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Asymmetric Synthesis of Modafinil and its Derivatives by using the Functionalized Silica-based Mesoporous MCM-41

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Abstract

Modafinil [2-[(diphenylmethyl)sulfinyl]acetamide] is used clinically in the treatment of narcolepsy and sleeping disorders. The synthesis of modafinil, begins with the reaction of benzhydrol and thioglycolic acid in trifluoroacetic acid to afford benzhydrylsulfinyl acetic acid. The reaction of acid with thionyl chloride in benzene followed by treatment with ammonium hydroxide gave acetamide. Synthesis of novel heterogeneous chiral catalyst by a simple and efficient method has been reported. The first, a new derivative of chiral ligand (containing amine group) in 6 steps from a cheap and readily available substrate (4-aminobenzoic acid) were synthesized in good yield. Then, this chiral ligand immobilized on silica-based mesoporous MCM-41 through its amine group. The obtained catalysts were characterized with FT-IR, XRD, BET, SEM, IR, 1H NMR, ^{13}C NMR and mass spectral and used for the first time in oxidation of benzhydrylsulfinyl acetic acid and its derivatives. The reaction using this catalysts exhibits very good yield.

***Keywords*:** *Modafinil [2-[(diphenylmethyl)sulfinyl]acetamide], Functionalized silica-based mesoporous, MCM-41.*

Introduction

Enantiopure sulfoxides are important auxiliaries in asymmetric synthesis and chiral ligands in enantioselective catalysis[1–4]. Several methods are developed for the preparation of enantiopure sulfoxides. The most popular method to was discovered independently by Kagan [5,6] and Modena [7] using a modified sharpless catalytic system (ROOH/Ti(OiPr)$_4$/DET). Among these systems, a catalytic organometallic complex of a vanadium-chiral Schiff base using

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hydrogen peroxide as a terminal oxidant was developed by Bolm[8,9]. This method was later improved by Anson using the Schiff base to give higher enantioselectivities [10, 11]. Salen–manganese complexes, can also be used for the enantioselective oxidation of thioethers [12].However, this method gave disappointing results on the related compounds, modafinic acid and diphenylmethylthioacetamide. We applied copper complex of the functionalized silica-based mesoporous MCM-41 with chiral amino oxazoline ligands (Fig 2) as a catalyst to synthesis of a small library of this important class of modafinil. In this paper, we wish to report a enantioselective oxidation reaction of solfide, benzhydrylsulfinyl acetic acid and its derivatives, with hydroperoxide by using bidendatebis(oxazoline)-Cu(II) complex 9, that can be readily assembled from commercially available a simple and efficient method has been reported. The first, a new derivative of chiral ligand 8 (containing amine group) in 6 steps from a cheap and readily available substrate (4-aminobenzoic acid 3) was synthesized in good yield (Figure 1) [13-15]. Then, this chiral ligand immobilized on silica-based mesoporous MCM-41 through its amine group, in optimized reaction condition[16-19]. The obtained new catalyst was used for the first time in oxidation of benzhydrylsulfinyl acetic acid and its derivatives. The reaction using this catalysts exhibits very good yield and a decrease in enantioselectivity.

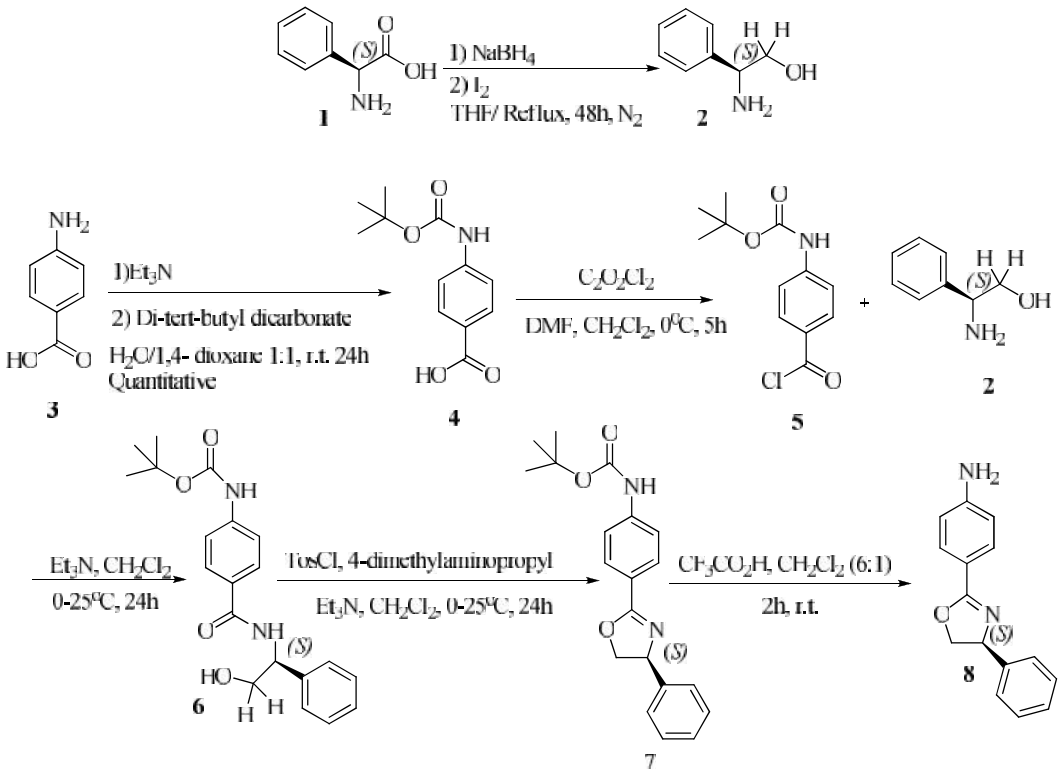


Figure 1.synthesis of chiral amino oxazoline**8**

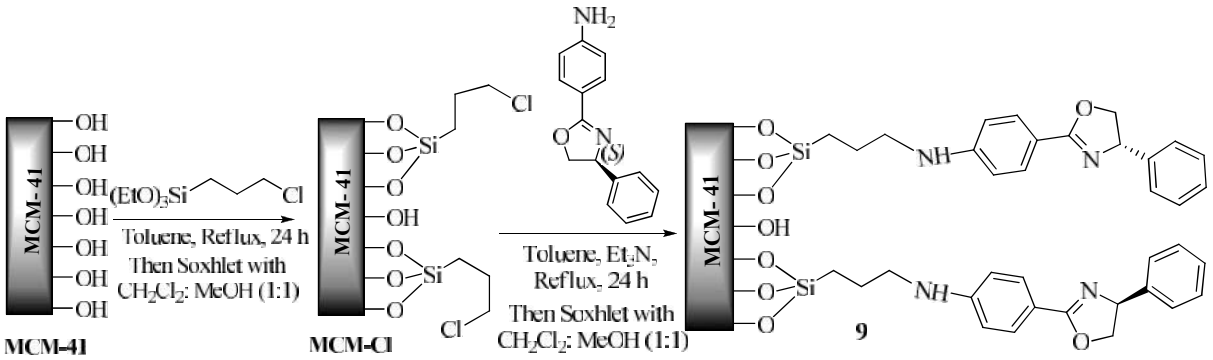
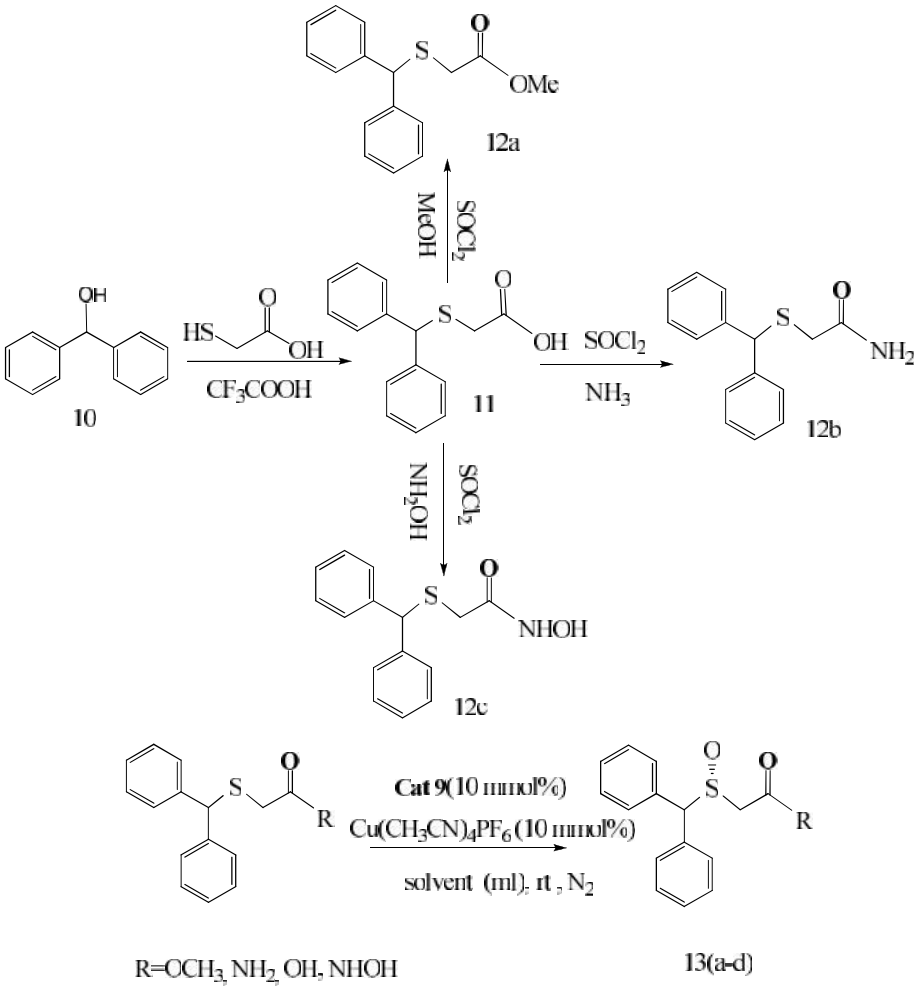


Figure 2.synthesis of functionalized silica-based mesoporous MCM-41 with chiral amino oxazoline



Scheme 1. Asymmetric synthesis of modafinil analogousof **13(a-d)**

Experimental

General melting points were recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a mattson 1000 FTIR. ^{1}H, ^{13}CNMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 MHz.All reactions were performed under a

nitrogen or argon atmosphere using Schlenk tube tech-niques. Enantiomeric excess were determined by HPLC analysis using a chiral cellulose carbamate-derived stationary phase (Chiralcel OD column) and phosphate buffer PH 9.0 mobile phase, UVdetector 254 nm. The samples were characterized by X-ray powder diffraction (XRD) using JEOL X-ray diffractometer with Cu Kα radiation. The low angle XRD pattern of mesoporous materials were exhibited by a diffractometer (PANalytical, model X'Pert Pro MPD) with monochromatized Cu Kα radiation (λ=1.54060 Å, 40.0 kV, 40.0 mA). Magnetic properties of the samples were determined by a vibrating sample magnetometer (VSM, Lakeshore). The particle morphologies of the as-prepared powders were observed by a Tescan (model Vega II) scanning electron microscopy (SEM) at 30 kV. DRS spectra was prepared via a Shimadzu (MPC-2200) spectrophotometer.

Synthesis of Cl-MCM-41

To prepare Cl-MCM-41,4.0 mL (16.6mmol) of CPTES was added slowly into a mixture of 2.0g of MCM-41and 30 mL of dry toluene. The reaction mixture was refluxed at 110◦C in a temperature controlled oil bath. After 24h of refluxing, the flask was cooled to room temperature. The solid phase was filtered and washed twice with dry toluene, once with methanol and dichloromethane to remove the un-reacted CPTES. The solid sample was then dried at100◦C for 24h.

*Synthesis of MCM-41-chiral amino oxazoline **9***

To prepare MCM-41-chiral amino oxazoline, chiral amino oxazoline (16.6mmol) was added to as uspensioncon-taining Cl-MCM-41(2.0g), dry toluene (30mL) and triethylamine (Et3N) (2.3mL,16.6mmol). The mixture was refluxed at 110◦C for 24h.The solid sample was separated by filtration and washed twice with dry toluene and thrice with methanol and dichloromethane to remove the excess to chiral amino oxazoline. After drying at 100◦C for 24h, the sample was ground to fine powder and labeled as MCM-41-chiral amino oxazoline.

*Synthesis of Benzhydrylsulfanylacetic acid **11***

A mixture of benzhydrol (50.0 g, 271.4 mmol) and thioglycolic acid (25.0 g, 271.4 mmol) in trifluoroacetic acid (280 mL) was stirred at room temperature for 4 h. The solvent was removed under reduced pressure to afford a crude solid. H_2O (280 mL) was added and the resulting precipitate collected by filtration. The solid was washed with hexane (350 mL) and dried to afford 69.2 g (99 %) of 11 as a white solid, mp 126–129 C: ^{1}H NMR (DMSO-d6): 7.1–7.6 (m, 10H); 5. (s, 1H); 3.0 (s, 2H); ^{13}C NMR (DMSO-d6): 171.5, 141.5, 129.3, 128.7, 128.0, 53.6, 34.4.

*Synthesis of Methyl Benzhydrylsulfanylacetate **12a***

A solution of thionyl chloride (20 mL, 274.8

mmol) in benzene (25 mL) was added in a dropwise manner to a solution of 11 (19.5 g, 75.5 mmol) in benzene (114 mL) and the resulting mixture heated at reflux for 2 h. The solvent was removed under reduced pressure to afford a crude orange oil. A solution of the oil in CH_3OH (300mL) was added cautiously to a vigorously stirred solution. The mixture was stirred vigorously for 2 h and the layers separated. The mixture was washed sequentially with CH2Cl2 (150 mL), 5% $NaHCO_3$(150mL), and saturated NaCl (200 mL), and then dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded 19.0 g (98%) of 12a as a white solid:^{1}H NMR ($CDCl_3$): 7.2–7.5 (m, 10H); 5.4 (s, 1H); 4.1 (q, $^2J_{H\text{-}H}$ 7 Hz, 2H); 3.1 (m, 2H); 1.2 (t, $^2J_{H\text{-}H}$ 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): 170.1, 140.2, 128.4, 128.3, 127.3, 61.1, 53.9, 33.5, 14.0.

Synthesis of 2-Benzhydrylsulfanyl acetamide ***12b***

A solution of thionyl chloride (20 mL, 274.8 mmol) in benzene (25 mL) was added in a dropwise manner to a solution of 11 (19.5 g, 75.5 mmol) in benzene (114 mL) and the resulting mixture heated at reflux for 2 h. The solvent was removed under reduced pressure to afford crude orange oil. A solution of the oil in CH_2Cl_2 (100mL) was added cautiously to a vigorously stirred solution of concd NH_4OH (250 mL). The mixture was stirred vigorously for 2 h and the layers separated. The aqueous mixture was extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 portion was washed with 5% NaHCO3 (75mL) and saturated NaCl (100 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a crude solid that was recrystallized from isopropyl ether to give 17.0 g (86%)of 12b as a white solid, mp 109–110 C : ^{1}H NMR ($CDCl_3$): 7.3–7.4 (m, 10H); 6.5 (bs, 1H); 5.4 (bs, 1H); 5.2 (s, 1H); 3.0 (s, 2H); ^{13}C NMR ($CDCl_3$): 171.3, 140.2, 128.7, 128.2, 127.6, 54.7, 35.5.

Synthesis of 2-Benzhydrylsulfanyl-N-hydroxyacetamide ***12c***

A solution of thionyl chloride (20 mL, 274.8 mmol) in benzene (25 mL) was added in a dropwise manner to a solution of 3 (19.5 g, 75.5 mmol) in benzene (114 mL) and the resulting mixture heated at reflux for 2 h. The solvent was removed under reduced pressure to afford crude orange oil. A solution of the oil in CH_2Cl_2 (100mL) was added cautiously to a vigorously stirred solution of concd. NH_4OH (250 mL). The mixture was stirred vigorously for 2 h and the layers separated. The aqueous mixture was extracted with CH_2Cl_2 (50 mL). The solvent was removed under reduced pressure and H_2O added to the residue. The aqueous mixture was made acidic by the addition of concd. HCl. The resulting precipitate was collected by filtration and dried to afford 9.5 g (92%) of 12c as a white solid, mp 105 C: ^{1}H NMR (DMSO-d6): 10.6 (bs, 1H); 8.9 (bs, 1H); 7.1–7.5 (m, 10H);

5.4 (s, 1H); 3.4 (s, 2H); ^{13}C NMR (DMSO-d6): 166.3, 141.8, 129.3, 128.7, 128.0, 127.9, 53.7, 32.7.

*Synthesis of Diphenylmethanesulfinylacetamide **R (-)-13b***

A solution of 12b (14.4 g, 56.0 mmol), $Cu(CH_3CN)_4PF_6$ (10mmol%) and 30% H_2O_2 (5.6 mL, 49.4 mmol) in CH_2Cl_2 (60 mL) was stirred at 25 C at 12 h. The mixture was poured into H_2O (230mL) and a white precipitate formed. The solid was collected by filtration and recrystallized from MeOH to afford 13.4 g (93%) of (-)-13b as a white solid, mp 162–163 C: ^{1}H NMR (DMSO-d6): 7.3– 7.7 (m, 10H); 6.1 (s, 1H); 5.3 (s, 1H); 3.7 (s, 1H); 3.3 (d, $^2J_{H-H}$ 13Hz, 1H); 3.2 (d, $^2J_{H-H}$ 13Hz, 1H); ^{13}C NMR (DMSO-d6): 166.3, 163.3, 137.2, 134.9, 133.2, 129.9, 129.7, 129.0, 128.8, 128.6, 128.5, 127.9, 127.9, 71.3, 68.7, 56.1, 55.8.

*Synthesis of [2-(Diphenyl)methanesulfinyl]-N-hydroxy-acetamide **R(-)-13c***

A solution of 12c (5.0 g, 18.3 mmol), MCM-41- chiral amino oxazoline9(10mmol%), $Cu(CH_3CN)_4PF_6$ (10 mmol%) and 30% H2O2 (2.0 mL, 40 mmol) in CH_2Cl_2 (50 mL) was stirred at 25 C at 12 h. The mixture was poured into H_2O (mL) and a white precipitate formed. The solid was collected and recrystallized from a mixture of ethyl acetate/isopropyl alcohol, 3:2 to afford 4.6 g (93%) of (-)-13c as a white solid, mp 156–157 C: ^{1}H NMR (DMSO-d6): 10.8 (bs, 1H); 9.1 (bs, 1H); 7.3–7.5 (m, 10H); 5.4 (s, 1H); 3.3 (d, $^2J_{H-H}$ 13Hz, 1H); 3.0 (d, $^2J_{H-H}$ 13 Hz, 1H); ^{13}C NMR (DMSO-d6): 161.1, 137.0, 134.9, 129.7, 129.1, 128.5, 128.0, 69.0, 53.8.

*Synthesis of Diphenylmethanesulfinylacetic acid **(R)(-)-13d***

A solution of 11 (5.0 g, 18.3 mmol), MCM-41-chiral amino oxazoline9(10mmol%), $Cu(CH_3CN)_4PF_6$ (10 mmol%) and 30% H_2O_2 (2.0 mL, 40 mmol) in CH_2Cl_2 (50 mL) was stirred at 25 C at 12 h. The mixture was poured into H_2O (mL) and a white precipitate formed. The solid was collected and recrystallized from a mixture of ethyl acetate/isopropyl alcohol, 3:2 to afford 4.3 g (86%) of (R)-13d as a white solid, mp 165–167 C : ^{1}H NMR (DMSO-d6): 13.2 (bs, 1H); 7.3–7.5 (m, 10H); 5.4 (s, 1H); 3.5 (d, $^2J_{H-H}$ 14 Hz, 1H); 3.3 (d, $^2J_{H-H}$ 14 Hz, 1H); ^{13}C NMR (DMSO-d6): 167.4, 136.6, 134.9, 130.3, 129.6, 129.1, 128.6, 128.5, 128.1, 128.0, 69.2, 55.4.

Result and discussion

The synthesis of (R)-modafinil, begins with the reaction of benzhydrol and thioglycolic acid in trifluoroacetic acid to afford benzhydrylsulfinyl acetic acid. The reaction of acid with thionyl chloride in benzene followed by treatment with ammonium hydroxide gave acetamide. The effects of the functionalized silica-based mesoporousMCM-41 with chiral amino oxazoline ligands were examined using 10

mol% Lewis acid as catalyst in a typical reaction of oxidation benzhydrylsulfinyl acetic acid and its derivatives with hydrogenproxide in various solvent (Scheme 1). Results are summarized in Table 1.The highest enantioselectivity (37%) and high yield were achieved by employing solvent of dichloromethane. The yields and enantiomeric rations of the products showed the temperature dependence of this process. A decrease in the reaction temperature from 25 oC to 0 oC and -25oC decreased the reaction yield and enantioselectivity (Table 1).

Table 1. Asymmetric synthesis of modafinilwith various solvent

Entry	Solvent	T (C)	Time(h)	**13b**[a]	
				Yield (%)[b]	Ee(%)[c]
1	CH_2Cl_2	0	32	88	17
2	CH_2Cl_2	25	12	93	37
3	CH_2Cl_2	-25	48	75	Race
4	MeOH	0	32	85	8
5	MeOH	25	28	93	Race
6	EtOH	0	16	90	10
7	EtOH	25	32	85	Race
8	$PhCH_3$	0	48	25	Race
9	$PhCH_3$	25	48	<15	n.d

[a]reaction was carried out in 5ml of solvent in the presence of 10% catalyst [$Cu(CH_3CN)_4PF_6$], unless otherwise noted
[b]Isolated yield.
[c]Determined by chiral HPLC analysis.

Considering the dichloromethane as the best solvent, we tested the effect of Cu salts (Table 2). In all cases, $Cu(CH_3CN)_4PF6$proved to be the best copper source while other Cu salts led to a decrease in the ee by race–17% and longer reaction times (entries 3-4 vs.2). The use of Cu (OTf)2 instead of $Cu(CH_3CN)4PF_6$ gave worse result in term of enantioselectivity (entry2). The effects of catalyst loading were also investigated and the best results were obtained when 10 mol % catalysts loading was used in the reaction. The ligand-to-metal ratio of 1:1 using 20mol % of ligand was investigated under the similar conditions and the isolated yields and enantioselectivityled to decrease in the results.Lowering the catalyst loading to less than 10 mol % led to a sharp decrease in the results. It should be noted, the addition of additives such as MS 4A, 3A did not give any observable changes in the results of the reaction and even lead to decreasing yields.

Table 2. Dependence of reaction with Lewis acid.

Entry	Lewis acid	Time(h)	**13a**[a]	
			Yield (%)[b]	Ee (%)[c]
1	$Cu(CH_3CN)_4PF_6$	12	93	37
2	$Cu(OTf)_2$	16	90	10
3	$Cu(OAc)_2$	23	92	Race
4	$Cu(Cl)_2$	28	76	Race
5	$Cu(CH_3CN)_4PF_6$[d]	22	88	Race

[a]reaction was carried out in 5ml of CH_2Cl_2 at room temperature in the presence of 10% catalyst, unless otherwise noted.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis.
[d]20% catalyst is used

Considering the optimized reaction conditions, we next examined the scope and generality of this reaction with various types of benzhydrylsulfinyl acetic acidand its derivatives and synthesized a small library of modafinil analogous **13(a–d)**(Table 3).

Table 3. Asymmetric synthesis of modafinil analogous**13(a-d)**

Entry	Metal	R	Product	Yield	Ee
1	$Cu(CH_3CN)_4PF_6$	OMe	13a	93	Race
2	$Cu(CH_3CN)_4PF_6$	NH_2	13b	90	37
3	$Cu(CH_3CN)_4PF_6$	NHOH	13c	93	17
4	$Cu(CH_3CN)_4PF_6$	OH	13d	86	10

The structures of products were assigned from their elemental and spectroscopic analyses including IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}HNMR spectrum of **13b** exhibits a doublet signal at δ = 3.2 ppmand a doublet at δ = 3.3 ppmwith $^3J_{HH}$ of about 13Hz which are related to H_b, H_a protons diastreotopics andconfirmed unambiguously the formation of a sulfoxide group. The obtained catalystwas characterized with FT-IR, XRD, BET, SEM, IR, ^{1}H NMR, ^{13}C NMR.FT-IR spectrum of the synthesized compound, has been assigned message group SiO-H in $\bar{\upsilon}$ = 3427 cm^{-1}, message group Si-O-Si asymmetric stretching in a $\bar{\upsilon}$ = 1086 cm^{-1} and symmetric stretching message in$\bar{\upsilon}$ = 807 cm^{-1}. X-ray diffraction pattern (XRD) was synthesized nanoporous MCM-41, be seen that the distribution of regular cylindrical symmetry hexagonal mesoporous which is entirely consistent with the pattern of resource. (Figure 3a)

Then nanoporous with chloropropyltriethoxysilane reacts to functionalized mesoporous

MCM-Cl is achieved. The consolidation of the group on the substrate, using a thermal bar graph, about% 61/15 was measured. The spectrum FT-IR functionalized MCM-41, reducing the severity of the message group, OH (br, $\bar{\upsilon}$ = 3427 cm^{-1}) and message stretching for 2 CH in the $\bar{\upsilon}$ = 2949 cm-1and message stretching C-Cl in the $\bar{\upsilon}$ = 707 cm^{-1} also indicates hang chloropropyltriethoxysilane groups. Reduce the severity of XRD functionalized nanoporousMCM-41, decreased symmetry of mesoporous and the reaction is it (Fig. 3b).Comparison of images Scanning Electron Microscope (SEM) of nanoporous Cl-MCM-41and MCM-41get them on the morphology Figure 4 is a substrate surface.

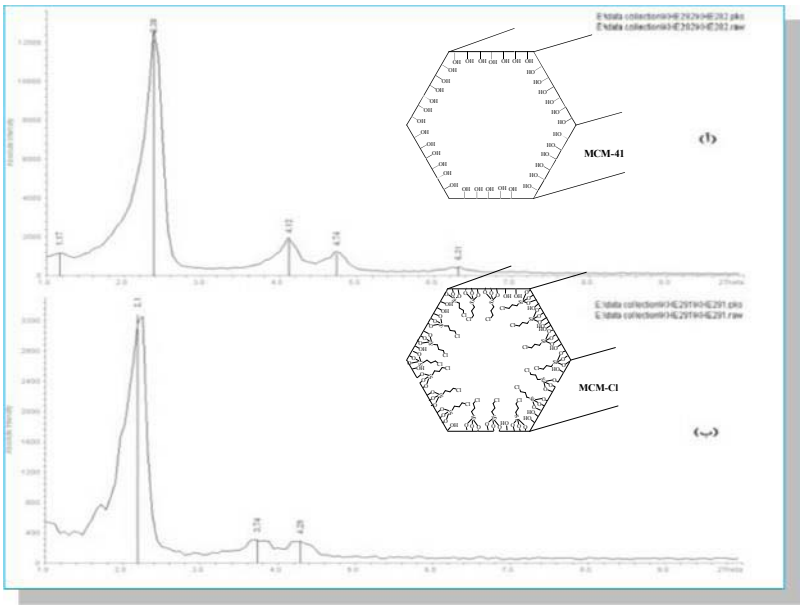


Figure 3. (a) X-ray diffractionpattern(XRD)nanoporousMCM-41(b) X-ray diffractionpattern(XRD)nanoporousCl-MCM-41.

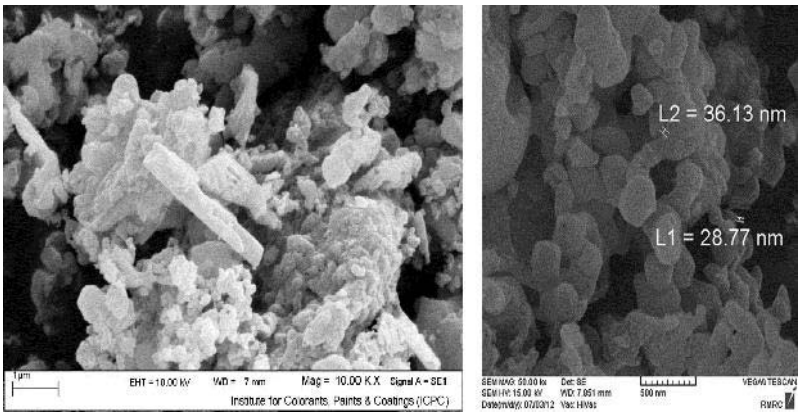


Figure 4. Comparison of scanning electronmicroscope (SEM)for theMCM-41 (right) andCl-MCM-41 (the left).

X-ray diffraction pattern (XRD) of compound9, MCM-41supports maintaining structural features, as well as reducing the intensity of diffraction XRD pattern of compound 9 in comparison with the XRD pattern of theCl-MCM-41,decreased symmetry of nanopores and reaction Figure 5.

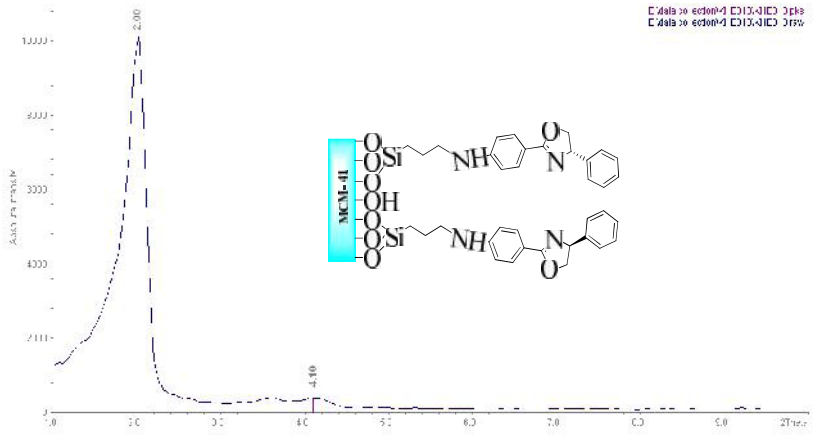


Figure 5. X-ray diffraction pattern (XRD) nanoporous MCM-chiral amino oxazolin **9.**

Conclusion

In conclusion, we applied copper complex of the functionalized silica-based mesoporous MCM-41 with chiral amino oxazoline ligands to synthesis of a small library of this important class of modafinil. We reported a enantioselective oxidation reaction of sulfide, benzhydrylsulfinyl acetic acid and its derivatives, with hydroperoxide by using bidendatebis (oxazoline)-Cu(II) complex 9, that can be readily assembled from commercially available a simple and efficient method has been reported. The structures of the products were elucidated using IR, ^{1}H NMR, ^{13}CNMR, and mass spectral data.

Acknowledgments

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