*(%) and *Anti*(%) of the products was determined by crystal clear peak of benzylic C-H bond in ¹H NMR spectrum.

**Figure 4.** Comparative FT-IR spectra of Pro-MWCNT (Top) and Pro-MWCNT-Recycled (Bottom).

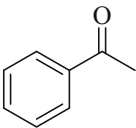
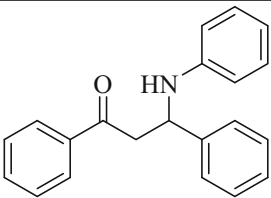
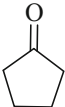
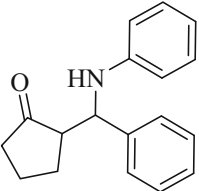
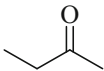
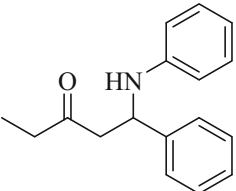
3.1a *FT-IR*: Comparative FT-IR spectra of MWCNT, MWCNT-OH and Prolinated MWCNTs (Pro-MWCNT) are shown in Figure 1. As it can be seen in Figure 1 (top), the raw MWCNT displays a band at 3464 cm^{-1} can be assigned to the -OH stretching vibrations of adsorbed water. The bands at 1572 cm^{-1} in MWCNTs spectra and 1511 cm^{-1} can be assumed for C=C stretching vibrations do to the graphitic structure of MWCNTs. The FT-IR spectrum of hydroxylated MWCNTs which proofs a great hydroxylation by a typical peak at 3428 cm^{-1} (middle). The bands at 1556 and 1045 shows C=C and C-O respectively. (Bottom), this spectrum demonstrates the localization of L-proline on the surface of the MWCNTs. $3000\text{--}3500\text{ cm}^{-1}$ peaks are

**Figure 5.** EDX spectrum of pro-MWCNT-Recycled.

O-H and N-H vibration of secondary amine. The appearance of new peaks at 2917 cm^{-1} and 1711 cm^{-1} which presumed to be C-H sp^3 and C=O stretching vibration (ester) respectively and also the bands at about 1150 cm^{-1} of C-N stretching vibration and 1070 cm^{-1} of C-O stretching vibration are great validations of prolation of the MWCNTs surface.

3.1b *EDX, SEM and elemental analysis (CHNS analysis)*: Morphology of the pro-MWCNT catalyst

Table 5. One-pot, three-component Mannich reaction in the presence of pro-MWCNT

Entry	Ketone	Product	Yield (%) ^a
1			86
2			79
3			83

a) Isolated yields.

was compared with raw-MWCNTs by SEM technique. The comparison of Figure 2(a) and Figure 2(b) revealed that MWCNTs have preserved their cylindrical structure during the prolineation. The EDX spectrum of the pro-MWCNT is represented in Figure 3 in order to investigate the elemental composition of the catalyst which confirmed the presence of C and O. (It should be noted that due to the closeness of C and N position on EDX analysis and also the amount of N which is trace in comparison with C it hasn't been detected clearly by this method). Another analysis which has been used to determine the elemental composition of the prepared catalyst and get certainty of the N presence is elemental analysis. According to the CHNS analysis, pro-MWCNT contains Nitrogen 0.88%, Carbon 74.26%, Hydrogen 2.27% and Sulphur 0%.

3.2 Investigation of pro-MWCNTs catalytic activity

In order to investigate the catalytic activity of the prepared Pro-MWCNT as a new heterogeneous nanocatalyst, it was compared with pure L-proline in

the synthesis of β -amino carbonyl compounds *via* mannich reaction.

Three-component Mannich reaction was firstly investigated by the simple substrates of benzaldehyde (1 mmol), aniline (1 mmol) and cyclohexanone (1 mmol) as a model reaction to optimize the reaction conditions.

According to the importance of respect to our environment and fidelity to the principles of green chemistry, we applied the following condition in all of our reactions.

Aldehyde (3 mmol), Amine (3 mmol) and cyclohexanone (3 mmol) was examined in the presence of both homogeneous proline and heterogeneous Pro-MWCNT as an organo nanocatalyst in H₂O at room temperature. The results of different derivatives are recorded in Table 1.

As can be seen from Table 1 the isolated yields are good and major product will be the *anti* isomer with high diastereoselectivity. Electron donating and electron-withdrawing groups gave the products in high yield and diastereoselectivity. Heterogeneous Pro-MWCNT nanocatalyst is efficient rather than homogeneous proline catalyst in some features such as;

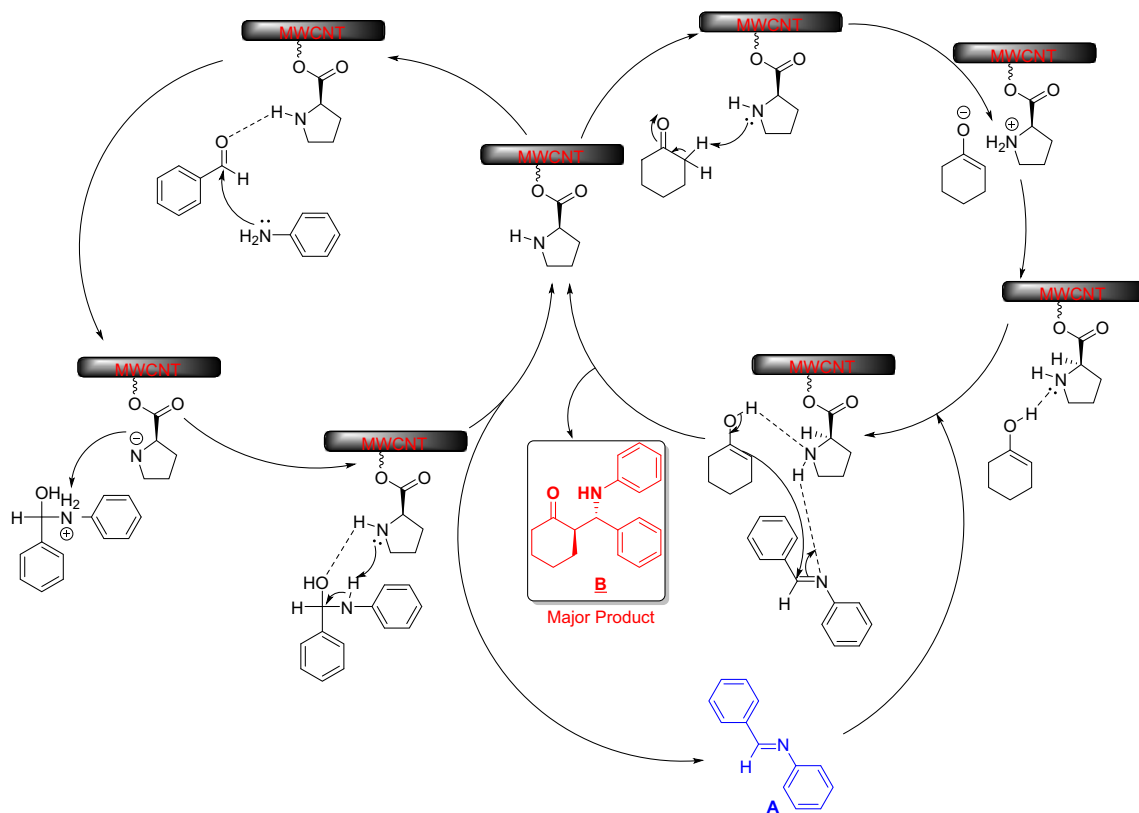


Figure 6. Proposed mechanism for one-pot three-component Mannich reaction.

isolated yield, diastereoselectivity and catalyst loading. In addition, we changed the solvent to investigate the effect of water on diastereoselectivity. The results of this experiment are shown in Table 2. Clearly, diastereoselectivity was increased in water rather than Solvent-Free, n-hexane (non-polar) and EtOH (polar) solvents.

The enantioselective feature of the new established heterogeneous Pro-MWCNT nano-catalyst has been investigated in a few examples and the results of ee% showed in Table 3. As can be seen, reactions take place in high diastereoselectivities with moderate enantioselectivities.

All the entries were monitored by TLC, and after the completion of the reaction, as the product was soluble in chloroform, 5 mL CHCl_3 was added to the reaction mixture and our insoluble nanocatalyst separated simply by centrifugation, the product was recrystallized from EtOH. The removed pro-MWCNT was washed with ethanol and dried under vacuum at 50 °C for 12 h. As can be seen in Table 4 the recycled pro-MWCNT could be used again up to 5 times without any appreciable decrease in its catalytic activity. Comparison of the FT-IR spectra of fresh pro-MWCNT and recovered one after 5 times use in the reaction is shown in Figure 4. In

addition, EDX analysis of pro-MWCNT-recycled as shown in Figure 5 proves that it has no obvious change in its structure after 5 times recovery.

The efficiency of the new pro-MWCNT catalyst was examined in the reaction with other ketones such as; cyclopentanone, acetophenone and 2-butanone and its data have been presented in Table 5. As can be seen, reactions take place in high yields.

The proposed mechanism for one-pot three-component Mannich reaction in presence of pro-MWCNT has been shown in Figure 6. Accordingly, Pro-MWCNT can catalyzed, (1) imine formation from aldehyde and amin, (2) enolization of cyclohexanone and (3) finally and most importantly diastereoselective and enantioselective Mannich reaction.

4. Conclusions

It can be concluded from the results of not only the detection of the catalysts but also the investigation of its catalytic activity and its recyclability that the Pro-MWCNT has much more quality and efficiency than proline in different aspects such as ease of separating, diastereoselectivity, reusability and better yield.

Supplementary Information (SI)

Figures S1-S18 are available at www.ias.ac.in/chemsci.

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