



Article

Unprecedented Proline-Based Heterogeneous Organocatalyst for Selective Production of Vanillin

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Abstract: An organocatalytic system based on an unprecedented proline analogue and iron oxide magnetic nanoparticles (Prn/Fe₂O₃@SiO₂) was designed and employed in vanillin production from isoeugenol and vanillyl alcohol. Full characterization of the obtained catalyst revealed the successful functionalization of the nanoparticle surface with the organic moieties. The activity of the magnetic bifunctional material was compared with its proton-unexchanged counterpart. Interestingly, the oxidation of isoeugenol resulted in being highly dependent on the acidic functionalities of the organocatalyst. Nonetheless, the catalytic performance of the proton-unexchanged catalyst suggested that the acidic and basic sites of the Prn/Fe₂O₃@SiO₂ exhibited a synergic effect, giving rise to higher conversion and selectivity. The presence of bifunctional groups in the proline analogue, together with the magnetic properties of the iron oxide nanoparticles, could lead to high efficiency, versatility, recoverability, and reusability.

Keywords: vanillyl alcohol; isoeugenol; organocatalyst; vanillin; magnetic core-shell

1. Introduction

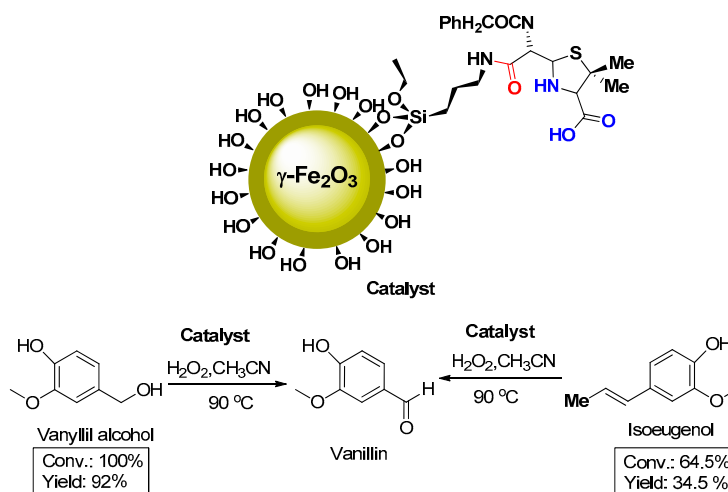
Valorization of lignocellulosic biomass has become an attractive approach for the production of added value chemicals and fuels, decreasing as well, environmental problems related to agricultural residues. Lignocellulosic biomass is typically composed by three main constituents: cellulose, hemicellulose, and lignin. In particular, lignin is a highly functionalized aromatic compound, which could lead to the design of outstanding chemical platforms. In this sense, vanillin is one of the most preminent molecules, which can be obtained from lignin derived compounds such as eugenol, isoeugenol, and ferulic acid via oxidation pathways [1]. Synthetic vanillin is commonly used as flavoring agent in food, cosmetic, pharmaceutical, and fine chemical industries. Nowadays, this molecule is mainly produced from petro-based intermediates, predominantly glyoxylic acid and guaiacol, employing non-sustainable synthetic methodologies such as Riedel process [2]. Although synthesis of vanillin has been explored for many years, much more effort should still be devoted to excavating facile an environmentally-friendly protocols for the catalytic oxidation of lignin model compounds using cost effective organo-catalytic based technologies.

Vanillin synthesis from isoeugenol and vanillyl alcohol should be further investigated in order to find new alternatives to the conventional oxidation methods that require stoichiometric amounts of inorganic oxidants such as potassium permanganate, which are highly toxic and polluting [3].

In order to minimize chemical waste, the scientific community is moving towards the use of green oxidants including, H_2O_2 [4,5] and molecular oxygen [6]. In addition, the inherent arduous separation and recovery of homogeneous catalysts have led to the development of heterogeneous systems, as a priority of research activity in the green chemistry field. Thus, the use of clean oxidants and heterogeneous catalytic systems, open new possibilities to further develop environmentally friendly catalyzed processes [7,8]. In this regard, supported iron oxide nanoparticles has been reported to convert the isoeugenol to vanillin using H_2O_2 [9].

Moreover, the use of heterogeneous catalytic systems usually requires a filtration or centrifugation step to recover the catalyst. In this regard, magnetic nanoparticles (MNPs) has attracted a great interest since they can be easily separated from the reaction mixture by using a magnetic external field and reused for several cycles [10–12]. Nonetheless, maintaining the stability of these particles for a long time without agglomeration or precipitation is still a challenge [13,14]. Aiming to stabilize MNPs, several strategies have been proposed, such as coating or encapsulation in the form of core–shell structures or nanocomposites [15]. In particular, core–shell frameworks composed of $\gamma\text{-Fe}_2\text{O}_3$ and silica ($\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$) are one of the most stable and efficient reported nanostructure for catalysis. Silica surface can be easily post-modified with a wide variety of catalytic species by using different organosiloxane precursors [16,17].

Functionalization of $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$ with organocatalysts could represent significant progress in the field of catalysis [18–20]. So far, many organocatalysts have been developed based on their carboxylic and amine functionalities, which could play a crucial role in the catalytic reaction [21–23]. Particularly, proline is an amino acid which contains α -amino and α -carboxylic acid groups [24,25]. Proline and its derivatives have been used as asymmetric catalysts in proline organocatalysis reactions [26], including aldol reaction [27], Knoevenagel [28], and multicomponent reaction [29]. To the far of our knowledge, the preparation of proline based solid-supported organocatalysts commonly requires several reaction steps and non-environmentally friendly procedures [30]. Although organocatalysis have been extensively explored, much remains to be accomplished, especially in the context of a truly sustainable protocols. Herein, we have developed an innovative strategy to produce a magnetic supported organocatalyst. This methodology includes the functionalization of $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$ with 3-aminopropyltriethoxysilane (APTES), aiming to obtain $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2\text{-NH}_2$. Subsequently, a proline analogue was synthesized using a one-step procedure by post-modifying the $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2\text{-NH}_2$ surface with penicillin G, which finally led to formation of an unprecedented proline analogue organocatalyst (Prn/ $\text{Fe}_2\text{O}_3@\text{SiO}_2$). In particular, this work has focused on penicillin G but it could be in principle extended to other proline derivatives. The obtained material was applied to the catalytic oxidation of isoeugenol and vanillyl alcohol (Scheme 1).



Scheme 1. Schematic depiction of vanillin production from the different reactants in this work.

2. Results and Discussion

A magnetic-separable proline-based heterogeneous organocatalyst was successfully prepared following the protocol depicted in Figure 1. The unique properties of MNPs, which simplify the recovery of the material, together with the outstanding functionalities provided by the proline analogue, make Prn/ $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ a potential candidate as catalyst in a broad range of reactions. An innovative protocol was designed for the in situ formation of a proline analogue on the surface of the aminofunctionalized $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ by reaction with penicillin G. The latest molecule contains a four-membered β -lactam ring which can react with the amine group of $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-NH}_2$. Consequently, a secondary amine adjacent to the carboxylate group was formed, corresponding to the proline analogue. Furthermore, the carboxylic acid group is formed from carboxylate to by proton exchange.

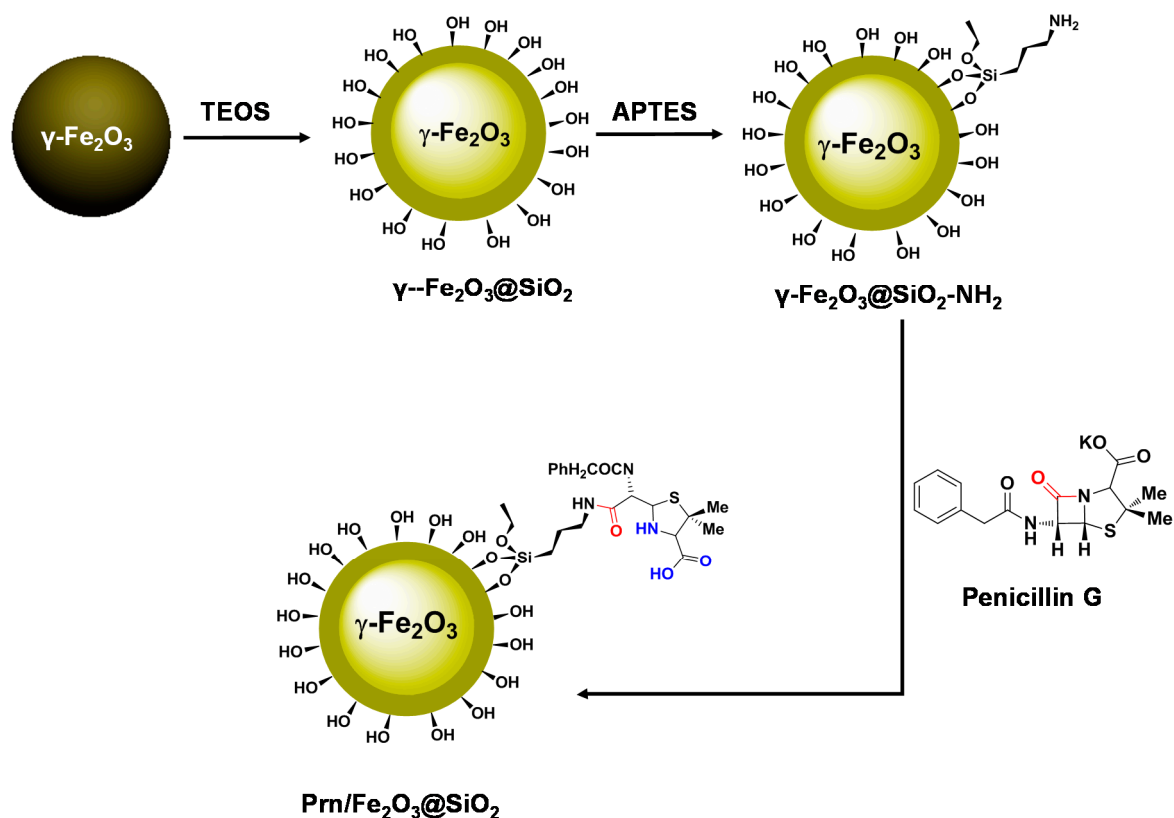


Figure 1. Overview of the preparation of Prn/ $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ magnetic organocatalyst.

SEM image of Prn/ $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ exhibited a homogeneous distribution with the formation of nanospherical particles (Figure 2a). This analysis displayed a certain tendency to form agglomerates, mostly associated with the magnetic properties of the obtained nanostructures. SEM analysis revealed a particle size average of 14.5 nm. As expected, EDS spectrum (Figure 2b) of Prn/ $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ showed the presence of Si, O, N, C, S, and Fe, which is in accordance with SEM-mapping results (Figure 2e–j). Both EDS and SEM-mapping techniques corroborates the effective functionalization of the iron oxide MNPs and therefore confirmed that penicillin G successfully reacted with the amine group on the $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-NH}_2$ surface, giving rise to the desired proline analogue. TEM analysis also confirmed the nanometric structure of Prn/ $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ γ (Figure 2c), in good agreement with SEM results. Selected area electron diffraction (SAED) pattern of Prn/ $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ (Figure 2d) revealed clear rings in accordance with the formation of crystalline gamma iron oxide [31].

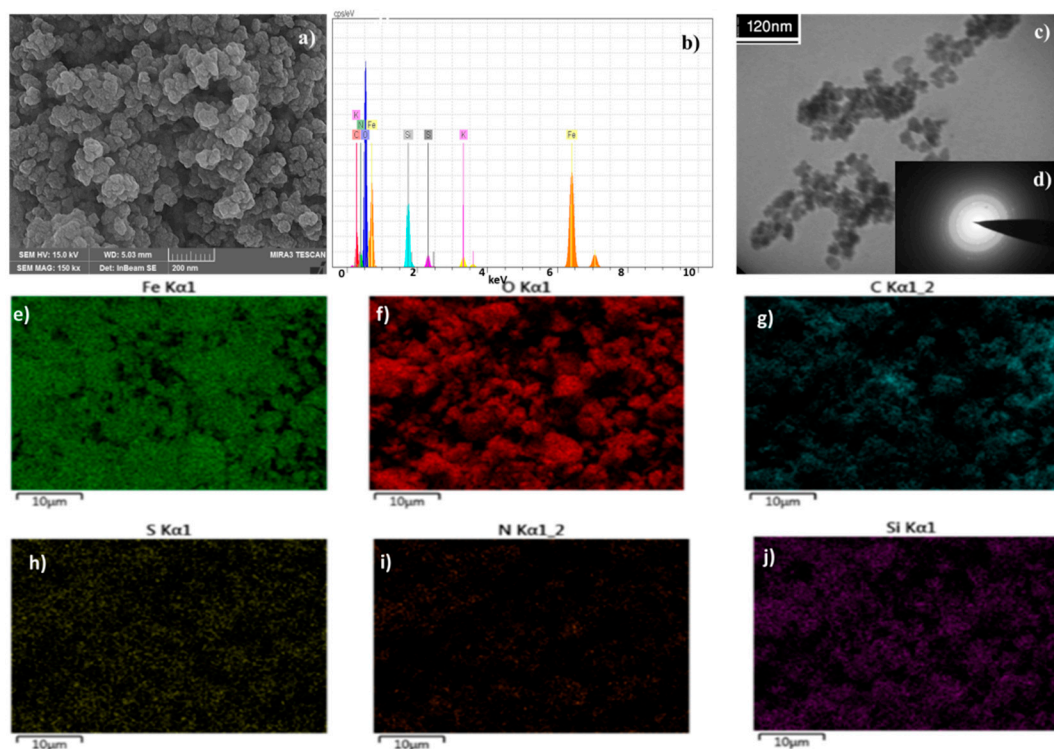


Figure 2. (a) SEM image, (b) EDS spectrum, (c) TEM image, and (d) SAED pattern of Prn/Fe₂O₃@SiO₂, (e–j) SEM elemental mapping of Prn/Fe₂O₃@SiO₂.

Thermal stability of Prn/Fe₂O₃@SiO₂ was investigated by thermogravimetric analysis (Figure 3a). A progressive weight loss of 5 wt % was observed from 100 °C to 420 °C owing to the presence of unbounded/physisorbed water and solvents, and the possible dehydration of some silanol groups [32]. In addition, Figure 3a displayed a drastically drop of weight (12 wt %) at 420 °C. This decrease can be attributed to the degradation of organic moieties in the Prn/Fe₂O₃@SiO₂ material. Moreover, DTA measurements displayed an exothermic band at 490 °C associated to the decomposition of the proline analogue.

The magnetic properties of the synthesized materials were investigated by VSM analysis (Figure 3b). The magnetization analysis of both, γ -Fe₂O₃ and Prn/Fe₂O₃@SiO₂ samples confirmed their remarkably magnetic properties. The saturation magnetizations of γ -Fe₂O₃ and Prn/Fe₂O₃@SiO₂, resulted in similar values, 65 and 40 emu/g, respectively [33]. The slightly lower magnetization of the functionalized γ -Fe₂O₃ could be attributed to the proline analogue loading after functionalization. In any case, without a considerably loss of magnetism after the preparation process, Prn/Fe₂O₃@SiO₂ features interesting properties of magnetic separation and manipulation in view of their potential catalytic applications.

X-ray diffraction analysis of γ -Fe₂O₃, γ -Fe₂O₃@SiO₂-NH₂, and Prn/Fe₂O₃@SiO₂ materials was carried out and is reported in Figure 3c. The X-ray diffraction patterns of the three samples exhibited characteristic peaks, which matched well with standard γ -Fe₂O₃ reflections and revealed their highly crystalline nature [34]. After introducing amorphous SiO₂, a small and expectable intensity decrease was observed. Nonetheless, these results suggest that after the functionalization process there is not considerable loss of crystallinity. Moreover, BET analysis (Figure 3d) showed a surface area of 75.2 m²·g⁻¹ and 53.1 m²·g⁻¹ for the γ -Fe₂O₃ and Prn/Fe₂O₃@SiO₂ materials, respectively. Both products present a mesoporous structure, with a pore size of around 15 nm (Table 1).

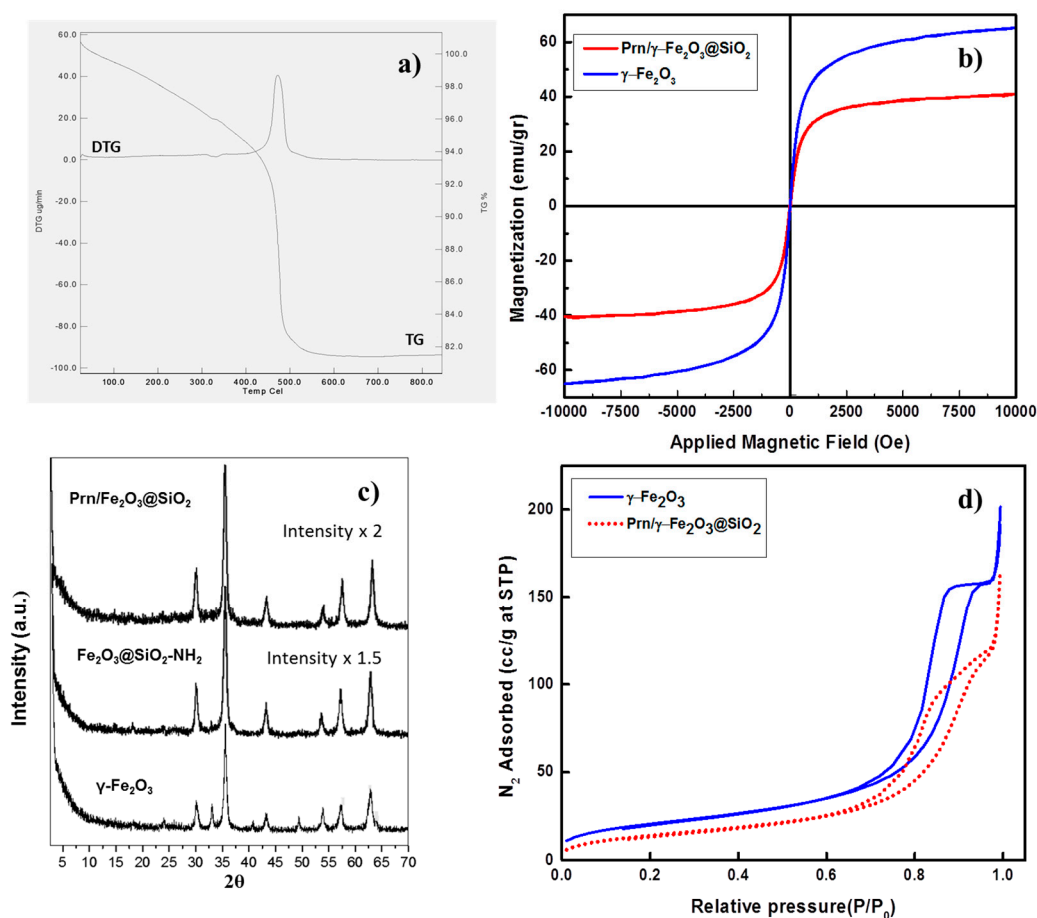


Figure 3. (a) Thermogravimetric (TG) and differential thermogravimetric (DTA) analyses of Prn/ γ - Fe_2O_3 @ SiO_2 , (b) VSM diagram of γ - Fe_2O_3 and Prn/ γ - Fe_2O_3 @ SiO_2 , (c) XRD pattern of γ - Fe_2O_3 , γ - Fe_2O_3 @ SiO_2 - NH_2 and Prn/ γ - Fe_2O_3 @ SiO_2 , (d) N_2 physisorption isotherms of γ - Fe_2O_3 and Prn/ γ - Fe_2O_3 @ SiO_2 .

Table 1. Textural properties.

Material	S_{BET} ^[a] ($\text{m}^2 \text{g}^{-1}$)	D_{BJH} ^[b] (nm)	V_{BJH} ^[c] ($\text{cm}^3 \text{g}^{-1}$)
γ - Fe_2O_3	75	14.5	0.27
Prn/ γ - Fe_2O_3 @ SiO_2	53	15.2	0.2

^[a] S_{BET} : specific surface area was calculated by the Brunauer–Emmett–Teller (BET) equation. ^[b] D_{BJH} : mean pore size diameter was calculated by the Barret–Joyner–Halenda (BJH) equation. ^[c] V_{BJH} : pore volumes were calculated by the Barret–Joyner–Halenda (BJH) equation.

The effective functionalization of γ - Fe_2O_3 @ SiO_2 surface with penicillin-derived proline analogue was corroborated by FT-IR (Figure 4). This conclusion can be inferred from the appearance of a peak at 1644 cm^{-1} , related to the amide group formed by the reaction between penicillin G and amino groups on the γ - Fe_2O_3 @ SiO_2 surface. In addition, the band associated with carbonyl group in the lactam ring of pure penicillin (1174 cm^{-1}) [35] was absent in Prn/ γ - Fe_2O_3 @ SiO_2 spectrum, pointing to ring opening upon functionalization. Furthermore, a strong band at 1080 cm^{-1} was observed for both γ - Fe_2O_3 @ SiO_2 and Prn/ γ - Fe_2O_3 @ SiO_2 materials, corresponding to Si–O–Si stretching vibration. FT-IR spectra also showed several peaks in the 2900 – 3000 cm^{-1} wavenumber range, which can be assigned to C–H bonds in the aliphatic chains. Besides, characteristic transmission bands at 625 cm^{-1} and 550 cm^{-1} were associated with iron oxide [36].

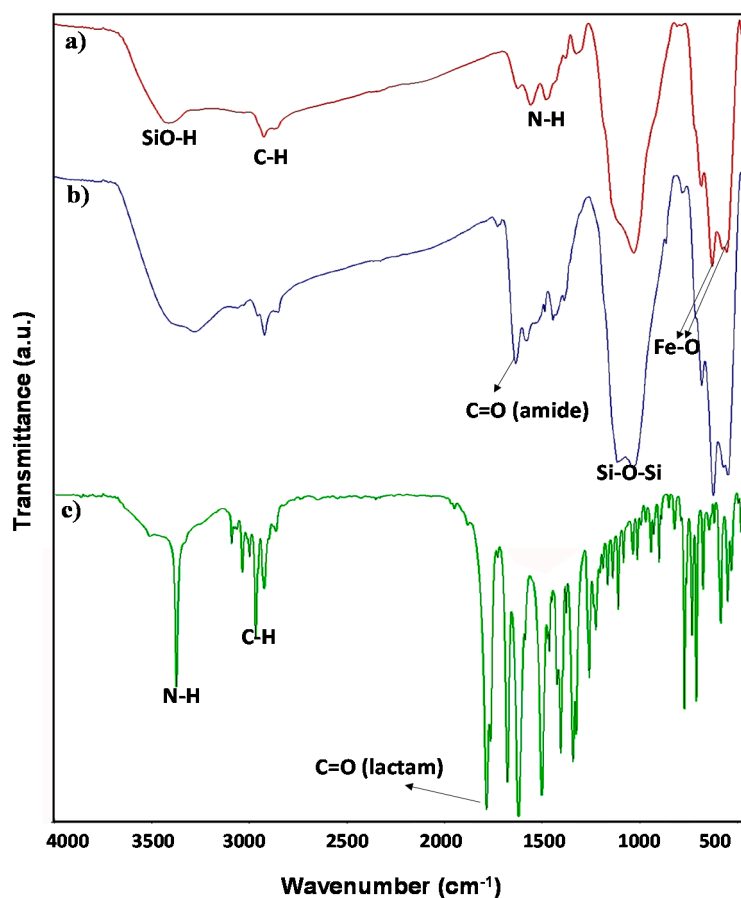


Figure 4. FT-IR spectra of (a) γ -Fe₂O₃@SiO₂-NH₂, (b) Prn/Fe₂O₃@SiO₂, and (c) penicillin G.

The catalytic activity of Prn/Fe₂O₃@SiO₂ was investigated in two reactions: (1) oxidation of isoeugenol and (2) vanillyl alcohol to vanillin. Firstly, the amount of catalyst was optimized to 20 mg of catalyst per each mmol of starting material. Subsequently, both reactions were studied using four oxidant agents: (a) hydrogen peroxide, (b) urea hydrogen peroxide (UHP), (c) *tert*-butyl hydroperoxide (*t*BHP), and (d) molecular oxygen. Although, the latest did not displayed satisfactory results, the other three oxidant agents resulted to be effective in this reaction, in particular, the best results were achieved using hydrogen peroxide. Moreover, the influence of the solvent on the effectiveness of the catalytic reaction was investigated using acetonitrile and toluene, the first one being the most appropriated. On the other hand, the effect of temperature was settled by performing the reaction at 80, 90, and 100 °C, establishing 90 °C as the most suitable temperature for the catalytic reaction (Table 2).

Under the model conditions, we monitored the reaction progress every 30 min. After 4 h, the reaction achieved the maximum conversion with a stable selectivity towards vanillin production. Compared to γ -Fe₂O₃ and catalyst-free reaction, Prn/Fe₂O₃@SiO₂ showed higher conversion and selectivity under similar conditions (Tables 3 and 4). The catalyst was also compared with its proton-unexchanged counterpart, for which a decrease in conversion for the latest material could be observed. These results indicated that the acidic nature, provided by the carboxylic group seems to have a crucial effect on the catalytic performance. In absence of the carboxylic acid, the amine group itself could promote the reaction. However, the oxidation reaction of isoeugenol, using the proton-unexchanged catalyst did not achieve a good catalytic activity towards vanillin production (Table 3). The presence of acidic species may be decisive in the catalytic conversion of isoeugenol to vanillin.

Table 2. Oxidation of vanillyl alcohol (A) and isoeugenol (B) to vanillin. (In bold: conditions for the best catalytic formance).

Entry	Solvent	Oxidant	Time (h)	T (°C)	Conversion A (%)	Selectivity A (%)	Conversion B (%)	Selectivity B (%)
1	CH ₃ CN	-	15	90	traces	-	traces	-
2	CH ₃ CN	O ₂	15	90	25	92	13	32
3	CH ₃ CN	<i>t</i> BHP	4	90	65	88	33	43
4	CH ₃ CN	UHP	4	90	85	86	52	48
5	CH₃CN	H₂O₂	4	90	100	92	83	51
6	Toluene	H ₂ O ₂	10	90	88	88	60	42

Table 3. Catalytic oxidation of isoeugenol [a]. (In bold: best catalytic system).

Entry	Catalyst	Time (h)	Conversion (mol %)	Selectivity (mol %)		
				Vanillin	Diphenyl ether	Others [b]
1	Blank (no catalyst)	2	<15	7	84	<10
2	γ-Fe ₂ O ₃	2	49	44	15	<40
3	proton-unexchanged catalyst	2	21	14	-	<10
4	Prn/Fe₂O₃@SiO₂	2	65	55	<10	<40

[a] Reaction conditions: 5 mmol isoeugenol, 1.2 mL H₂O₂, 8 mL acetonitrile, 0.1 g catalyst, 90 °C. [b] Oligomers and high molecular weight lignin-like compounds were detected as major reaction side products.

Table 4. Catalytic oxidation of vanillyl alcohol [a]. (In bold: best catalytic system).

Entry	Catalyst	Time (h)	Conversion (mol %)	Selectivity Vanillin (mol %)
1	Blank (no cat.)	4	<10	>85
2	γ-Fe ₂ O ₃	4	60	90
3	proton-unexchanged catalyst	4	72	91
4	Prn/Fe₂O₃@SiO₂	4	>99	92

[a] Reaction conditions: 5 mmol vanillyl alcohol, 1.2 mL H₂O₂, 8 mL acetonitrile, 0.1 g catalyst, 90 °C.

Reusability studies prove the high inherent stability and activity of Prn/Fe₂O₃@SiO₂ catalyst (Figure 5). For both reactions, the catalyst exhibited an excellent reusability for five consecutive cycles. Particularly, a drop in the activity of the catalyst after the fifth cycle was observed for isoeugenol conversion, which could be associated to the poisoning of the catalyst surface by side products of isoeugenol oxidation, in good agreement with the moderate selectivity observed to other products including lignin-like oligomers from vanillin oxidative polymerisation.

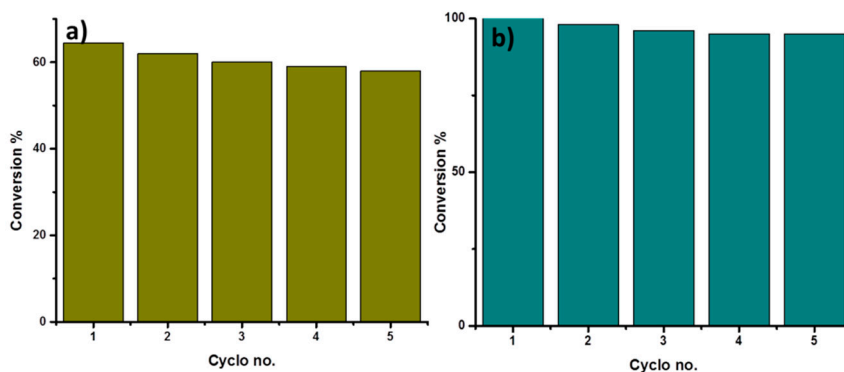


Figure 5. Reusability of the catalyst in conversion of the (a) isoeugenol and (b) vanillyl alcohol to vanillin under the optimal reaction conditions.

3. Materials and Methods

All chemicals were purchased from Sigma-Aldrich and used as received without further purification. Deionized (DI) water was used throughout this study. In order to characterize the synthesized materials, several techniques have been employed, including scanning electronic microscopy (SEM), electron dispersive spectroscopy (EDS) analysis, transmission electronic microscopy (TEM), selected area (electron) diffraction (SAED), thermogravimetric analysis (TGA), magnetization analysis, X-ray diffraction (XRD), N₂ physisorption, and Fourier transform infrared spectroscopy (FT-IR).

Electron dispersive spectra and SEM images were acquired using a Leo 1450vp scanning electron microscope equipped with a SC7620 energy dispersive spectrometer (Carl Zeiss AG, Oberkochen, Germany). TEM images were recorded in a Zeiss EM 900 microscope (Carl Zeiss AG, Oberkochen, Germany). Previously, the sample was dispersed in ethanol and transferred to a copper grid. Thermogravimetric analysis was accomplished using the System Setaram Setsys 12 TGA instrument (Setaram Instrumentation, Caluire, France), by heating the sample up to 800 °C at a rate of 10 °C·min⁻¹ under N₂ flow. X-ray diffraction patterns were collected using the D8 Advanced Diffractometer (Bruker AXS, Billerica, MA, USA) with the Lynxeye detector at room temperature. FT-IR spectra were recorded on the ABB MB3000 infrared spectrophotometer (ABB, Zurich, Switzerland), equipped with an ATR PIKE MIRacle™ sampler, a window of ZnSe, and 256 scans at a resolution of 8 cm⁻¹.

The catalytic reactions were investigated by gas chromatography (GC) in an Agilent 6890N gas chromatograph (60 mL min⁻¹ N₂ carrier flow, 20 psi column top head pressure) using a flame ionization detector (FID) (Agilent, Santa Clara, California, USA). The capillary column HP-5 (30 m × 0.32 mm × 0.25 mm) was employed. The conversion and selectivity were calculated from the chromatograms by

$$\text{Conversion}(\%) = \frac{[C_{\text{Initial}} - C_{\text{Final}}]}{C_{\text{Initial}}} \times 100$$

$$\text{Selectivity}(\%) = \frac{C_{\text{Product}}}{[C_{\text{Initial}} - C_{\text{Final}}]} \times 100$$

where C_{Initial} and C_{Final} are the concentrations of the reagents before and after the reaction, respectively. C_{Product} is the concentration of the product.

3.1. Synthesis of $\gamma\text{-Fe}_2\text{O}_3@SiO_2$

Synthesis of $\gamma\text{-Fe}_2\text{O}_3$ was carried out employing a reported chemical co-precipitation protocol with a slight modification [37,38]. Accordingly, FeCl₂·4H₂O (0.495 g) and FeCl₃·6H₂O (1.35 g) were first dissolved in acetic acid (3 wt %, 100 mL) and stirred at room temperature. Subsequently, a NH₄OH solution (0.7 M, 50 mL) was added to the mixture at room temperature to reach a pH value of 12.

After 15 min, a black precipitate was observed. The obtained solid was collected by an external magnet, washed three times with a mixture water/ethanol (1:1) and dried at 100 °C for 12 h. Finally, the material was calcined at 300 °C for 3 h. The obtained γ -Fe₂O₃ (1 g) was dispersed in ethanol (40 mL) and sonicated for 30 min at room temperature. Afterward, TEOS (5 mL) was added dropwise and the mixture was stirred at 40 °C for 24 h. The final core–shell nanostructure was collected by an external magnet, washed three times with ethanol and dried at 80 °C under vacuum for 6 h to obtain a γ -Fe₂O₃@SiO₂ nanomaterial.

3.2. Synthesis of Prn/ γ -Fe₂O₃@SiO₂

The obtained γ -Fe₂O₃@SiO₂ (2.0 g) was dispersed in dry toluene (20 mL) and sonicated for 45 min. Then, APTES (0.5 mL) was added to the dispersion and slowly heated up to 105 °C. The reaction mixture was stirred for 24 h under reflux conditions. The resulted amino-functionalized material (γ -Fe₂O₃@SiO₂-NH₂) was redispersed in 20 mL of distilled water and thereafter, a solution of penicillin G potassium salt (1 g) in ethanol:water (1:1, 10 mL) was added to the dispersion. The reaction mixture was stirred for 48 h at 60 °C. The obtained material was washed several times with ethanol and oven-dried at 60 °C for 5 h. In addition, the product was redispersed in a dilute HCl solution (pH = 4.5) and stirred for 6 h. Finally, the synthesized Prn/Fe₂O₃@SiO₂ was washed with distilled water and dried at 100 °C in a vacuum oven.

3.3. Catalytic Experiments

The oxidation of isoeugenol to vanillin was performed using 0.8 mL of isoeugenol, 1.2 mL of H₂O₂, 8 mL of acetonitrile (CH₃CN), and 0.1 g of the previously synthesized organocatalyst (0.01 g/mL). The reaction mixture was stirred at 90 °C for 24 h by using a multiple parallel synthesis system (Carrusel Reaction Station, Radleys Discovery Technologies Ltd., Saffron Walden, UK). During the reaction, samples were taken every 30 min and characterized by gas chromatography. The oxidation of vanillyl alcohol was carried out employing the same procedure.

4. Conclusions

In summary, an unprecedented proline analogue was generated in situ from the reaction between penicillin G and the amino-functionalized surface of γ -Fe₂O₃@SiO₂. The magnetic γ -Fe₂O₃@SiO₂ core shell structure facilitated the recovery and reusability of the resulted organocatalyst. The obtained material was applied to the conversion of vanillyl alcohol and isoeugenol to vanillin. The presence of acidic functionalities in the catalyst was decisive for the isoeugenol oxidation. In both reactions, the acidic and basic sites of the Prn/Fe₂O₃@SiO₂, exhibiting a synergic effect, enhancing the catalytic efficiency towards higher conversion and selectivity.

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Author Contributions: Rafael Luque, Farveh Saberi and Araceli Garcia conceived and designed the experiments; Farveh Saberi and Daily Rodríguez-Padrón performed the experiments; Rafael Luque, Farveh Saberi and Hamid Reza Shaterian analyzed the data; Rafael Luque and Hamid Reza Shaterian contributed with reagents/materials/analysis tools for all experiments; Farveh Saberi and Daily Rodríguez-Padrón wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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