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## FULL PAPER



## Manganese(II) tetrasulfophthalocyanine covalently supported on natural silk: A new highly active catalyst for synthesis of benzoxazepine derivatives in water

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Ahmad Shaabani, Faculty of Chemistry, Shahid Beheshti University, GC, PO Box 19396-4716, Tehran, Iran. Email: a-shaabani@sbu.ac.ir Natural silk as a biodegradable, biocompatible, renewable, green and abundant biomaterial was used as a support for chemical immobilization of a water-soluble manganese(II) complex with a phthalocyanine ligand possessing covalent binding ability. The prepared manganese(II) tetrasulfophthalocyanine complex supported on natural silk revealed efficient catalytic activity and reusability for the synthesis of benzoxazepine derivatives in water at room temperature.

#### KEYWORDS

benzoxazepine, manganese(II) tetrasulfophthalocyanine, natural silk

## **1 | INTRODUCTION**

The utilization of natural protein fibres as green, biodegradable and renewable alternatives to current petroleum-based polymers is an area of growing research interest for the design and fabrication of new and applicable biomaterialbased systems. Silk as a fibroin-based biopolymer is among the most commonly used natural biopolymers in the world, which used extensively as good candidate for biomedical utilization. Silk fibres exhibit crystalline structure, with the polypeptide chains folded into specific β-sheets conformation.<sup>[1]</sup> The β-sheets conformation is stabilized by intramolecular bonds. Silk fibres (obtained from the cocoons of silkworm) are mainly composed of fibroin and sericin proteins.<sup>[2]</sup> Fibroin protein is the structural protein component of silk, which is covered by sericin protein.<sup>[3]</sup> Fibroin has attracted attention as an applicable protein due to its high tensile strength, mechanical properties, biodegradability, biocompatibility, renewability and ease of processing.<sup>[4-6]</sup> Silk fibroin protein has been investigated as a modifier for functionalization of nanomaterials to yield novel materials with specific properties due to its unique chemical properties.<sup>[7-9]</sup> Since silk proteins have various functional groups which can interact with metals or organometallic compounds, silk protein-based materials have found application as

supports for the immobilization of catalysts.<sup>[10–14]</sup> Primary structure of fibroin protein of silk is mainly based on the recurrent amino acid sequence (Gly-Ser-Gly-Ala-Gly-Ala).<sup>[9,15,16]</sup> Because of the structurally ordered amino acid chains in the fibroin protein, silk itself is highly desirable to maximize uniform catalyst loading.<sup>[9]</sup>

Macrocyclic porphyrin-like compounds known as phthalocyanines (Pcs) have unusual molecular stability caused by the symmetrically coordinated central atom and the ideal conjugation of double bonds in the aromatic skeleton. Metallophthalocyanines (MPcs) are simply accessible from a preparation point of view. MPcs are widely used in a variety of catalytic transformations due to their virtually zero toxicity.<sup>[17,18]</sup> The efficiency of MPcs in catalytic processes depends on the metal and complex structure.<sup>[19]</sup> Incorporation of various kinds of catalytically active metals in the Pc ligand and appropriate structural modifications of complex structure can be done to prepare MPcs with a variety of catalytic effects in organic transformations. Immobilization of MPcs onto various supports can provide recyclable catalysts with increased catalytic utility and activity, which simplifies the separation process and increases the effective surface area of the MPcs.

Sulfonated Pcs have a reactive anchor group that helps them to chemically bind to free amino or hydroxyl groups

of wool or cellulose in the dyeing procedure. This procedure is done in a two-stage process involving the adsorption of dye followed by fixing via reaction of the anchor group with the free amino or hydroxyl groups of the fibres.<sup>[20]</sup> The fibroin protein of natural silk has different kinds of amino acids among which serine has the -OH functional group. The presence of serine amino acid in fibroin protein of natural silk makes it possible to attach different compounds chemically using nucleophilic substitution reactions because of the presence of the -OH functional group in serine. Due to the presence of amino acid chains in the fibroin protein, natural silk as a suitable support can react with sulfonated Pc complexes of metals; therefore, we used natural silk as a support to covalently immobilize water-soluble manganese(II) tetrasulfophthalocyanine (MnTSPc). By immobilization of MnTSPc onto natural silk, a recyclable catalyst can be obtained with improved catalytic utility and activity.

In view of our interest in the synthesis of catalytic systems and their applications in organic transformations,<sup>[14,21-24]</sup> herein we report the successful preparation of MnTSPc covalently supported on natural silk (MnTSPc@silk). The synthesized MnTSPc@silk was investigated as a catalyst for the synthesis of benzoxazepine derivatives in water at room temperature.

### 2 | MATERIALS AND METHODS

#### 2.1 | General

Natural white silk (silkworm cocoons of Gilan, Iran) was washed with distilled water and ethanol, and then cut into very short pieces. All reagents were obtained from Aldrich or Merck and used without further purification. Manganese determination was carried out using flame atomic absorption spectrometry (FAAS; Shimadzu model AA-680 with a Mn hollow cathode lamp at 279.5 nm, using an air–acetylene flame) and inductively coupled plasma optical emission



**FIGURE 1** UV-visible spectra of natural silk and MnTSPc@silk in H<sub>2</sub>O-H<sub>2</sub>SO<sub>4</sub> (4:1)

spectrometry (ICP-OES; Varian Vista PRO Radial). UV–visible spectra were recorded employing an Analytik Jena Specord S600 diode array spectrometer. X-ray diffraction (XRD) pattern of the catalyst was recorded using a STOE STADI P with scintillation detector and secondary monochromator using Cu K $\alpha$  radiation ( $\lambda = 0.1540$  nm). Thermogravimetric analysis (TGA) was carried out using an STA 1500 instrument at a heating rate of 10 °C min<sup>-1</sup> in air. Scanning electron microscopy (SEM) observations were carried out with a Philips XL-30 ESEM instrument. All samples were sputtered with gold before observation. Microwave



FIGURE 2 EDS result for MnTSPc@silk



FIGURE 3 IR spectra of natural silk, MnTSPc and MnTSPc@silk

irradiation experiments were carried out with a Microsynth Milestone SRL microwave apparatus. Melting points were measured with an Electrothermal 9200 apparatus. Infrared (IR) spectra were recorded with a Shimadzu IR-470 spectrometer. <sup>1</sup>H NMR spectra were recorded with a Bruker









FIGURE 4 SEM images of (a, b) natural silk and (c, d) MnTSPc@silk

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DRX-300 Avance spectrometer at 300.13 MHz; chemical shifts are reported in parts per million (ppm). <sup>13</sup>C NMR spectra were recorded at 75.47 MHz; chemical shifts are reported in parts per million (ppm). Elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL.

# 2.2 | Experimental: synthesis of MnTSPc and MnTSPc@silk

## 2.2.1 | Synthesis of MnTSPc

Manganese(II) phthalocyanine (MnPc) was prepared using the controlled microwave heating of homogeneous powder, containing phthalic anhydride (0.88 g, 6.0 mmol), urea (1.6 g, 26.0 mmol), manganese(II) sulfate (0.27 g, 1.8 mmol) and ammonium heptamolybdate (0.02 g, 0.02 mmol) according to our previously reported procedures for the synthesis of metal(II) phthalocyanines.<sup>[25]</sup> Sulfonation of the synthesized MnPc was carried out by reaction of 1.0 mmol of MnPc with chlorosulfonic acid (7.0 mmol) in 1,2,4-trichlorobenzene (50 ml) at 180–190 °C for 2 h to afford manganese(II) trisulfophthalocyanine sulfonyl chloride.

## 2.2.2 | Synthesis of MnTSPc@silk

Natural silkworm cocoons were boiled for 30 min in an aqueous solution of  $Na_2CO_3$  (5% *w/v*) to extract the silk sericin, wax and impurities. The extracted silk fibroin was washed with deionized water and dried at room temperature (for a period of two days). Silk (0.1 g) was completely dispersed in dry dimethylformamide (DMF; 50 ml) with sonication and a solution of manganese(II) trisulfophthalocyanine sulfonyl chloride in 50 ml of dry DMF was added to the mixture and sonicated for 20 min. The temperature of the reaction mixture was raised to 100 °C and the mixture was magnetically stirred for about 24 h until the MnTSPc was substantially supported of the surface of the silk. The mixture of reaction was then filtered and the obtained catalyst washed



FIGURE 5 TGA curves of silk and MnTSPc@silk in air



FIGURE 6 XRD patterns of natural silk, MnTSPc and MnTSPc@silk

with water and ethanol in sequence, and dried (under vacuum at 60  $^{\circ}\mathrm{C}).$ 

## 2.3 | General procedure for catalytic reactions

To a magnetically stirred mixture of amine source (1.0 mmol) and 2-(2-formylphenoxy)acetic acid (1.0 mmol) in water (5.0 ml), MnTSPc@silk (0.06 g) was added. The reaction mixture was stirred at room temperature for 8 h. After completion of the reaction (monitored using TLC), the contents were filtered. The contents of the filtrate were extracted from reaction media with EtOAc. After drying (anhydrous  $Na_2SO_4$ ) and filtration of the organic phase, the filtrate was evaporated under reduced pressure to afford the crude product. The crude product was further purified by separation on a silica gel column to give the final product.

In the cases of amide formation from carboxylic acid and primary amine, a similar method was used by adding benzylamine (1.0 mmol) to the reaction medium containing diamine source (1.0 mmol) and 2-(2-formylphenoxy)acetic acid (1.0 mmol) in the presence of MnTSPc@silk catalyst (0.06 g) in water (5.0 ml) at room temperature for 8 h.

## **3** | **RESULTS AND DISCUSSION**

In our approach, natural silk was used as green, biodegradable, renewable and abundant support. First, water-soluble

TABLE 1 Optimization of reaction conditions for synthesis of benzoxazepine derivatives catalysed by MnTSPc@silk<sup>a</sup>

		$ \begin{array}{c}  & \text{H}_{2} \\  & \text{H}_$	,он —			
Entry	Catalyst	Amount of catalyst (g)	Solvent	Temperature	Time (h)	Yield (%) <sup>b</sup>
1	_	_	$H_2O$	r.t.	24	—
2	MnTSPc	0.01	$H_2O$	r.t.	8	65
3	MnTSPc@silk	0.06	$H_2O$	r.t.	8	97
4	MnTSPc@silk	0.05	$H_2O$	r.t.	8	85
5	MnTSPc@silk	0.04	H <sub>2</sub> O	r.t.	8	51
6	MnTSPc@silk	0.06	$H_2O$	Reflux	3	99
7	MnTSPc@silk	0.06	$CH_2Cl_2$	r.t.	8	62
8	MnTSPc@silk	0.06	$CH_2Cl_2$	Reflux	3	94
9	MnTSPc@silk	0.06	CHCl <sub>3</sub>	r.t.	8	60
10	MnTSPc@silk	0.06	CHCl <sub>3</sub>	Reflux	3	89
11	MnTSPc@silk	0.06	THF	r.t.	8	53
12	MnTSPc@silk	0.06	THF	Reflux	3	95
13	MnTSPc@silk	0.06	MeOH	r.t.	8	57
14	MnTSPc@silk	0.06	MeOH	Reflux	3	86
15	MnTSPc@silk	0.06	EtOH	r.t.	8	52
16	MnTSPc@silk	0.06	EtOH	Reflux	3	91
17	MnTSPc@silk	0.06	Toluene	r.t.	8	25
18	MnTSPc@silk	0.06	Toluene	Reflux	3	88

<sup>a</sup>Reaction conditions: *o*-phenylenediamine (1.0 mmol), 2-(2-formylphenoxy)acetic acid (1.0 mmol), solvent (5.0 ml). <sup>b</sup>Isolated yield.

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manganese(II) complex with a Pc ligand possessing covalent binding ability was synthesized. Next, a simple mixing of the manganese(II) complex with natural silk and a subsequent

separation yielded MnTSPc@silk catalyst. FAAS and ICP-OES methods were used for determination of manganese metal in the prepared MnTSPc@silk catalyst. The amount



	$(W) = NH_2 + V = CHO OH - Ia-i 2 O OH - Ia-i 1a-i 1a-i 1a-i 1a-i 1a-i 1a-i 1a-i 1$		
Entry	Amine source	Product	Yield (%) <sup>b</sup>
1	<i>o</i> -Phenylenediamine ( <b>1a</b> )	N N 0 3a	97
2	4-methylbenzene-1,2-diamine (1b)		95
3	4,5-Dimethylbenzene-1,2-diamine (1c)	$ \underbrace{ \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	95
4	4-nitrobenzene-1,2-diamine (1d)	$0_2N$ $N$ $3d$	92
5	(3,4-Diaminophenyl)(phenyl)methanone (1e)	O N N O Se	93
6	2,3-Diaminomaleonitrile (1f)	NC $N$ $NC$ $N$ $N$ $NC$ $N$ $N$ $NC$ $N$ $N$ $NC$ $N$ $N$ $N$ $NC$ $N$	95
7	2-aminophenol (1 g)	$\bigcup_{0}^{0} \bigcup_{3g}^{0}$	97
8	2-amino-5-methylphenol (1 h)		94
9	2-Aminobenzenethiol (1i)		98

<sup>a</sup>Reaction conditions: amine (1.0 mmol), 2-(2-formylphenoxy)acetic acid (1.0 mmol), H<sub>2</sub>O (5.0 ml), MnTSPc@silk (0.06 g), room temperature, 8 h. <sup>b</sup>Isolated yield.



SCHEME 1 Mechanism for synthesis of benzoxazepine derivatives catalysed by MnTSPc@silk

of MnTSPc in the catalyst was determined to be 9.94 wt%. The UV-visible spectral method was used to confirm the presence of MnTSPc in the prepared MnTSPc@silk catalyst. MnTSPc readily dissolves in water and the obtained solution is different in colour from forest green at lower pH values to light blue at higher pH; therefore MnTSPc@silk catalyst was dissolved with sonication in H<sub>2</sub>SO<sub>4</sub>. Upon addition to water, the forest green solution was obtained. The UV-visible absorption spectra of natural silk and the synthesized MnTSPc@silk catalyst dissolved in  $H_2O-H_2SO_4$  (4:1) are shown in Figure 1. As can be seen, silk does not show any characteristic bands in the region 250-850 nm. The UV-visible spectrum of MnTSPc@silk shows four bands centred at 360, 511, 638 and 717 nm due to the backbone of MnTSPc. The two strong bands centred at 638 and 717 nm and the weaker bands at 360 and 511 nm have been previously assigned to the monomeric species of MnTSPc at acidic pH values.<sup>[26,27]</sup> Since MnTSPc shows these characteristic bands in the UV-visible region, after attaching onto the silk support, the absorption intensities of MnTSPc can be used to estimate the amount of it anchored onto the silk. The concentration of MnTSPc was determined using calibration curves of prepared MnTSPc solution standards. The obtained result for the amount of MnTSPc using the UV-visible method is consistent with results of FAAS and ICP-OES methods.

Energy-dispersive spectroscopy (EDS) analysis was used to determine the chemical composition of MnTSPc@silk, which corroborates the presence of manganese and sulfur in the catalyst (Figure 2). The serine amino acid of the fibroin protein of silk which has —OH functional group can participate in a nucleophilic substitution reaction with the —SO<sub>2</sub>Cl group of manganese trisulfophthalocyanine sulfonyl chloride to produce MnTSPc@silk. The covalent interaction between silk and the MnTSPc complex in MnTSPc@silk was investigated using the IR spectral method (Figure 3). The covalent attachment of MnTSPc to the silk is confirmed by the observation of new adsorption bands at 1165 and 1384 cm<sup>-1</sup>, related to the S=O of sulfonate functional group via the reaction between the —OH group of the silk and the —SO<sub>2</sub>Cl group of manganese trisulfophthalocyanine sulfonyl chloride.

Metal phthalocyanine molecules are prone to aggregation that greatly decreases the active sites of a catalyst. So, by attaching Pc molecules to natural silk, aggregation between the Pc molecules is prevented during the reaction processes, maintaining isolation between catalytically active sites.<sup>[28]</sup> Due to the unique structure of silk, use of this biopolymer as a support for covalent immobilization of MnTSPc prevents the aggregation of MnTSPc. Preventing of aggregation of MnTSPc provides more active sites for catalytic application. To prove this claim, images of the surface morphology of the prepared MnTSPc@silk catalyst were obtained. The surface morphology of natural silk and MnTSPc@silk was analysed using SEM. The SEM images in Figure 4(a,b) show the uniform surface of silk. Because MnTSPc covalently immobilizes on the silk as monomeric molecules, the aggregation of MnTSPc should not occur on the silk surface. The SEM images of the MnTSPc@silk catalyst do not show any aggregation of MnTSPc, which corroborates the good dispersion of MnTSPc on the surface of silk (Figure 4c,d). The difference between the surface morphology of natural silk and MnTSPc@silk (Figure 4b,d) is caused by material processing. The preparation of the MnTSPc@silk catalyst is done by covalent attachment of MnTSPc to the natural silk, the reaction conditions needed for which alter the surface morphology of silk in MnTSPc@silk.

TGA is widely used to rapidly evaluate the thermal stability and thermal degradation behaviours of various materials. Figure 5 shows the TGA curves of silk and MnTSPc@silk under air atmosphere. As can be seen from Figure 5, silk and MnTSPc@silk start to lose weight below 255 and 252 °C, which is attributed to the removal of adsorbed water on the surface of silk and MnTSPc@silk, respectively. With increasing the temperature, the main mass loss for silk takes place in two steps above 255 °C. The process of decomposition of MnTSPc@silk occurs in the temperature range 252-700 °C related to the decomposition of the silk support and MnTSPc. The difference between the thermal stability behaviours of natural silk and the prepared catalyst is expected, because the material processing changes the surface morphology of natural silk and MnTSPc@silk. Since the extraction of the silk sericin, wax and impurities was done

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TABLE 3	Amide formation c	catalysed by MnTSPc@silk <sup>a</sup>	Chemist	try
		$(W) = \begin{bmatrix} NH_2 \\ NH_2 \\ NH_2 \\ H_2 \\ H_2 \\ 0 \\ 0 \\ H_2 \\ H_2$	$W \models N + f$ $8a-g \qquad H^{-R}$ $W \models N + f$ $3a,b,e,f$	
Entry	Amine 1	Amine 7	Product	Yield (%) <sup>b</sup>
1	1a	Phenylmethanamine (7a)	N Sa N O NH	96
2	1a	Methanamine (7b)	3a	91
3 4		Ethanamine (7 <b>c</b> ) Propan-1-amine (7 <b>d</b> )		95 89
5 6		2-Methylpropan-1-amine ( <b>7e</b> ) Butan-2-amine ( <b>7f</b> )		90 93
7	1a	(2-Chlorophenyl)methanamine (7g)	N N H CI	88
8	1b	7a	N Sc N O NH	95
9	1b	7b	3b	88
10 11		7c 7d		85 92
12 13		7e 7f		96 91
14	1b	<i>p</i> -Tolylmethanamine ( <b>7h</b> )	H O H	92
15	1b	7g	N N H O NH CI	99

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### TABLE 3 (Continued)



<sup>a</sup>Reaction conditions: amine **1** (1.0 mmol), 2-(2-formylphenoxy)acetic acid (1.0 mmol), amine **7** (1.0 mmol), H<sub>2</sub>O (5.0 ml), MnTSPc@silk (0.06 g), room temperature, 8 h. <sup>b</sup>Isolated yield.

by boiling of natural silkworm cocoons in an aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, the temperature of completion of degradation for MnTSPc@silk is lower than that for natural silk.

Further characterization of the structure of the MnTSPc@silk catalyst was conducted using XRD analysis. The parent natural silk exhibits two broad characteristic diffraction peaks at  $2\theta$  values of around  $9.5^{\circ}$  and  $19.5^{\circ}$ . The XRD pattern of MnTSPc shows diffraction peaks at  $2\theta$  values of 23.0°, 26.2°, 27.2°, 29.4°, 31.6°, 32.9°, 45.3°, 56.4°, 66.1° and 75.2°. As shown in Figure 6, the pattern of the MnTSPc@silk catalyst manifests two broad peaks at  $2\theta = 9^{\circ}$  and 21°. In the XRD pattern of MnTSPc@silk, the characteristic diffraction peaks of constituent MnTSPc are

not observed because the diffraction peaks of silk are stronger than those of MnTSPc. These results indicate that MnTSPc is dispersed completely onto the surface of silk as molecular dispersion.

The initial catalytic study was carried out by treating *o*-phenylenediamine with 2-(2-formylphenoxy)acetic acid in water at room temperature for 24 h. The obtained result shows that no benzoxazepine formation occurs (Table 1, entry 1). When the same reaction is carried out in the presence of MnTSPc@silk catalyst, the yield of benzoxazepine is increased to 97% (entry 3). If reflux conditions are used, the rate of formation of **3a** is increased (entry 6). In continuation, various parameters like amount of catalyst, solvent and



**SCHEME 2** Mechanism for synthesis of primary and secondary amides catalysed by MnTSPc@silk

temperature were screened in order to increase the efficiency of catalyst in the tandem condensation–cyclization– amidation– $C(sp^3)$ –H bond oxidation reaction sequence. The mentioned reaction was screened with various amounts of catalyst. The obtained results show that all of reactions are inferior than when using 0.06 g of MnTSPc@silk (entries 3–5). In the case of optimization of reaction



FIGURE 7 Successive use of the prepared MnTSPc@silk catalyst in the synthesis of **3a** 

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conditions using various solvents, the results indicate that product formation is observed with dichloromethane, chloroform, tetrahydrofuran (THF), ethanol and methanol at room temperature in moderate yields (entries 7, 9, 11, 13, 15). In all cases, if high temperature (reflux conditions) is used, the rate of formation of **3a** is higher and the yield of the product also increases (entries 8, 10, 12, 14, 16). When the reaction is carried out in toluene as reaction medium, the product is obtained in low yield (entry 17). Increasing the temperature to reflux conditions increases the reaction rate of benzoxazepine formation and **3a** is produced in 88% yield (entries 17 and 18). With regard to the results obtained, water was selected as preferred solvent at room temperature.

To show the role of the support in the mentioned reactions, the synthesis of benzoxazepine using *o*-phenylenediamine and 2-(2-formylphenoxy)acetic acid was carried out using MnTSPc and MnTSPc@silk under the same reaction conditions (entries 2 and 3). The obtained results show that MnTSPc@silk has higher catalytic activity than unsupported MnTSPc. By covalent immobilization of MnTSPc on the silk support as monomeric molecules, the stability and dispersity of MnTSPc are improved in the reaction media. This immobilization of MnTSPc on the silk support as monomeric molecules seems to enhance the efficiency of the prepared catalyst.

After optimization of the reaction conditions, the MnTSPc@silk-catalysed benzoxazepine synthesis was explored with a wide range of amine sources. The obtained results are summarized in Table 2.

The possible mechanism for the formation of products  $3\mathbf{a}-\mathbf{i}$  is shown in Scheme 1. The initial event is the condensation of amine group with aldehyde group in the presence of the MnTSPc@silk catalyst. Then, intermediate 5 is produced from the nucleophilic attack of X on the imine site of intermediate 4. By intramolecular amide formation from the secondary amine and carboxylic acid, intermediate 6 (if X = NH) or products  $3\mathbf{g}-\mathbf{i}$  (if X = O and S) are produced. Finally, C(sp<sup>3</sup>)—H bond oxidation of intermediate 6 in the presence of the MnTSPc@silk catalyst produces benzoxazepine derivatives  $3\mathbf{a}-\mathbf{f}$ .

In the mentioned reactions, amide formation from carboxylic acid and secondary amine takes place in water at room temperature using the green catalyst. Because of the importance of amide formation under green conditions including green solvent (water), ambient temperature and use of green catalyst, the prepared MnTSPc@silk catalyst was investigated in the synthesis of amide products from carboxylic acid and both primary and secondary amines. Hence, benzylamine was added to the reaction media containing *o*-phenylenediamine and 2-(2-formylphenoxy) acetic acid in the presence of the MnTSPc@silk catalyst in water at room temperature (Table 3). The obtained results

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show that benzylamine reacts with carboxylic acid and **8a** is obtained. More reactions with various diamines and primary amines were examined in the presence of the MnTSPc@silk catalyst in water at room temperature. In the cases of benzylamines, reaction between carboxylic acid and primary amine occurs in competition with secondary amine (entries 1, 7, 8, 14, 15, 21, 22). So, benzylamines deliver the corresponding primary amides in good yields. In the cases of primary aliphatic amines, secondary amine reacts with carboxylic acid in competition with primary amine and products of cycloaddition reaction are obtained (entries 2–6, 9–13, 16–20, 23–27).

The possible mechanism for the synthesis of primary and secondary amides is shown in Scheme 2. After the condensation of amine group with aldehyde group, intermediate 4 is produced. By nucleophilic attack of NH<sub>2</sub> on the imine site of intermediate 4, intermediate 5 is obtained. In the cases of primary benzylamines, benzylamine reacts with carboxylic acid and product 8 is obtained. But, in the cases of primary aliphatic amines, secondary amine reacts with carboxylic acid in competition with primary amine. Therefore, products of cycloaddition reaction are obtained.

Since water-soluble MnTSPc is supported on insoluble silk via covalent attachment, the separation process of the homogeneous MnTSPc is simplified. Thus, recyclability of the MnTSPc@silk catalyst was examined in the synthesis of benzoxazepines. Accordingly, the MnTSPc@silk catalyst was separated from reaction media by filtration, dried (under vacuum at 60 °C), and reused for five repeat cycles in the synthesis of **3a**. The obtained results (Figure 7) indicate only minor decreases in the reaction yields, which means the activity of the MnTSPc@silk catalyst is maintained during successive uses.

## **4** | **CONCLUSIONS**

Water-soluble MnTSPc which has covalent binding ability was supported on natural silk. The prepared MnTSPc@silk was introduced as a novel catalytic system. An efficient MnTSPc@silk-catalysed method was developed for the synthesis of benzoxazepines in water as the reaction medium. The obtained catalytic system is an efficient heterogeneous catalyst for widely applicable syntheses of benzoxazepines. More importantly, water as a green medium was used for these reactions. The MnTSPc@silk catalyst has good recyclability in the synthesis of benzoxazepines. By covalent immobilization of water-soluble MnTSPc on silk, not only are the stability and dispersity of the catalyst improved in aqueous solution but also separation of the homogenous MnTSPc catalyst from water as the reaction medium is simplified.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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