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A Novel Star-Shaped Triazine-Based Vitamin B_5 Copper (II) Nanocatalyst for Tandem Aerobic Synthesis of Bis(indolyl)methanes

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Abstract: In this work, the catalytic efficiency of a novel bio-relevant triazine (TA)-based pantothenate (vitamin B_5) copper(II) complex [Cu(II)-TA/B_5] in the aerobic oxidation of benzyl alcohols and tandem synthesis of bis(indolyl)methanes was exploited. The star-shaped catalyst was characterized by different techniques such as FT-IR, EDX, ICP, TEM and TGA. TEM images revealed a honeycomb structure resulting from accumulation of nanopaticles with size ranging between 2-6 nm. The high yields and excellent selectivity were obtained for production of various benzaldehydes and bis(indolyl)methans under aerobic conditions. Recycling tests, spectral data and leaching experiments testified that the title heterogeneous bio-relevant catalyst preserved its activity and structural integrity during oxidation and coupling reactions. The presented catalytic systems qualify all requirements for efficient catalytic systems for applied goals.

Introduction

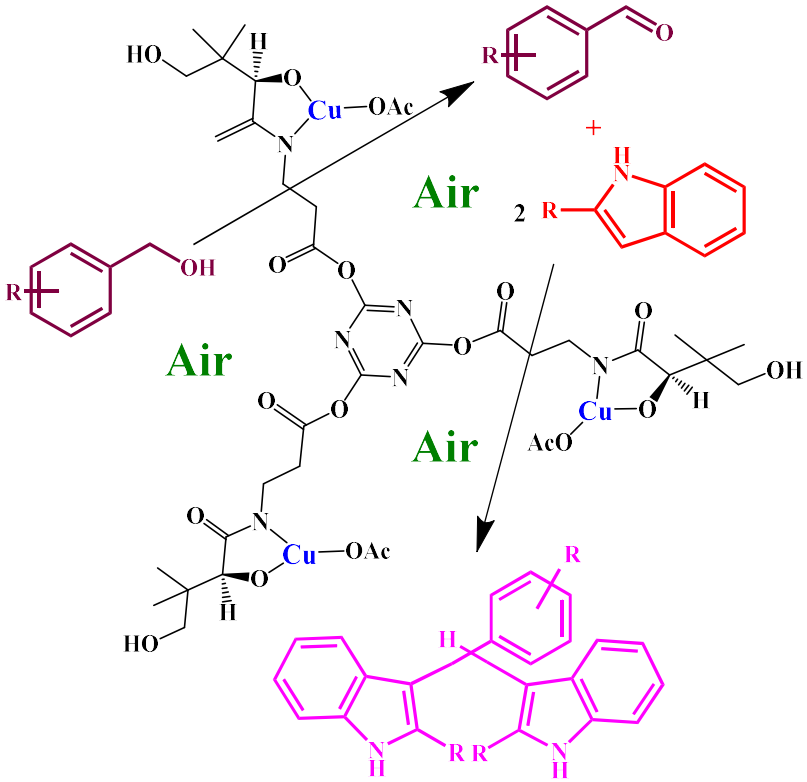
The use of biologically active materials has always been the ultimate source of inspiration for scientists working across all disciplines. Among these, biocatalysts, an emerging group of catalysts, which facilitate the syntheses of complex organic molecules by chemo-, region-, and stereoselective bond-forming reactions are of extreme interest.[1] Because of high turnover numbers and frequencies, mild reaction conditions, high product selectivity, and low environmental impact, biocatalysts have been employed for both simplified chemical synthesis routes and improved outcomes.[2]

Vitamins constitute a group of large number of chemically unrelated organic compounds which are necessary for all animals to maintain normal metabolic functions. They are different from the other biological compounds in that generally cannot be synthesized in amount sufficient to meet bodily needs and hence must be supplied in the diets. Relatively small quantities of vitamins are needed to complete their functions, which are of a catalytic or regulatory nature, facilitating or controlling vital chemical reactions in the body's cells. [3] Vitamin B_5, also known as pantothenic acid, is an essential vitamin consists of pantoic acid and β-alanine bound in amide linkage, which serve as the metabolic precursor for coenzyme A. In the form of coenzyme A and as a component of acyl carrier protein, pantothenic acid is a participant in a myriad of metabolic reactions involving lipids, proteins, and carbohydrates. [4]

Metal complexes of vitamins have been prepared either as a single ligand or as mixed ligand complexes in order to disclose various stereochemical arrangements of the ligands around the metal atom and different types of connection between the complexes. Recently, more attention has been paid to catalytic activity of the vitamin transition metal complexes to imitate and understand the function of biochemical catalysts. [5] Among the transition metals, copper has been the most studied metal ions because of its inherent electronic properties, accessible redox potentials and particularly taking part in many biological functions such as structural shaping, electron transfer and catalysis. [6] The presence of copper in the active sites of different enzymes, [6] makes it an appropriate choice for the development of catalysts for alcohol oxidation, a fundamental bio-relevant transformation which is also of extreme interest in organic synthesis. [7] The oxidation products of alcohols, carbonyl compounds, are key materials in the production of many valuable fine chemicals. [7] Condensation of carbonyl compound particularly aldehydes with a two-fold excess of indole molecule produces biologically and medicinally important

bis(indolyl)methanes (BIM), [8] which have attracted much attention in organic synthesis. They are widely found in the structure of many bioactive compounds extracted from various plants can act on the central nervous system and are used as antibiotics. Other methods such as C-H bond activation/C-C bond forming of alcohols and indoles to bis(indolyl)methanes with I_2/O_2 and NBS have been reported. [9] However, side reactions such as multiple condensations, polymerizations, and rearrangements are common to occur in many of the reported protocols for the synthesis of BIM derivatives. [10]

Following our research on the synthesis and catalytic applications of transition metal vitamin complexes, [11] herein, we wish to design a novel bio-relevant catalyst, consisting of Cu(II) pantothenate complex attached to triazine ring. The as-prepared copper (II) complex proved to be efficient and recyclable catalyst for the selective aerobic oxidation of benzylic alcohols to aldehydes followed by coupling with indole molecules through carbon-carbon bond to afford the Bis(indolyl)methane without any side reactions (**Scheme 1**).

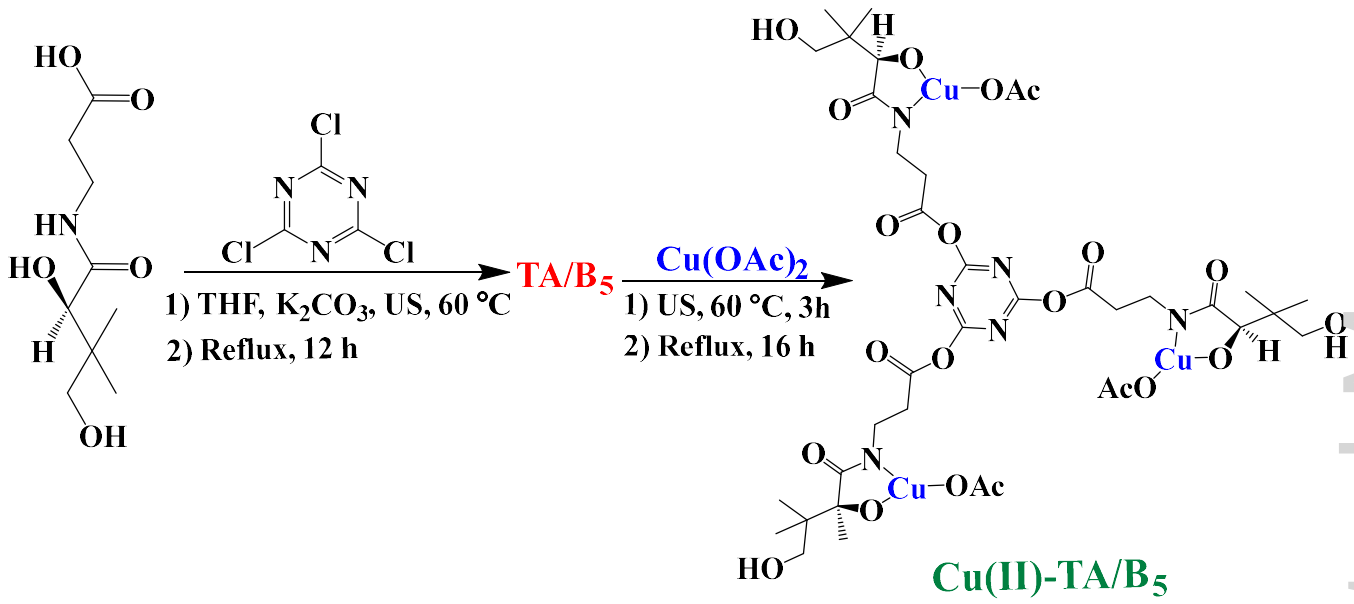


Scheme 1. One pot synthesis of bis(indolyl)methanes through aerobic oxidation of benzylic alcohols catalyzed by [Cu(II)-TA/B_5]

Results and Discussion

Synthesis and Characterization of Catalyst

As shown in scheme 2, reaction of cyanuric chloride (CC) with vitamin B_5 (panthothenic acid) was carried out in THF under ultrasonic agitation to substitute chlorine atoms of cyanuric chloride to afford vitamin B5 triazine derivative (TA/B_5) as a star-shaped ligand. The copper (II) complex of the as-prepared ligand [Cu(II)-TA/B_5] was obtained by adding $Cu(OAc)_2$ under ultrasonic agitation followed by reflux for 16 h (Scheme 2). The Cu content of [Cu(II)-TA/B_5] complex was found to be 3.2 mmol g^{-1} based on ICP-AES analysis.



Scheme 2. Preparation route for [Cu(II)-TA/B_5]

The FT-IR spectra of vitamin B_5, TA/B_5 ligand and [Cu(II)-TA/B_5] nanocomplex are depicted in Figure S1. The spectrum of B_5 (Fig. S1a) reveals the presence of major bands at 1606 and 1576 cm^{-1} attributed to the acid and amide carbonyl groups. Broad peak at 3410 cm^{-1} corresponds to the hydroxyl groups which overlaps with the N-H amide peak. The significant spectral changes in Fig. S1b affirms the formation of TA-B_5 ligand. The appearance of a new band at 1776 cm^{-1} and vanishing the broad peak of O-H testify the formation of ester group. Also, the intense band at 1692 cm^{-1} is attributed to C=N triazine ring. A shift in N-H amide band from 3212 to 3206 as

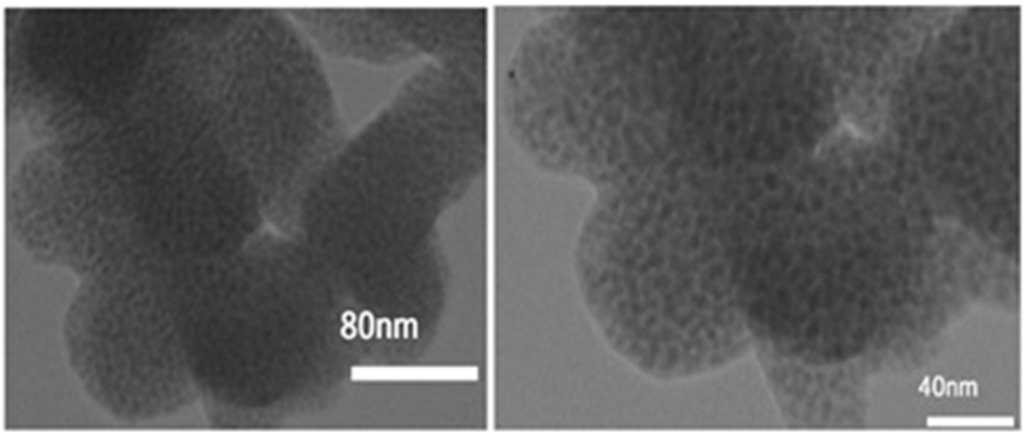


Figure 1. TEM images of [Cu(II)-TA/B_5] nanocomplex

well as appearance of new peaks at 593 and 495 cm^{-1} in Fig. S1c testify the coordination of the TA-B_5 ligand to the Cu(II) center.

The TEM images in Figure 1, shows a honeycomb structure resulting from accumulation of [Cu(II)-TA/B_5] nanopaticles with size ranging between 2-6 nm.

The TGA curve (Figure S2, ESI) demonstrates its thermostability up to 150 ºC and the organic parts decomposition continued up to 800 ºC. Compositional analysis through energy dispersive X-ray (EDX) spectrometer (Figure S3) confirmed the presence of Cu atoms alonside C, N and O in nanocomplex.

Catalytic Tests

Aerobic Oxidation of Alcohols

Elucidating the catalytic role of the as-prepared [Cu(II)-TA/B_5] nanocomplex, some control experiments were conducted. A catalyst-free reaction using 4-chlorobenzyl alcohol (0.125 mmol) as a model substrate in combination with TEMPO (10 mol%) in EtOH (0.2 mL) under air led to isolation of starting alcohol. Parent materials such as $Cu(OAc)_2$, vitamin B_5, TA-B_5 ligand as well as [Cu(II)-B_5] complex were also inferiour catalysts for aforementioned reaction under the same catalyst concentration (5 mol%, Figure 2). Nevertheless, a small amount of the as-prepared [Cu(II)-TA/B_5] nanocomplex triggered the oxidation reaction in combination with (2,2,6,6-

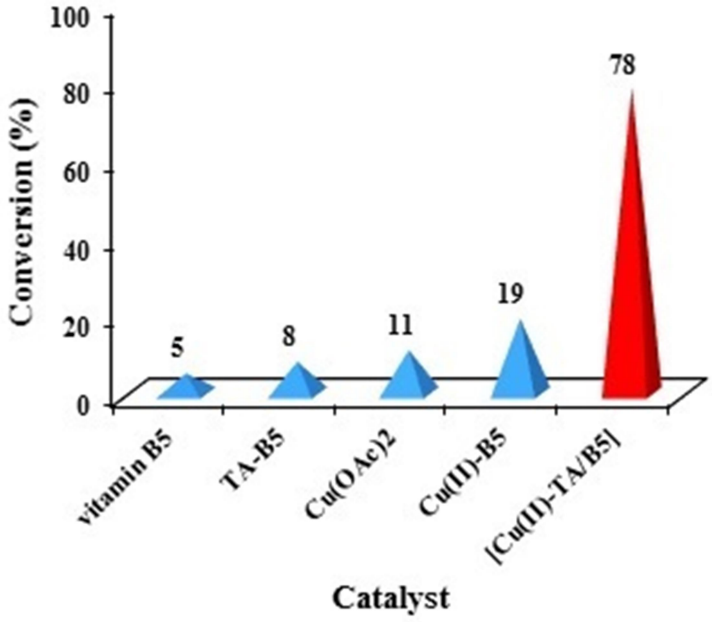


Figure 2. Comparison of the catalytic activity of [Cu(II)-TA/B_5] with parent materials (5 mol%) in the oxidation of 4-chlorobenzyl alcohol (0.125 mmol) in the precense of TEMPO (10 mol%) at 70 °C under air after 8 h in 0.2 mL EtOH.

tetramethylpiperidin-1-yl) oxyl TEMPO and the conversion reached to about 80% after 8 h and the pertinent aldehyde was formed as the sole product.

Afterward, the reaction conditions were optimized with respect to different factors such as solvent, temperature, catalyst and TEMPO amounts and also oxidant nature (Figure 3). The high conversion rates were observed in EtOH and water as green solvents at 70 ºC. Nevertheless, apart from the benefits of solubility of materials in ethanol, more selectivity was obtained in this solvent. Our findings revealed that the catalytic efficiency affected seriously by TEMPO and the reaction needs 8 mol% of this additive for reaching to the highest performance (Figure 3, iv, v). The other common oxidants such as O_2, H_2O_2, TBHP, Oxone® and tetra-*n*-butylammonium Oxone® (TBAOX) was tested in the title model reaction under optimized conditions. The highest oxidation performances were observed under air as well as continuous stream of oxygen and magnetic stirring is more effective than ultrasonic agitation (Figure 4). Obviously, the conducting the reaction under air in an open-flask agitated by a magnetic stirrer is preferred

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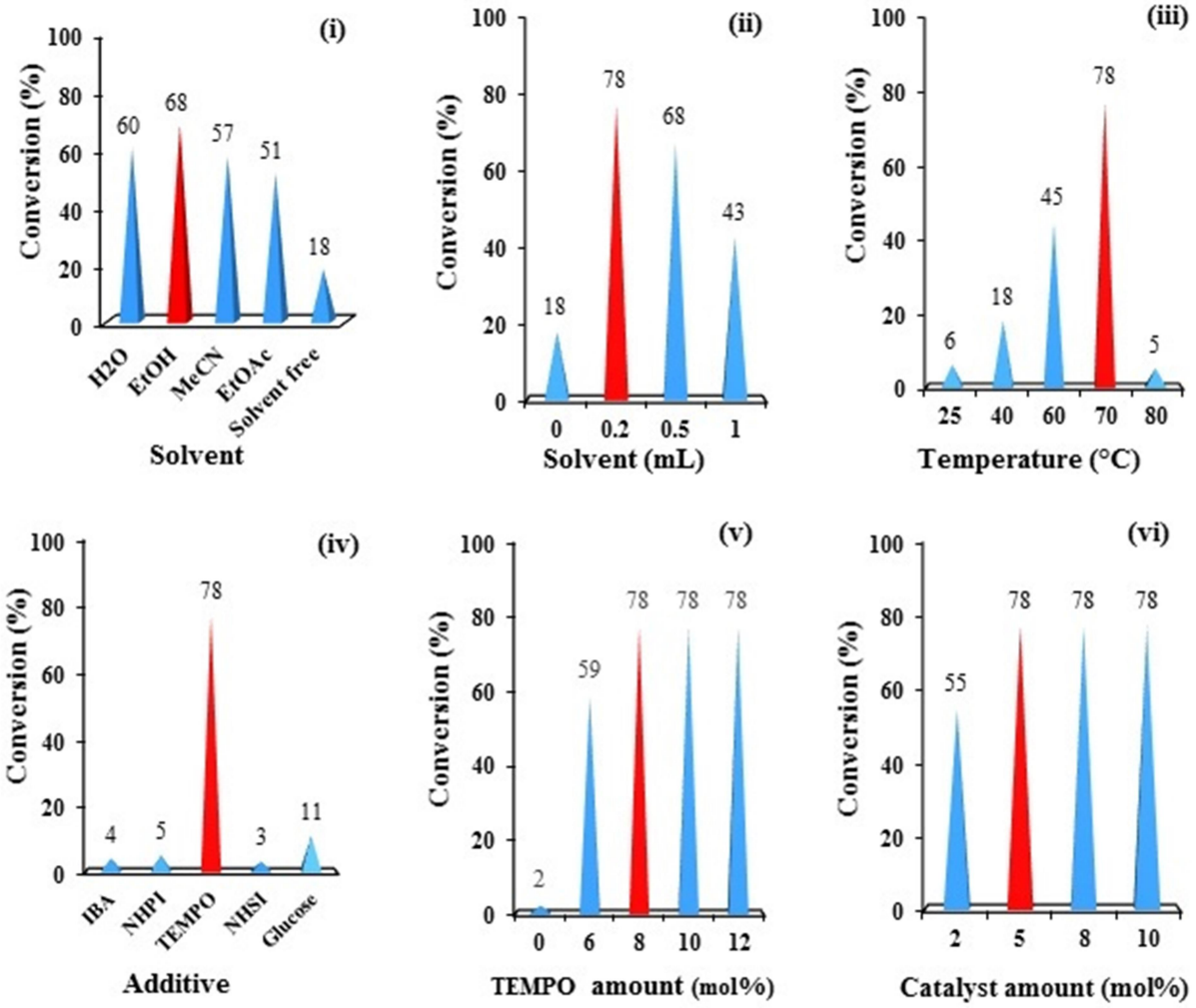


Figure 3. The screening results for the solvent type (i) and solvent amount (ii), temperature (iii), additive, IBA: Isobutyraldeyde, NHPI: N-Hydroxyphthalimide, NHSI: *N*-Hydroxysuccinimide (iv), TEMPO amount (v) and catalyst amount (vi). The reactions for oxidation of 4-chlorobenzyl alcohol (0.125 mmol, 0.018 g) were run for 8 h under air in an open-flask in 0.2 ml ethanol at 70 °C using 8 mol% TEMPO and 5 mol% catalyst, except in each case where the desired factor is varied (see experimental details in SI).

(Figure 4). Based on the aforementioned screening results, aerobic oxidation of 0.125 mmol 4-chlorobenzyl alcohol in EtOH (0.2 mL) at 70 °C needs 8 mol% TEMPO (0.01 mmol, 0.0017 g), and 5 mol% [Cu(II)-TA/B_5] catalyst (0.006 mmol, 0.002 g) to furnish the highest yield of the pertinent aldehyde.

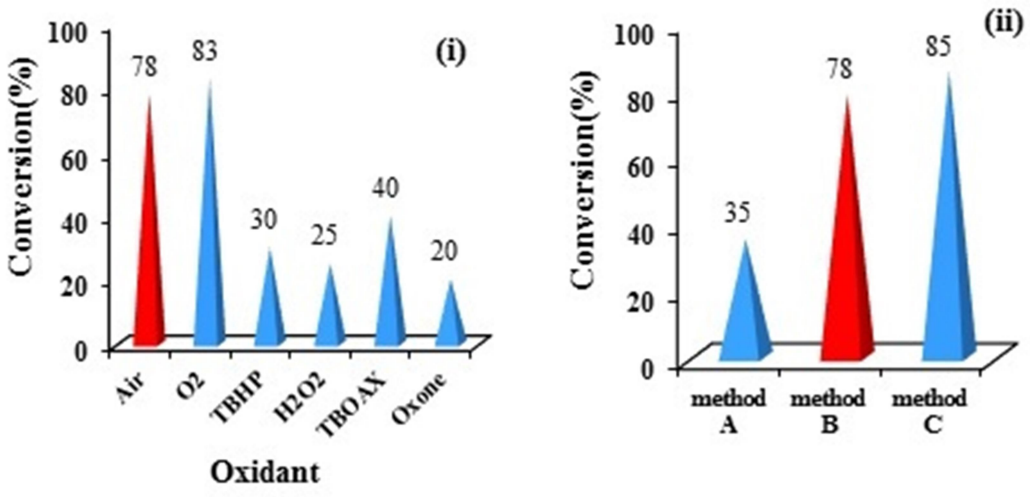
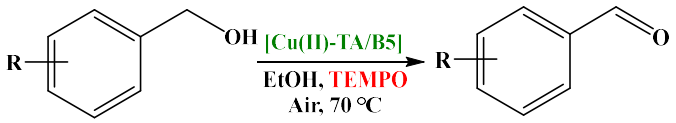


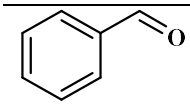
Figure 4. (i) The effect of various oxidants in the oxidation of 4-chlorobenzyl alcohol (0.125 mmol) (ii) and agitation conditions: (method A) open flask under air agitated by ultrasonic waves, (method B): open flask under air agitated by a magnetic stirrer, (method C): a continuous stream of O_2 (5-7 mL min^{-1}) agitated by a magnetic stirrer. The reactions were run in EtOH (0.2 mL) at 70 °C using 5 mol% [Cu(II)-TA/B_5] and 8 mol% TEMPO for 8 h.

Under this optimized conditions, a wide range of primary and secondary benzylic alcohols (1a-o) oxidized effeciently and selectively as given in Table 1 (2a-o). Based on our data, the oxidation performance affected by electronic properties of substrates. Electron-withdrawing groups on the phenyl rings of alcohols accelerated the reaction (entries 2h and 2i), while the electron-releasing groups reduced the reactivity (entries 2b-2g). The chemoselectivity of the procedure is noteworthy. When cinnamyl alcohol as an allylic alcohol subjected to the reaction condition, the olefin moiety remained intact and the unsaturated carbonyl compounds was produced exclusively (entry 2j). Moreover, 4-(methylthio)benzyl alcohol, oxidized selectively to the corresponding aldehyde in 68% yield and more susceptible sulfide group was tolerated in the reaction (entry 2n). It should be noted that the title catalytic oxidation system was ineffective for aerobic oxidation of aliphatic primary and secondary alcohols.

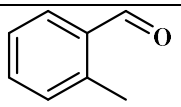
Table 1. Aerobic oxidation of benzylic alcohols catalyzed by [Cu(II)-TA/B_5]. [a-c]



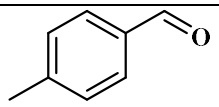
1 a-o *2 a-o*



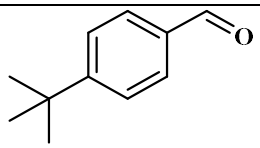
***2a*, 83%, 7.5h**



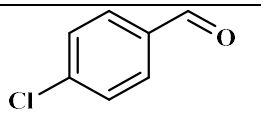
***2b*, 79%, 7h**



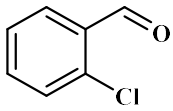
***2c*, 83%, 7h**



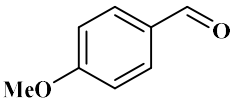
***2d*, 81%, 7.5h**



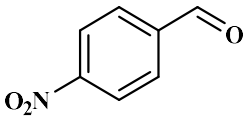
***2e*, 78%, 8h**



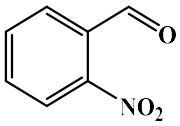
***2f*, 72%, 8h**



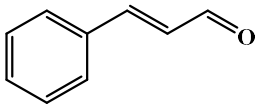
***2g*, 74%, 8.5h**



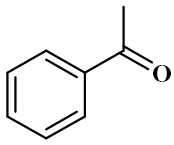
***2h*, 87%, 6.25h**



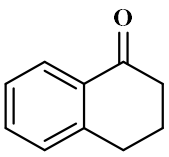
***2i*, 79%, 6.75h**



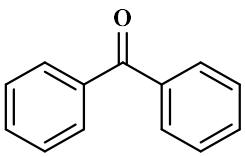
***2j*, 78%, 6.5h**



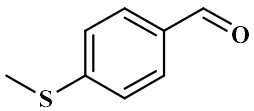
***2k*, 72%, 6.5h**



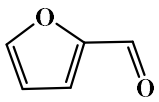
***2l*, 77%, 6h**



***2m*, 63%, 6h**



***2n*, 68%, 9h**



***2o*, 72%, 7.5h**

[a]Reaction conditions: Alcohol: 0.125 mmol, TEMPO: 8 mol% (0.01 mmol, 0.0017 g), catalyst: 5mol% (0.006 mmol, 0.002 g) in EtOH (0.2 mL) in an open-flask over a hot plate stirrer at 70 °C under air. [b] The products were identified by comparison of GC retention times and NMR spectral data with authentic samples. [c] GC Yield. The selectivity of products was >99% based on GC analysis.

Aerobic Tandem Synthesis of Bis(indolyl)methanes

The promising results obtained in the oxidation of benzyl alcohols to the related aldehydes which are key intermediates in organic synthesis prompted us to apply this catalytic system for tandem synthesis of bis(indolyl)methanes. Following the completion of the oxidation of alcohol under aerobic condition mentioned above, indole was added to the reaction mixture to produce bis(indolyl)methanes. Nevertheless, our screening study (Figure 5) demonstrated that the reaction needed more catalyst and TEMPO, so that a solvent-free condition (i) at 80 °C (ii) using

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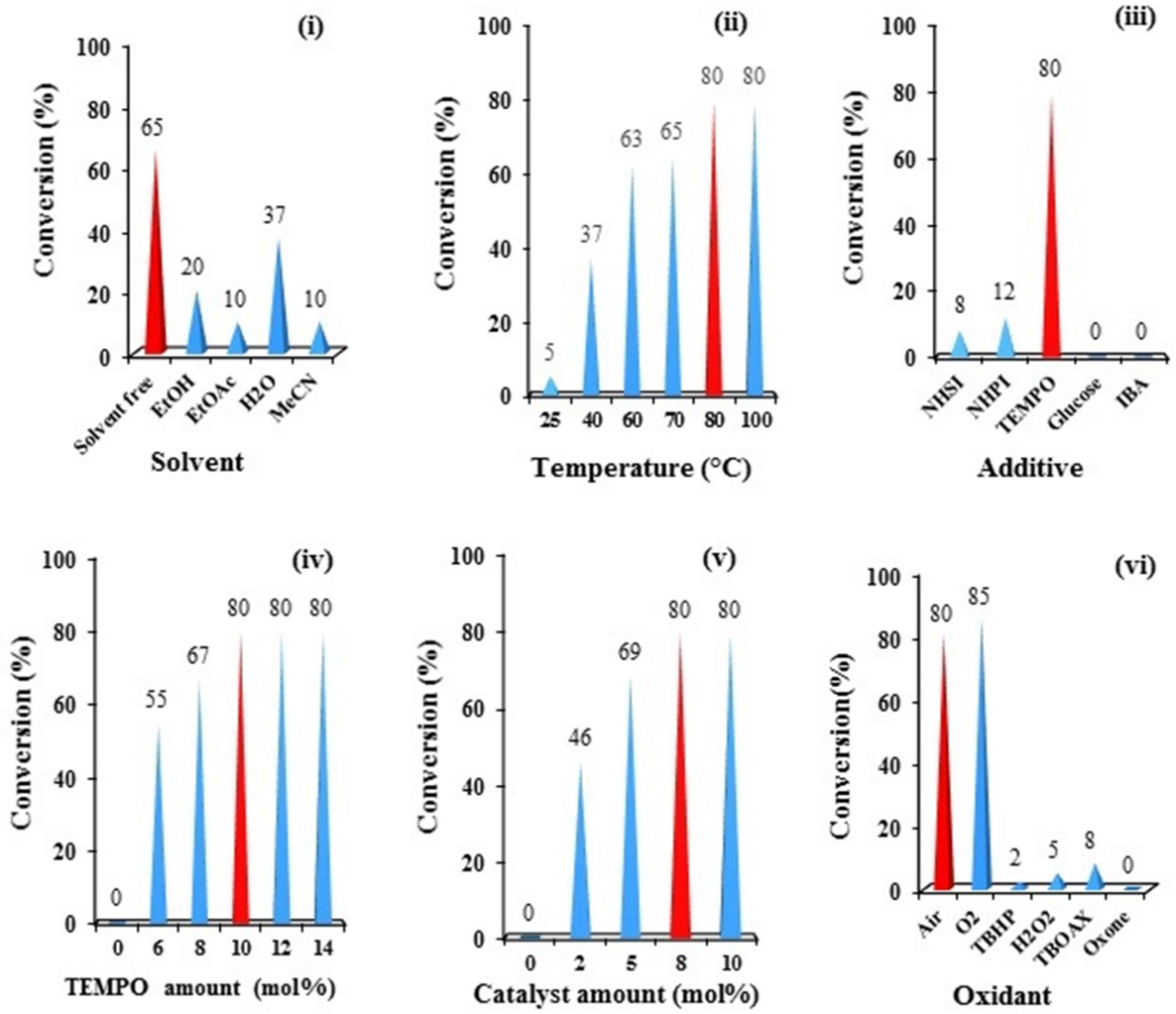
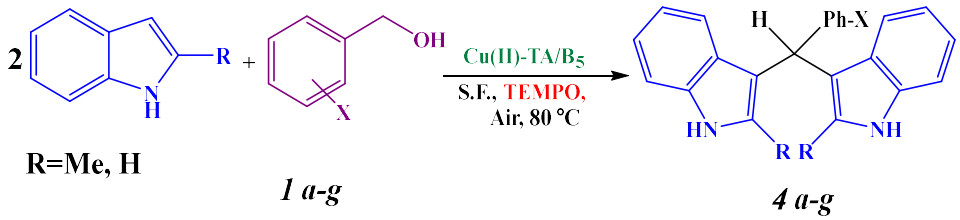
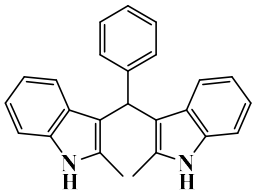


Figure 5. The screening results for the solvent type (i), temperature (ii), additive, IBA: Isobutyraldeyde, NHPI: N-Hydroxyphthalimide, NHSI: *N*-Hydroxysuccinimide (iii), TEMPO amount (iv) catalyst amount (v) and oxidant type (vi). The reactions were run under air in an open-flask under solvent-free condition at 80 °C using 10 mol% TEMPO and 8 mol% catalyst, except in each case where the desired factor is varied (see experimental details in SI).

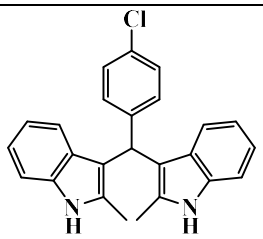
10 mol% (0.012 mmol, 0.002 g) TEMPO (II, iv) and 8 mol% (0.01 mmol, 0.003 g) [Cu(II)-TA/B_5] nanocatalyst (v) under air (vi) was the best condition for tandem synthesis of bis(indolyl)methanes from alcohols.

Table 2. Aerobic bis(indolyl)methanes synthesis via condensation of benzyl alcohols and Indoles by [Cu(II)-TA/B_5] [a,b]

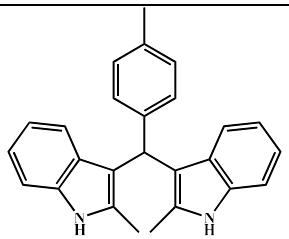




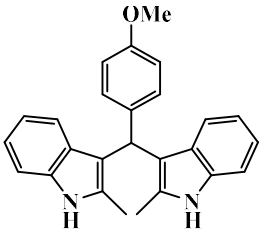
***4a*, 79%, 6.25h**



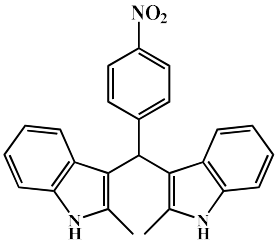
***4b*, 80%, 6.5h**



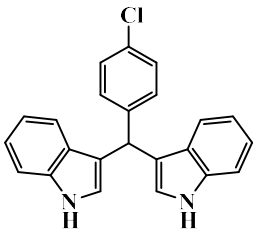
***4c*, 74%, 7.5h**



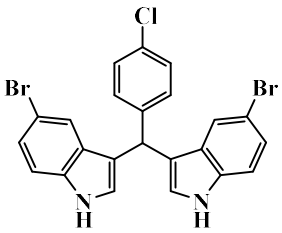
***4d*, 65%, 8.75h**



***4e*, 83%, 5.75h**



***4f*, 55%, 9.5h**



***4g*, 70%, 9.75h**

[a] Reaction conditions: 1.25 mmol: 2.62 mmol: 10 mol% (0.012 mmol, 0.002 g): 8 mol% (0.01 mmol, 0.003 g) for alcohol: indole: TEMPO: catalyst, solvent-free condition and magnetic stirrer under air at 80 ˚C. [b] The products were identified by NMR spectroscopy. [c]The reported yields are the isolated products.

With the optimized conditions in hand, the catalytic performance of the [Cu(II)-TA/B_5] nanocomplex in the reaction of benzylic alcohols and indoles in the coupling reaction was investigated (Table 2). As shown in Table 2, structurally and electronically diverse benzylic alcohols and indoles are desired substrates for this reaction, so that bis(indolyl)methanes were

produced in good to high yields of (65-83%). However, as mentioned in the previous section, alcohols substituted by electron-releasing groups exhibited less reactivity (entry 4d). As expected, no coupling reaction occurred when benzylic alcohols were replaced by aliphatic ones.

Recyclability and Stability of Catalyst

The recyclability and heterogeneous nature of catalyst were examined in the aerobic oxidation of 4-chlorobenzylalcohol (**1e)** as a model substrate and tandem aerobic bis(indolyl)methanes (**4b)** synthesis. After each run according to experimental section, the catalyst was separated from the product by centrifugation followed by decantation (3×5 ml EtOH for aerobic oxidation of benzyl alcohols and 3×5 ml EtOAc for aerobic bis(indolyl)methanes synthesis), dried in vacuum oven and then reused. Indeed, the catalyst showed a superb performance during five consecutive cycles (Figure 6). In order to clarify whether the reaction takes place at the surface of the solid catalyst as a truly heterogeneous reaction or leached Cu(II) drives the homogeneous reaction, the hot filtration test was done. The filtrate solution containing 4-chlorobenzylalcohol produced just 5% of the pertinent aldehyde after 8 h ruling out any homogeneous catalysis resulting from Cu-leaching as confirmed by ICP-AES analysis. The stability of catalyst during oxidation of alcohol as well as synthesis of bis(indolyl)metane was also demonstrated by FT-IR spectra of recycled catalyst (Figure S4). The lacking of any noticeable changes after five runs testified the structural stability of catalyst during aerobic oxidation and coupling reactions. Thus, the present methodologies employing a heterogeneous and reusable bio-relevant copper catalyst under air as an ideal oxidant in green ethanol for alcohol oxidation and solvent-free condition for coupling reaction without formation of any by-products qualify all requirements of cost-effective and eco-friendly catalytic systems for applied goals. .

Conclusion

In summary, we have successfully synthesized a novel star-shaped [Cu(II)-TA/B_5] nanocatalyst by incorporating of $Cu(OAc)_2$ within 2,4,6-tripantothenate-1,3,5-triazine under ultrasonic agitation. The catalytic system involves oxidation of alcohols to aldehydes followed by condensation with indol derivatives to afford bis(indolyl)methanes in one-pot operation with good to excellent yield without any side reactions. Notably, the presented catalytic oxidation systems showed remarkable selectivity. The use of air as an environmentally friendly oxidant

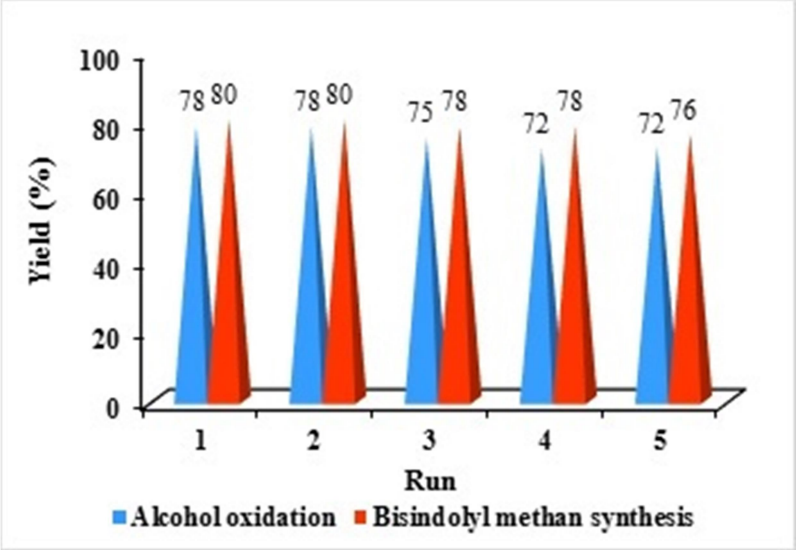


Figure 6. Recycling study of [Cu(II)-TA/B_5] catalyst in model reactions (compounds **2e**, **4b**), according to procedures mentioned in experimental sections.

under the influence of a reusable and durable active bio-relevant catalyst with low catalyst loading, along with easy isolation of organic products is the strengths of the presented work.

Experimental Section

General: All chemicals were purchased from Chemical Companies. The FT-IR spectra were recorded on NICOLET system. TEM images were obtained by TEM instrumentation (Philips CM 10). Progresses of the reactions were monitored by TLC using silica-gel SIL G/UV 254 plates and also by GC-FID on a Shimadzu GC-16A instrument using a 25 m CBP1-25 (0.32 mm ID, 0.5 mm coating) capillary column. Thermogravimetric analysis (TGA) of powders carried out on Netzsch-TGA 209 F1 under air flow at a uniform heating rate of 10 ˚C min-1 in the range of 30-800˚C. EDX performed by TESCAN Vega Model. The Cu content of the catalyst was measured by an inductively coupled plasma optical emission spectrometry (ICP-OES), using the Optima-7300 ICP analyzer.

Preparation of [Cu(II)-TA/B_5] Nanocatalyst

A solution of 0.18 g cyanuric chloride (1 mmol) in 5 mL dry THF was gradually added to 0.44 g vitamin B_5 (2 mmol) in 5 mL dry THF at 60 °C under ultrasonic agitation. After adding 0.138 g K_2CO_3 (1 mmol), the reaction mixture remained under the same condition for 3 h and afterward, it was stirred for 12 h at 70 °C. The reaction mixture was centrifuged and the resulted solid (TA/B_5) was washed with THF and dried in a vacuum oven at 70 ºC. Then, an ethanolic solution of $Cu(OAc)_2$ was added drop by drop to a solution of TA/B5 (0.2 g) in 10 mL EtOH under ultrasonic agitation at 60 ˚C, and remained under the same condition for 3 h. Heating the solution at 70 °C for 16 h, resulted a green powder which was washed with ethanol and dried under air.

General procedure for aerobic oxidation of benzyl alcohols (2a-o)

To a mixture of benzyl alcohols (0.125 mmol) and 2mg [Cu(II)-TA/B_5] catalyst (0.006 mmol, 5 mol%) in EtOH (0.2 mL) was added 1.7 mg TEMPO (0.01 mmol, 8 mol%), and the reaction mixture was stirred under air at 70 °C for the required time. The reaction progress was monitored by GC, and the yields of products were determined by GC analysis. The pure product was secured by plate silica chromatography using *n*-hexane/EtOAc (10:3).

Benzaldehyde (2a)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.1 (s, 1 H), 7.9-7.5 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 192.0, 136.2, 135.1, 129.3, 128.1.

2-Methybenzaldehyde (2b)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.3 (s, 1 H), 7.8 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.5 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.4-7.0 (m, 2 H), 2.6 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 191.0, 137.3, 134.1, 133.7, 131.3 129.6, 127.3, 19.6.

4-Methylbenzaldehyde (2c)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.96 (s, 1H, CHO), 7.77 (d, *J*=8.1 Hz, 2H, Ar-H), 7.33 (d, *J*=7.8 Hz, 2H), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 191.9, 145.5, 134.1, 129.7, 21.8.

4-tert-butylbenzaldehyde (2d)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.98 (s, 1 H, CHO), 7.82 (d, *J* = 8.4, 2 H, Ar-H), 7.55 (d, *J* = 8.4 Hz, 2 H, Ar-H), 1.35 (s, 9H, 3CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 192.0, 158.4, 134.0, 129.7, 125.9, 35.3, 31.0.

4- Chlorobenzaldehyde (2e)[12]: White solid; m.p.: 44-45 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.90 (s, 1 H, CHO), 7.70 (dd, *J* = 8.8, 2.0 Hz, 2 H, Ar-CH), 7.70 (dd, *J* = 8.6, 2.0 Hz, 2 H, Ar-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 191.0, 135.0, 132.4, 130.9, 129.7.

2- Chlorobenzaldehyde (2f)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.40 (s, 1 H, CHO), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar-CH), 7.50-7.30 (m, 3 H, Ar-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 188.0, 138.1, 134.1, 133.7, 131.3, 129.6, 127.5.

4-Methoxybenzaldehyde (2g)[12]: Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.83 (s, 1 H, CHO), 8.17-7.55 (m, 2 H, Ar-CH), 6.59 (d, J= 8.7Hz, 2H, Ar-CH), 3.83 (m, 3 H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 190.6, 164.4, 131.8, 129.8, 114.2, 55.4.

4-Nitrobenzaldehyde (2h)[12]: Yellow crystalline powder; m.p.: 104-106 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.18 (s, 1 H, CHO), 8.41 (d, *J* = 8.0 Hz, 2 H, Ar-CH), 8.10 (d, *J* = 8.0 Hz, 2 H, Ar-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 190.2, 151.0, 139.9, 130.4, 124.2.

2- Nitrobenzaldehyde (2i)[12]: Pale yellow solid; m.p.: 44-45 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.40 (s, 1 H, CHO), 8.10 (dd, *J* = 7.6, 1.6 Hz, 1 H, Ar-CH), 7.90 (dd, *J* = 7.2, 1.6 Hz, 1 H, Ar-CH), 7.80-7.70 (m, 2 H, Ar-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 188.1, 149.6, 134.1, 133.7, 131.3, 129.6, 124.5.

Trans-Cinnamaldehyde (2j)[12]: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.71 (d, *J* = 7.6 Hz, 1 H, CHO), 7.49-7.57 (m, 2 H, Ar-CH), 7.42-7.45 (m, 4 H), 6.73 (q, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 193.6, 152.6, 133.8, 131.1, 128.9, 128.7, 128.4, 128.2.

Acetophenone (2k)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.90 (d, *J* = 7.2 Hz, 2 H, Ar-CH), 7.50 (t, *J* = 7.2 Hz, 1 H, Ar-CH), 7.40 (t, *J* = 8.0 Hz, 2 H, Ar-CH), 2.60 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 198.1, 137.1, 133.1, 128.5, 128.3, 26.6.

α-Tetralone (2l)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.07-8.05 (m, 1 H, Ar-CH), 7.5-7.4 (m, 1 H, Ar-CH), 7.35-7.31 (m, 1 H, Ar-CH,), 7.29-7.27 (m, 1 H, Ar-CH), 3.0 (t, *J* = 6 Hz, 2 H), 2.60 (t, *J* = 6 Hz, 2 H), 2.20-2.10 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 198.4, 144.5, 133.4, 132.6, 128.8, 127.1, 126.6, 39.2, 29.7, 23.3.

Benzophenone (2m)[12]: White solid; m.p.: 49-50 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.85-7.83 (m, 2 H, Ar-CH), 7.60 (t, *J* = 7.6 Hz, 1 H, Ar-CH), 7.50 (t, *J* = 7.6 Hz, 2 H, Ar-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 196.8, 137.6, 132.4, 130.1, 128.3.

4-Methylthiobenzaldehyde (2n)[12]: Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.90 (s, 1 H, CHO), 7.80 (d, *J* = 8.8 Hz, 2 H, Ar-CH), 7.30 (d, *J* = 8.4 Hz, 2 H, Ar-CH), 2.50 (s, 3 H, SCH3). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 191.2, 147.9, 132.9, 130.0, 125.2, 14.7.

2-Furaldehyde (2o)[12]: Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.63 (s, 1 H, CHO), 7.67 (d, *J* = 1.0 Hz, 1 H, Ar-CH), 7.23 (t, *J* = 4.8 Hz, 1 H, Ar-CH), 6.58 (dd, *J* = 4.4, 1.9 Hz, 1H, Ar-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 177.7, 152.8, 147.9, 112.4.

General procedure for aerobic bis(indolyl)methanes synthesis via condensation of benzyl alcohols and indoles (4a-g)

3 mg [Cu(II)-TA/B_5] catalyst (8 mol%, 0.01 mmol) was added to a mixture of benzyl alcohols (0.125 mmol), 34 mg 2-methylindole (0.262 mmol) and 2 mg TEMPO (10 mol%, 0.0128 mmol), and stirred under air and solvent-free condition at 80 °C for the required time. The reaction progress was monitored by TLC. After completion of the reaction, ethyl acetate (5 mL) was added to the mixture and then [Cu(II)-TA/B_5] nanocatalyst (solid phase) was separated by centrifuging followed by decantation (3×5 mL ethyl acetate). Desired product (liquid phase) was extracted by plate chromatography eluted with n-hexane/EtOAc (10/6).

3,3'-(phenylmethylene)bis(2-methyl-1H-indole) (4a): Red solid. m.p.: 244-246˚C (243—245 °C)[13]; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 10.72(s, 2H, NH), 7.27-7.18 (m, 7H, Ar-CH), 6.91-6.87 (m, 2H, Ar-CH), 6.81 (d, J=8.0 Hz, 2H, Ar-CH), 6.69-6.66 (m, 2H, Ar-CH), 5.93(s, 1H, CH), 2.07(s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 144.0, 135.2, 132.2, 129.0, 128.4, 128, 125.8, 119.6, 118.56, 118, 112.5, 110.4, 38.8, 12.3.

3,3'-((4-chlorophenyl)methylene)bis(2-methyl-1H-indole) (4b): Pink solid. m.p.: 233-235 ˚C (202-204)[13]; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 10.76(s, 2H, NH), 7.3 (d, J = 7.1 Hz, 2H), 7.23-7.18 (m, 4H, Ar-CH), 6.90 (t, J = 7.5 Hz, 2H, Ar-CH), 6.81 (d, J = 7.9 Hz, 2H, Ar-CH), 6.70 (t, J = 7.5 Hz, 2H, Ar-CH), 5.92 (s, 1H, CH), 2.08 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 142.5, 135.2, 132.0, 131.4, 130.0, 129.0, 121.0, 119.5, 113, 110.0, 38.8, 12.4.

3,3'-(p-tolylmethylene)bis(2-methyl-1H-indole) (4c): Purple solid. m.p.: 176-177 ˚C (175-176)[13]; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 10.69 (s, 2H, NH), 7.21 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.08-7.04 (m, 4H, Ar-CH), 6.90-6.87 (t, *J* = 7.5 Hz, 2H, Ar-CH), 6.84-6.82 (d, *J* = 7.9 Hz, 2H, Ar-CH), 6.69 (t, *J* =7.9 Hz, 2H, Ar-CH), 5.88 (s, 1H, CH), 2.28 (s, 3H, CH_3), 2.05 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 140.6, 135.2, 131.8, 130.0, 129.6, 129.0, 120.7, 119.5, 119.0, 113.7, 109.8, 100.0, 38.8, 21.2, 12.5.

3,3'-((4-methoxyphenyl)methylene)bis(2-methyl-1H-indole) (4d): Pink solid. m.p.: 207-210 ˚C (194-195)[13]; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 10.68 (s, 2H, NH), 7.20 (d, *J* = 8.0 Hz,

2H, Ar-CH), 7.08 (d, *J* = 8.5 Hz, 2H, Ar-CH), 6.90-6.81 (m, 6H, Ar-CH), 6.69-6.66 (m, 2H, Ar-CH), 5.85 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 2.06 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm): 157.5, 135.9, 135.2, 131.7, 129.4, 128.7, 121.0, 119.7, 119.0, 113.5, 114.0, 109.8, 55.5, 38.4, 12.2.

3,3'-((4-nitrophenyl)methylene)bis(2-methyl-1H-indole) (4e): Yellow solid. m.p.: 239-241 ˚C (240-242)[13]; ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 10.82 (s, 2H, NH), 8.10 (d, J=9.2 Hz, 2H, Ar–H) 7.51-7.48 (d, J = 7.6 Hz, 2H, Ar-CH), 7.22-7.24 (m, J = 8.0 Hz, 4H, Ar-CH), 6.93-6.89 (m, 4H, Ar-CH), 5.90 (s, 1H), 2.03 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm): 152.0, 146.4, 135.0, 132.0, 130, 128.6, 123.5, 121.0, 119.5, 119.0, 111.8, 110.2, 39.5, 12.5.

3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (4f): Pink solid. m.p.: 78-80 ˚C (79—80 °C)[13]; ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 10.84(s, 2H, NH), 7.37-7.30(m, 6H, Ar-CH), 7.26(d, J=7.6 Hz, 2H, Ar-CH), 7.06-7.02(m, 2H, Ar-CH), 6.89-6.82(m, 4H, Ar-CH), 5.85(s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm): 144.2, 136.6, 130.3, 130.2, 128.0, 126.5, 123.7, 121.0, 119.0, 118.3, 117.6, 111.5, 39.0.

3,3'-((4-chlorophenyl)methylene)bis(5-bromo-1H-indole) (4g): Red solid. m.p.: 212-214˚C (206—208 °C)[13]; 1H NMR (400 MHz, DMSO-d_6): δ ppm: 11.10 (s, 2H, NH), 7.42 (s, 2H, Ar-CH), 7.34-7.33(m, 6H, Ar-CH), 7.16 (dd, J=2.0, 8.8 Hz, 2H, Ar-CH), 6.90 (d, J=1.6 Hz, 2H, Ar-CH), 5.90 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm): 143.4, 135.3, 130.6, 130.0, 128.3, 128.2, 125.3, 123.6, 121.1, 117.2, 113.7, 111.0, 38.1.

Reusability of Catalyst

To a mixture of benzyl alcohol (0.125 mmol) and 2mg [Cu(II)-TA/B_5] nanocomplex (5 mol%, 0.006 mmol) in EtOH (0.2 mL) was added 1.7 mg TEMPO (8 mol%, 0.01 mmol), and the reaction mixture was stirred under air at 70 °C for the required time. At the end of the reaction, the mixture was cooled to room temperature, [Cu(II)-TA/B_5] was separated by centrifuging followed by decantation (3×5 ml ethanol and then ethyl acetate) and dried in a vacuum oven at 50 °C. Catalyst recovery was also investigated in the aerobic bis(indolyl)methanes synthesis.

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Keywords: Panthothenic acid (Vitamin B_5), Triazine, Copper complex, Nano-bio-complex, Aerobic oxidation, Bis(indolyl)methanes (BIMs)

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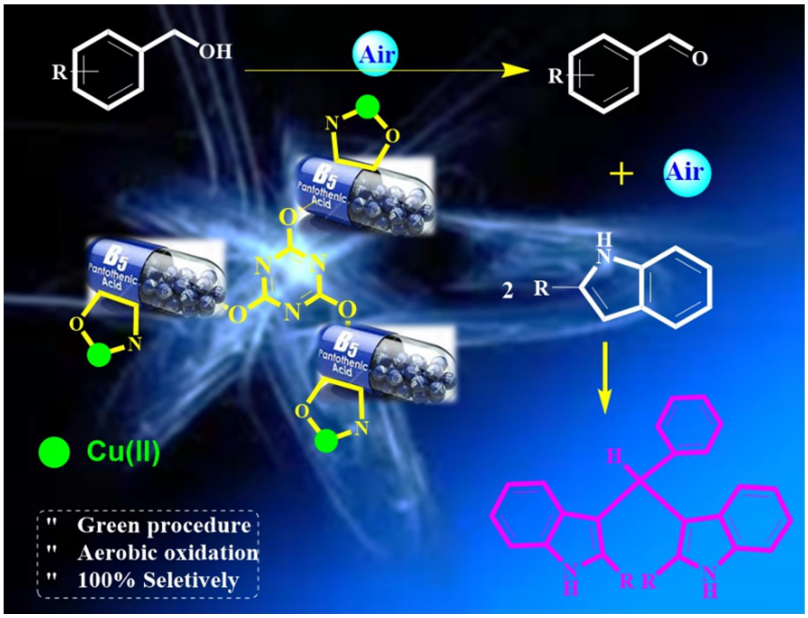
Table of content

Aerobic Oxidation



A bio-relevant Cu(II) vitamin B5 complex anchored on triazine ring resulting in a novel reusable star-shaped catalyst for TEMPO mediated aerobic oxidation of benzylic alcohols followed by coupling with indole derivatives producing bis(indolyl)methanes in desired yields and excellent selectivity.