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MnO₂@Fe₃O₄ MNP: An Efficient and Recyclable Heterogeneous Catalyst for Benzylic sp³ C-H Oxidation

Akanksha M. Pandey,^a Sandip G. Agalave,^a Chathakudath P. Vinod,^b and Boopathy Gnanaprakasam^{a*}

Abstract: Herein, we report highly chemoselective and efficient heterogeneous $MnO_2@Fe_3O_4$ MNP catalyst for the oxidation of benzylic sp³ C-H group of ethers using greener TBHP as an oxidant to afford ester derivatives in high yield under batch/continuous flow module. This catalyst was also effective for the benzylic sp³ C-H group of methylene derivatives to the ketone in high yield which can be easily integrated into continuous flow condition for scale up. The catalyst is fully characterized by spectroscopic techniques and found that 0.424% $MnO_2@Fe_3O_4$ catalyzes the reaction and magnetic nanoparticle of this catalyst render easy recovery from the reaction mixture. The recovered catalyst was recycled for twelve cycles without any loss of the catalytic activity. The advantages of $MnO_2@Fe_3O_4$ MNP are its catalytic activity, easy preparation, recovery, and recyclability, gram scale synthesis with TOF of up to 8670.6 h⁻¹ and low metal leaching during the reaction.

Introduction

Designing a sustainable chemical process for the functional group transformation is one of the formidable challenges in organic synthesis.^[1] Metal-catalyzed direct conversion of the C-H bond to carbonyl compounds using oxidant is greatly increased in the last few decades among the synthetic chemist due to the molecular economy and reaction greenness. Hence, oxidation of a saturated sp³ C-H bond can rapidly install an oxygen atom on a carbon atom and have attracted considerable attention, given that most of the recognized drugs and natural products are oxygen-containing compounds.^[2] In recent years, a plethora of methodologies have been developed for direct benzylic sp³ C-H bond oxyfunctionalization.^[3] However, most of the commonly employed conditions include stoichiometric quantities of transition metal salts which pose problems in terms of cost, toxicity and atom economy.[4] Selective benzylic oxidation using catalytic amount of transition metals such as Cr,^[5] Mn,^[6] Co,^[7] Ru,^[8] Rh,^[9] Fe,^[10] Re,^[11] etc and post-transition metal Bi^[12] has been reported. The reported homogeneous transition metal catalysts for the direct transformation of activated methylene group have several advantages to afford the ketone in moderate to good yield. However, in spite of the advances, there are limitations exist in this transformation such as the decomposition of the metal catalysts, the lack of regioand stereoselectivity, exothermic reactions, the problems of catalyst extraction and recycling as well as product purification

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[b] Chathakudath P. Vinod CSIR-NCL Catalysis and Inorganic Chemistry Division, Pune, India Supporting information for this article is given via a link at the end of the document. make them less ideal for the synthesis of fine chemicals where product contamination with heavy metal is highly undesirable which led to environmental and economic concern in large scale synthesis.^[13] Thus, there is ongoing interest in finding more sustainable catalysts that assist catalytic transformation to take place under more realistic and environmentally benign conditions. Also, there is a report for transition metal free benzylic sp³ C-H bond oxidation of activated methylene group to form ketone or ester which requires external additives NaNO₂ and HCI.^[14] Recently, J. Tan and coworkers^[15] showed tert-Butyl hydrogen peroxide (TBHP) mediated direct oxidation reaction of benzylic sp³ C-H bonds to ketones, but there is no such report on the continuous flow benzylic sp³ C-H bond oxidation of ether to ester.

Heterogenization of the presented homogeneous catalysts, particularly expensive and/or toxic heavy metal complexes could resolve these problems. From these perspectives various materials such as mesoporous silica,^[16] activated carbon,^[17] polymers,^[18] biomass,^{[19],} etc. have been used as a support to generate a heterogeneous catalytic system. Recently, Sekar, *et.al.* reported the oxidation of alkylarene using binaphthyl stabilized Pt nanoparticles (Pt-BNP) as a catalyst. ^[20]Advantageously, these supported catalyst systems can be effectively recycled and reused with the inherent catalytic activity.

Magnetic nanomaterials are found to be more selective and effective than conventional heterogeneous materials as a robust, readily available, extremely small size and large surface area of heterogeneous catalyst support. Further, it has more volume ratio which allows more reactions to occur at the same time and consequently speed up the reaction process.[21-22] Advantageously, they are magnetically separable, which eliminates the requirement of catalyst filteration or centrifugation after completion of the reaction. The Fe₃O₄ MNPs, due to their unique physicochemical properties becoming increasingly significant in the field of catalysis, imaging, photonics, nanoelectronics, sensors, biomaterials, and biomedicine.^[23] In literature, these Fe₃O₄ nanoparticles are used for the selective oxidation of benzylic and allylic C-H bonds to carbonyl compounds using TBHP as an oxidant.^[24] Manganese-based catalyst has attracted considerable research interest because of its nanostructures have a large surface area and highest catalytic activity as well as it is cheap, mild and nontoxic oxidative reagent used for the selective oxidation of various functional groups.^[25] Thus, developing an Mn supported on Fe₃O₄ MNPs for benzylic sp³ C-H oxidation of ether and methylene compounds are highly attractive and desirable approach in terms of the green chemistry points of view; which will also allow finding a more economical and environmentally benign procedure.

Herein, we wish to disclose a facile and atom-economical methodology for the direct oxidation of benzylic sp³ C-H bond using $MnO_2@Fe_3O_4$ as an MNP supported catalyst for the oxidative esterification of benzylic ethers to form various ester derivatives (Scheme 1).



Scheme 1. General protocol for the benzylic sp^3 C-H oxidation using $MnO_2@Fe_3O_4\ MNP$ catalyst.

The newly developed catalytic system proceeds with high selectivity and broad substrate scope under mild reaction conditions with TBHP as the environmentally benign terminal oxidant. It is also found that the present catalytic system was effective and versatile for the oxidative benzylic sp³ C-H group to form various ketone derivatives. This novel and chemoselective methodology work well in batch and continuous flow module. To date, to the best of our knowledge, MnO₂@Fe₃O₄ MNP catalyzed benzylic sp³ C-H group oxidation of ethers and methylene derivatives using TBHP as an oxidant have not been reported.

Results and Discussion

The synthesis of nano-sized MnO₂@Fe₃O₄ was achieved by the procedure reported for Fe(OH)₃@Fe₃O₄.^[26] The % of Mn on Fe₃O₄ support was analyzed by Microwave Plasma Atomic Emission Spectroscopy (MP-AES) analysis which showed that catalyst contains 0.424% of Mn.

Figure 1 represents the XRD pattern of 0.424% MnO₂@Fe₃O₄ nanocomposites, showing that the peaks of both Fe₃O₄ and MnO₂ appear along with enhanced peak intensity which is caused by overlapping of both the peaks. As revealed, diffraction peaks are completely corresponding to the standard pattern characteristic peaks of the magnetite cubic inverse spinel structure (JCPDS 01-074-2435).



Figure 1. PXRD data of (a) Fe₃O₄; (b) MnO₂; (c) MnO₂@Fe₃O₄

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Figure 2. TEM images of $MnO_2@Fe_3O_4$ catalyst (a) Fresh catalyst, (b) used catalyst; Lattice fringes for (c) fresh catalyst, (d) used catalyst; Histograms generated for (e) fresh, (f) used $MnO_2@Fe_3O_4$ catalyst.

The morphology of the fresh and used $MnO_2@Fe_3O_4$ catalyst was evaluated by TEM analysis (Figure 2). From TEM analysis it is found that, the average particle size of fresh catalyst is 10.48 nm, whereas average particle size of used catalyst is 12.34 nm.

The N₂ adsorption-desorption isotherms and pore size distribution of fresh $MnO_2@Fe_3O_4$ catalyst is shown in Figure 3. From figure 3, it is clear that pure $MnO_2@Fe_3O_4$ catalyst exhibited isotherm of type IV, which is a typical characteristic of the mesoporous material.^[27] Specific surface area (SBET) was calculated by employing the Brunauer–Emmett–Teller (BET) method and the pore size distribution is obtained by means of Barrett–Joyner–Halenda (BJH) method equation using the adsorption isotherm branch. Figure 3 shows that the volume adsorbed increases with increasing relative pressures for all isotherms which are due to the volume filling of micropores in Fe₃O₄ membrane. The BET specific surface area and the pore diameter of $MnO_2@Fe_3O_4$ were found to be 13.19 m²/g and 0.059 cm³/g respectively.

Thermal gravimetric analysis (TGA) of the $MnO_2@Fe_3O_4$ composite nanoparticles were also performed at the range of 25 to 800 °C, with a temperature ramp rate of 10 °C min⁻¹ under a nitrogen atmosphere (Figure 4). As shown in Figure 4, the first weight loss stage (below 150 °C) can be attributed to the evaporation of water and solvent molecules onto the surface of

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Figure 3. BET isotherm of MnO2@Fe3O4 catalyst



Figure 4. Thermogravimetric analysis of (a) Fe₃O₄; (b) MnO₂@Fe₃O₄ catalyst

the catalyst. The weight loss of nanocomposites is about 3.3 % at 300-550 °C, corresponding to the thermal decomposition of the crystal phase transformation of Fe₃O₄ to γ -Fe₂O₃. Thus, the results indicate that MnO₂@Fe₃O₄ catalyst has excellent stability at temperatures as high as 800 °C. Surface morphology of fresh MnO₂@Fe₃O₄ nanocomposite was determined by FESEM (Figure 5). The FESEM image of MnO₂@Fe₃O₄ showing the formation of spherical particles with an average size 14-23 nm range. The EDAX analysis reveals that Fe, O, and Mn are the main elements present with Fe being the most abundant in the selected field.

To confirm the XRD results, the compositions and the valence states of fresh $MnO_2@Fe_3O_4$ MNP were further characterized with XPS and the results are shown in Figure 6. The Mn peak is analyzed in figure 6a, which shows that each broad peak can be classified into two parts at 641.52 and 643.06 eV for $Mn2p_{3/2}$ and 653.58 and 656.34 for $Mn2p_{1/2}$. The peaks at 641.52 and 643.06 eV are the characteristics of Mn^{3+} while





Figure 5. (a) FESEM images of $MnO_2@Fe_3O_4$ catalyst; (b) EDAX of $MnO_2@Fe_3O_4$ catalyst



Figure 6. XPS for fresh MnO_2@Fe_3O_4 MNP catalyst of (a) Mn $2p_{3/2}$ and $2p_{1/2};$ (b) Fe $2p_{3/2}$ and $2p_{1/2};$ (c) O 1s

those at 653.58 and 656.34 eV are the characteristics of Mn⁴⁺. ^[28-29] Moreover, the Fe spectrum is depicted in Fig. 6b, and two dominant peaks located at 711.0 and 724.23 eV are in good accordance with Fe $2p_{3/2}$ and Fe $2p_{1/2}$ spin orbit peaks along with other peaks which are consistent with the standard Fe₃O₄ XPS spectrum in which Fe is present in the form of Fe²⁺ and Fe³⁺. For the O1s XPS spectrum (Figure 6c), the spectrum contains three main peaks located at 530.09, 530.70, and 531.98 eV.[^{30]} The XPS results for used MnO₂@Fe₃O₄ MNP is in ESI.

Catalytic studies

Initially, the conversion of (benzyloxy)benzene 1a into phenyl benzoate 2a was chosen as a model reaction using 7 mmol of TBHP (5-6 M in decane) as an oxidant in acetonitrile (ACN) solvent at room temperature for 24 hrs. To identify the importance of the catalyst for the oxidation of (benzyloxy)benzene 1a, a blank control experiment was performed (Table 1, entry 1), and no phenyl benzoate 2a was detected. Heating of 1a in ACN by using 5 mol % Mn(OAc)₃.2H₂O gave 23% of phenyl benzoate 2a along with the recovery of starting material (Table 1, entry 2). In another control experiment only with Fe₃O₄, 33% yield of phenyl benzoate 2a was observed when the reaction carried out at 80 °C (Table 1, entry 3).

Table 1. Optimization of the reaction conditions (solvent) for the benzylic sp³

MnO₂@Fe₃O₄ MNP afforded 55% of 2a (Table 1, entry 5). Increasing the temperature up to 100 °C has no influence on the outcome of the reaction (Table 1, entry 6). Performing this reaction with other solvents such as dichloroethane (DCE), dichloromethane (DCM), chlorobenzene, diethyl carbonate (DEC) and dimethylsulfoxide (DMSO) has not improved the yield (Table 1, entry 7-11). However, no phenyl benzoate was detected when 1,4-dioxane, dimethoxyethane (DME) and acetone were employed as a solvent (Table 1, entry 12-14).

Table 2. Optimization of the reaction conditions (oxidant/additive) for the benzylic sp³ C-H group^a



C-H group											
		catalyst			entry	catalyst (50 mg)	oxidant	Additive /ligand	yield (%)		
	0 0 -	TBHP in decane solvent, temp.			1	MnO ₂ @Fe ₃ O ₄	TBHP	-	55		
	1a		2a		2	MnO2@Fe3O4	4-Methyl pyridine-N- oxide	-	-		
entry	catalyst (50 mg)	solvent	temp (°C)	yield (%)	3	MnO ₂ @Fe ₃ O ₄	$K_2S_2O_8$	-	-		
1	-	ACN	80	nd	4	$MnO_2@Fe_3O_4$	TEMPO	-	-		
2	Mn(OAc) ₃ .2H ₂ O	ACN	80	23	5	$MnO_2@Fe_3O_4$	NHPI	-	30		
3	Fe ₃ O ₄	ACN	80	33	6	MnO ₂ @Fe ₃ O ₄	TBHP	NEt ₃	-		
4	MnO2@Fe3O4	ACN	rt -	38	7	$MnO_2@Fe_3O_4$	TBHP	Pyridine	66		
5	MnO ₂ @Fe ₃ O ₄	ACN	80	55	8	$MnO_2@Fe_3O_4$	4-Methyl pyridine-N- oxide	Pyridine	-		
6		ACN	100	55	9	MnO ₂ @Fe ₃ O ₄	$K_2S_2O_8$	Pyridine	-		
7	MnO ₂ @Fe ₃ O ₄	DCE	80	48	10	MnO ₂ @Fe ₃ O ₄	TEMPO	Pyridine	-		
8		DCM Oblassharesea	80	30	11	MnO ₂ @Fe ₃ O ₄	NHPI	Pyridine	60		
9		Chiorobenzene	80	50	12	MnO ₂ @Fe ₃ O ₄	TBHP	2,2'-bipyridine	80		
10		DEC	80	50	13	Mn@Al ₂ O ₃	TBHP	2,2'-bipyridine	75		
11	MnO2@Fe3O4	DMSO	80	55	14	Ru@Fe ₃ O ₄	TBHP	2,2'-bipyridine	72		
12	MnO ₂ @Fe ₃ O ₄	1,4-Dioxane	80	nd							
13	MnO ₂ @Fe ₃ O ₄	DME	80	nd	additive	aReaction conditions: (benzyloxy)benzene 1a (1mmol), oxidant (7 mmol), additive (10mol%) and 50 mg of catalyst were stirred at 80 °C (see table 1) for					
14	MnO ₂ @Fe ₃ O ₄	Acetone	80	nd	24 hrs.						

Reaction conditions: (benzyloxy)benzene 1a (1mmol), TBHP in decane (7 mmol), and 50 mg of catalyst were stirred at various temperature (see table 1) for 24 hrs.

Whereas 0.424% MnO₂@Fe₃O₄ catalyst at room temperature condition afforded 1a in 38% yield (Table 1, entry 4). Further, heating of 1a in ACN solvent using 50 mg of 0.424 % Furthermore, we have also optimized the effect of various oxidants and additives for the oxidation reaction. Oxidants such as 4-methyl pyridine-N-oxide, K₂S₂O₈, TEMPO, and NHPI are failed to deliver or giving less yield of phenyl benzoate 2a (Table 2, entries 2-5). Based on the previous studies,^[31] the role of the nitrogen-containing ligand was pivotal in the benzylic sp³ C-H oxidation reaction. This is because that nitrogen-containing

ligand such as triethylamine, pyridine, 2,2'-bipyridine could behave as a hydrogen bond acceptor with TBHP to speed up the formation of t-butoxyl radical. This radical could abstract the hydrogen from a benzylic carbon atom of the substrate.[32]There is no (benzyloxy)benzene 2a formation when triethylamine was used as a additive (Table 2, entry-6). Moreover, the good conversion of about 66% was obtained when 10 mol% of pyridine used as a additive (Table 2, entry 7). Other oxidants have no effect on the conversion of (benzyloxy)benzene when pyridine used as a base (Table 2, entries 8-10). The reactions proceeded smoothly when the reaction carried out by using TBHP as the oxidizing agent and 2,2'-bipyridine as an additive in ACN as the solvent, afforded the desired (benzyloxy)benzene 2a in 80% yield (Table 2, entry 12). Furthermore, other supported catalysts such as Mn@Al2O3 and Ru@Fe3O4 under similar reaction conditions are also afforded esters 2a in good yield (Table 2, entries 13-14). From the results of optimization, the reaction condition was obtained bv best reacting (benzyloxy)benzene 1a (1 mmol), 50 mg of 0.424% MnO₂@Fe₃O₄ MNP as a catalyst, 10 mol% 2,2'-bipyridine as an additive and 5-6 M TBHP in decane (7 mmol) as an oxidant in ACN solvent (2.0 mL) at 80 °C for 24 hrs.

After the optimal conditions established, the scope of this reaction was investigated with various benzylic ethers and the results are summarized in Scheme 2. This oxidative reaction is well tolerated with various electron donating (**2b-2d**). It is noteworthy that, the reaction conditions were compatible with the presence of halogenated groups which can extend the possibility for further functionalization. Interestingly, reaction with benzylic aliphatic ether **1k-n** is smoothly converted into corresponding ester **2k-n** in excellent yield. This reaction is highly chemoselective for benzylic ethers giving corresponding esters in excellent yields; however, there is no ester formation with alkylated phenol **10** and allylic ether **1p**.

In order to demonstrate the general utility of this synthetic strategy, we carried out gram scale reactions in batch (Scheme 2). Two representative benzyloxy benzene, one with a methyl substituted **1b** and the other with a halogen-substituted **1g**, were chosen to react with TBHP in presence of supported $MnO_2@Fe_3O_4$ MNP catalyst under optimized reaction condition. The reactions were performed in 10 mmol scales using 0.500 g of $MnO_2@Fe_3O_4$ at 80 °C for 24 hrs. after which **2b** and **2g** were obtained in 86% and 80% yields, with TON = 208095.7; TOF = 8670.0 h⁻¹ and TON = 208095.7; TOF = 8670.6 h⁻¹ respectively.

To expand this reaction for sustainable continuous flow process, the optimized batch reaction condition was transferred to a continuous flow reactor. In continuous flow, the reaction and separation of the $MnO_2@Fe_3O_4$ MNP can be performed simultaneously which avoid the mechanical degradation of the supported catalyst. Developing a continuous flow process for sp³ C-H oxidation reaction using 0.424% $MnO_2@Fe_3O_4$ MNP catalyst can improve efficiency and safety for the TBHP mediated reaction. Hence, continuous flow reactions were performed using Holmarc syringe pump (Model no.-HO-SPLF-2D) and by preparing the catalyst bed in the Omnifit column reactor (Scheme 3).

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Scheme 2. Substrate scope for ester synthesis in batch condition

Table 3. Optimization of the reaction conditions for the benzylic ${\rm sp}^3$ C-H group in continuous flow^a

entry	catalyst/ additive ^b	substrate (1a): TBHP	flow rate (ml/min)	temp (°C)	t _R (min)/ cycle	yield (%) ^c
1	MnO ₂ @Fe ₃ O ₄	0.05:0.25	0.1	rt	17.10/1	10
2	MnO ₂ @Fe ₃ O ₄	0.05:0.35	0.1	rt	17.10/1	10
3	MnO ₂ @Fe ₃ O ₄	0.05:0.35	0.1	80	17.10/2	50
4	MnO ₂ @Fe ₃ O ₄	0.05:0.35	0.1	100	17.10/2	50
5	MnO ₂ @Fe ₃ O ₄	0.05:0.45	0.1	80	17.10/2	50

^aReaction conditions: 0.05 M solution of 1a + 0.25-0.45 M solution of TBHP (5.0–6.0 M in decane) prepared from in 20 mL ACN and flown on 0.424% MnO₂@Fe₃O₄ catalyst loaded bed reactor with the help of 1.7 mL syringe pump (Model no.-HO-SPLF-2D). ^b0.1 mmol of 2,2'-bipyridine ligand used, t_R = residence time. ^clsolated yields.

For our initial study, we chose (benzyloxy)benzene **1a** as a model substrate and a set of reaction conditions was attempted (Table 3). Initially, 0.05:0.25 M solution of **1a**:TBHP in presence of 0.10 mmol of 2,2'-bipyridine as a ligand in acetonitrile solvent was reacted by flowing it through the Omnifit fixed bed reactor containing 0.424% $MnO_2@Fe_3O_4$ catalyst (1.0 g; void volume 1.7 mL; flow rate 0.1 mL/min) at room temperature it furnished 10 % of product **2a** after one cycle (Table 3, entry 1). Increase in the molar concentration of TBHP up to 0.35 does not improve the outcome of the reaction (Table 3, entry 2). Effect of temperature has a great influence on the esterification of ether

1a. A best-optimized condition was obtained by increasing temperature up to 80 °C, to afford the product **2a** in 50% yield after two cycles (Table 3, entry 3). This reaction required only 17.10 min. to afford the final product of ester **2a**. Further increase in the temperature and molar concentration of TBHP has no effect on the formation of product **2a** (Table 3, entries 4 and 5).

Having established the optimal reaction conditions, various benzylic ethers (**1a-n**) were tested in a continuous flow to explore the generality of this oxidative transformation. By screening different substrate in a continuous flow, and we found that the present catalytic system was not compatible in a continuous flow and afforded moderate yields (15 to 50%) of the ester product after 2 runs (Scheme 3).



Scheme 3. Continuous flow setup and substrate scope for ester synthesis

The catalytic selective oxidation of benzylic sp³ C-H group to the corresponding carbonyl compounds is one of the mainly significant reactions in the synthesis of fine chemicals and pharmaceutically important ingredients.^[1] We also investigated the catalytic activity of $MnO_2@Fe_3O_4$ catalyst in batch as well as in continuous flow reactor for ketone synthesis using ethylbenzene **3a** as a model substrate and using TBHP as an oxidant Table 4. In batch, the oxidation of ethylbenzene (1mmol) **3a** for the generation of acetophenone **4a** was carried out using 5 mmol of TBHP (5-6 M in decane) in 2.0 mL acetonitrile at 80 °C for 7 h (Table 4). Control catalytic experiments of ethylbenzene **3a** were performed on $Mn(OAc)_3.2H_2O$ and Fe_3O_4 (Table 4, entries 1-2) and under the same reaction conditions.



Reaction conditions: ^aEthylbenzene **3a** (1mmol), TBHP in decane (5 mmol), and 50 mg of catalyst were stirred at 80 $^{\circ}$ C (see table 4) for 7 hrs. ^b 5 mol% catalyst was used

The conversions were 72 % and 48% when using Mn(OAc)₃.2H₂O and Fe₃O₄ respectively. 0.424% MnO₂@Fe₃O₄ was found to be superior to the others and produced the desired product acetophenone 4a in 83 % in isolated yield. The present catalytic system has been optimized again in a continuous flow to acclimatize the benzylic sp3 C-H oxidation reaction of ethylbenzene 3a. The reaction solvents such as toluene and methanol led poor yield of desired product 4a. The bestoptimized condition was obtained by a flowing mixture of a 0.05M solution of ethylbenzene 3a and 0.25M solution of TBHP (5-6 M in decane) by keeping a flow rate of 0.1 mL/min. affording 95 % of desired product 4a in residence time of $t_R = 17.10$ min (Table 5).

Having established the optimal reaction conditions in batch and in a continuous flow, a series of substrates were used to examine the generality of substrates and the catalytic activity of the $MnO_2@Fe_3O_4$ MNP catalyst (Scheme 4). The reactions proceeded smoothly in acetonitrile as the solvent and using TBHP as the oxidizing agent afforded the desired oxidative product **4a** in excellent yields in both batch and continuous flow. The yields were generally comparable to the batch reaction, but reactions are completed in a shorter duration of time in continuous flow (17.10 minutes) as compared to the batch condition (7 hrs.).

Besides model substrate, other substrates such as 9*H*-xanthene, diphenylmethane, 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1H-indene, 9H-fluorene, and 2-ethylnaphthalene afforded the desired ketones (**4b-g**) in good to excellent yield under batch and continuous flow module. Substituted ethylbenzene containing an electron-donating functional group also afforded respective ketone products (**4h-i**) in good to excellent yield (72-90%). On the other hand, methylene groups adjacent to a heterocyclic ring in 1*H*-oxindole, and 1-methyl oxindole were also converted into the corresponding ketones (**4j-k**) in excellent yield.



^aReaction conditions: 0.05 M solution of 3a + 0.25 M solution of TBHP (5.0–6.0 M in decane) was flown on 0.424% MnO₂@Fe₃O₄ catalyst loaded on Omnifit fixed bed reactor with the help of 1.7 mL syringe pump (Model no.-HO-SPLF-2D).



 $\ensuremath{\textbf{Scheme}}$ 4. Substrate scope for ketone synthesis in a batch as well as in a continuous flow module

To check the stability and productivity of the heterogeneous $MnO_2@Fe_3O_4$ MNP catalyst, we have performed a long time experiment in continuous flow. For this, substrate **3a** was chosen as a model substrate. For instance, 11 mmol of **3a** was pumped continuously for 12 hrs with a flow rate of 0.1 mL/min to afford 10.43 mmol of product **4a**. The progress of product **4a** formation was monitored by using ¹H-NMR which clearly indicates that the present catalyst is highly efficient and productive.

Recyclability of the catalyst

The recyclability of a heterogeneous catalyst is an important application in industry. The reusability and recyclability of the $MnO_2@Fe_3O_4$ MNP catalyst were studied for the benzylic oxidation of compound **1b** (Figure 7) and **3b** (Figure 8) for the ten and twelve catalytic cycles respectively in batch condition. Furthermore, this catalyst is still active for the further oxidation reaction. After completion of each cycle, the catalyst was separated from the reaction mixture simply with the help of a magnetic needle retriever, washed with acetonitrile and ethyl acetate three times, dried at 100 °C for 2 hrs and then the catalyst was used directly for the next cycle without any additional treatment. The yield of the product remained the same without any extension of reaction time. This result clearly indicates the efficiency of the catalyst which was not lost over a prolonged reaction.





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Figure 8. Recyclability of $MnO_2@Fe_3O_4$ MNP for the synthesis of 9H-xanthen-9-one $(\mbox{4b})$

Hot filtration test

In order to check the heterogeneity of the catalyst, a hot filtration test was performed for the benzylic sp³ C-H oxidation of **1a** to investigate whether the reaction proceeded in a heterogeneous or a homogeneous approach. After continuing the reaction for 16 h, the catalyst was separated by magnetic retriever and found that 60% of the product **2a**. No further enhancement in the product **2a** formation was observed after the separation of the MNP catalyst. Moreover, Microwave Plasma Atomic Emission Spectroscopy measurement of the filtrate showed the absence of Mn in the supernatant solution of the reaction mixture. This study clearly shows that Mn was intact to a great extent with the heterogeneous support and no leaching occurred during the catalytic reaction.

Conclusions

In summary, we demonstrated that MnO₂@Fe₃O₄ MNP is an efficient heterogeneous catalyst for the direct benzylic sp³ C-H oxidation of ethers by using TBHP as an oxidant to afford the ester in higher yield. This process was also applicable to benzylic sp³ C-H oxidation of methylene compounds to furnish ketone derivatives under batch and continuous flow module in higher yield. The main advantages of this procedure are mild reaction conditions, a demonstration in batch as well as in continuous flow module, scalable synthesis with high TOF values, easy and quick isolation of products, and recyclable of catalyst for more than 12 cycles. Hence, we believe that the present catalyst will find a wide range of applications in organic synthesis as well as in industry.

Experimental Section

Materials and characterization: All the chemicals are purchased Sigma Aldrich or Alfa-Aesar. Deuterated solvents were used as received. All the solvents used were dry grade. Column chromatographic separations performed over 100–200 Silica-gel. Visualization was accomplished with UV light and phosphomolybdic acid (PMA), Ceric ammonium molybdate

(CAM) stain followed by heating. The iron (III) chloride (product number: 44939) was purchased from Sigma Aldrich. All the experiments were carried out without maintaining the inert condition. The flow chemistry experiments were carried on Holmarc syringe pump (Model no.-HO-SPLF-2D). 1H and 13C NMR spectra were recorded on 400 and 100 MHz, respectively, using a Bruker 400 MHz or JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Highresolution mass spectra were recorded with Waters-synapt G2 using electrospray ionization (ESI-TOF). Fourier-transform infrared (FTIR) spectra were obtained with a Bruker Alpha-E Fourier transform infrared spectrometer. Powder X-ray diffraction (PXRD)patterns were measured on Bruker D8 Advanced X-ray diffractometer at room temperature using Cu Karadiation (λ = 1.5406 Å) with a scan speed of 0.5° min-1 and a step size of 0.01° in 20. BET was recorded on Quantachrome Instruments. Thermogravimetric analysis was recorded on a Perkin Elmer STA 6000, TGA analyzer under air atmosphere with a heating rate of 10 °C/min. The Hi-Resolution Transmission Electron Microscopy (HRTEM) imaging was performed using Jeol JEM2200FS (200 kV) HRTEM instrument. The XPS was collected using Thermo Scientific Kalpha+ spectrometer using a monochromated Al Kalpha (1486.6 eV) source. The base pressure of the spectrometer was always better than 5x 10-9 mbar. The electron flood gun was on during acquisition for charge neutralization. The wide area spectrum was collected using 200 eV pass energy and individual corelevels at 50 eV.

1. General procedure for the synthesis MnO2@Fe3O4 MNP catalyst

A mixture of FeCl₃.6H₂O (4.32 g, 16 mmol) and FeCl₂.4H₂O (1.60 g, 8 mmol) was dissolved in 40 mL deionized water. The resultant solution was left to be stirred for 30 min at 80° C. Then ammonia solution (25% (w/w)) was added in a drop-wise manner over 5 min to the stirring mixture to maintain the reaction pH about 11. The resulting black dispersion was stirred vigorously for 1h at room temperature and then was refluxed for 1h. The black magnetite Fe₃O₄ nanoparticles were isolated by magnetic decantation, washed several times with deionized water and then dried at 80 °C for 4 h. To introduce reactive Mn on the surface of the magnetic nanoparticle (MNP), 0.6 g of dried Fe₃O₄ nanoparticles were suspended in a mixture of 50 mL ethanol and then, 0.6 g of Mn(OAc)_{3.2H2}O was ultrasonically dispersed. After complete dissolution and dispersion, the nanoparticles were separated from the ethanol solution by magnetic decantation and dried at 80 °C for 4h. MnO2@Fe3O4 magnetic nanoparticles were obtained by drop-wise addition of aqueous ammonia (25% (w/w)) to the dried brown nanoparticles under vigorous stirring. Finally, the MnO2@Fe3O4 MNP were magnetically separated, washed with water, and dried in an oven at 100 °C for overnight.

2. General procedure for the synthesis of the esters from sp³-CH oxidation of (benzyloxy)benzene derivatives in batch

In a 20 mL glass seal tube, catalyst (25 mg), (benzyloxy)benzene derivatives (0.5 mmol, 1 equiv) in ACN (2 mL) were added TBHP (5-6M in decane, 3.5 mmol, 7 equiv), 0.05 mmol of 2,2'-bipyridine and the tube was sealed by using a crimper. The mixture was stirred at 80 °C for 24 hrs. After completion, the reaction mixture was allowed to cool to room temperature. It was then diluted with EtOAc and the catalyst was separated with an external magnet and washing twice with EtOAc. The mixture was extracted with EtOAc, the volatiles were removed under reduced pressure, and the crude product was purified by column chromatography to afford the ester products. All of the esters were identified by spectral comparison with literature data.

3. General procedure for the synthesis of the esters from sp³-CH oxidation of (benzyloxy)benzene derivatives in a continuous flow

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0.05 M solution of the substrate and 0.35 M of 5.0-6.0 M TBHP in decane and 0.1 mmol of 2,2'-bipyridine in 20 ml of ACN solvent was pumped through syringe pump packed with 1.5 g of 0.424% MnO₂@Fe₃O₄ (up to 5cm) is heated at 80 °C with the flow rate of 0.1 mL min⁻¹. A 3.5 to 3.8 psi back pressure regulator was placed after the reactor. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using ethyl acetate: hexane as an eluent to afford the ketone product.

4. General procedure for oxidation of benzylic ${\rm sp^3}$ C-H group of methylene derivatives to the ketone in batch

In a 20 mL glass seal tube, catalyst (50 mg), alkyl benzene (1 mmol, 1 equiv) in ACN (2mL) was added t-BuOOH (5-6M in decane, 5 mmol, 5 equiv) and the tube was sealed by using a crimper. The mixture was stirred at 80 °C for 7 h. After completion, the reaction mixture was allowed to cool to room temperature. It was then diluted with EtOAc and the catalyst was separated with an external magnet and washing twice with EtOAc. The mixture was extracted with EtOAc, the volatiles was removed under reduced pressure, and the crude product was purified by column chromatography to afford the desired product.

5. General procedure for oxidation of benzylic ${\rm sp}^3$ C-H group of methylene derivatives to the ketone in a continuous flow

0.05 M solution of the substrate and 0.25 M of 5.0-6.0 M TBHP in decane in 20 ml of ACN solvent was pumped through syringe pump packed with 1.5 g of 0.424% MnO₂@Fe₃O₄ (up to 5cm) is heated at 80 °C with the flow rate of 0.1 mL min⁻¹. A 3.5 to 3.8 psi back pressure regulator was placed after the reactor. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using ethyl acetate: hexane as an eluent to afford the desired product.

6. Study of lifetime of the catalyst and gram scale synthesis of benzylic sp³ C-H group of methylene derivatives to the ketone in a continuous flow

0.05 M solution of the substrate **3a** (1.166g, 10.99 mmol) and 0.25 M of TBHP (5.0-6.0 M in decane, 7.08 g, 54.99 mmol) in 110 ml of ACN solvent was pumped through syringe pump packed with 1.3 g of 0.424% $MnO_2@Fe_3O_4$ (up to 3 cm) is heated at 80 °C with the flow rate of 0.1 mL min⁻¹ at 3.5 bar pressure for 12 hrs. The reaction mixture was monitored at regular intervals by ¹H-NMR analysis. The entire reaction fraction was concentrated in a rotary evaporator to afford 1.25 gm of acetophenone **4b** as yellowish oil.

7. General procedure for catalyst recovery for the synthesis of the esters from (benzyloxy)benzene derivatives in batch

In a 20 mL glass seal tube, catalyst (25 mg), (benzyloxy)benzene derivatives (0.5 mmol, 1 equiv) in ACN (2 mL) were added TBHP (5-6M in decane, 3.5 mmol, 7 equiv), 0.05 mmol of 2,2'-bipyridine and the tube was sealed by using a crimper. The mixture was stirred at 80 °C for 24 h. After completion, the reaction mixture was allowed to cool to room temperature; the supported catalyst was separated by an external magnet and washed with acetonitrile and ethyl acetate for three times, then dried and directly used in the next run.

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Keywords: MnO₂@Fe₃O₄ MNP • Benzylic sp³ C-H Oxidation • TBHP • Continuous flow • Carbonyl Compounds

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MnO₂@Fe₃O₄ MNP: An Efficient and Recyclable Heterogeneous Catalyst for Benzylic sp³ C-H Oxidation

Highly chemoselective and efficient heterogeneous $MnO_2@Fe_3O_4$ MNP catalyst for the oxidation of benzylic sp³ C-H group to afford ester and ketone derivatives in high yield under batch and continuous flow module was reported.