4.1 Synthesis and characterization of Co(0) nanoparticles immobilized onto L-dopa functionalized magnetic graphene oxide

The water-dispersible and magnetically recoverable, Co(0) nanoparticles immobilized onto L-dopa functionalized magnetic graphene oxide (Co@GO/Fe₃O₄/L-dopa) was successfully synthesized. The procedure for the synthesis of Co@GO/Fe₃O₄/L-dopa is schematically presented in **Scheme 1**. Firstly, graphene oxide was synthesized from graphite powder using modified Hummer’s method. Fe₃O₄ nanoparticles were grafted over the graphene oxide by co-precipitation of Fe³⁺ and Fe²⁺ salts using ultrasonication technique. Although, graphene oxide-magnetite composite is quite stable but the aggregation and leaching of metal nanoparticles from its surface remains the drawback. Recently, L-dopa was reported as an excellent binding agent which plays important role

![Scheme 1](image.png)

**Scheme 1.** General scheme for the synthesis of Co@GO/Fe₃O₄/L-dopa.
in preventing the leaching of active metal nanoparticles and also enhanced its catalytic efficiency. The synthesized GO/Fe₃O₄ was functionalized with L-dopa and finally, Co(0) nanoparticles were immobilized onto the support using Co(acac)₂ followed by reduction with aqueous NaBH₄ solution. The novel catalyst, Co@GO/Fe₃O₄/L-dopa was characterized by different techniques such as SEM, HR-TEM, XPS, XRD, TGA, FTIR, VSM, CHN analysis, EDX and ICP-AES studies.

**General procedure for the synthesis of Co@GO/Fe₃O₄/L-dopa**

For the synthesis of core-shell particles of GO/Fe₃O₄, graphene oxide (2 g) prepared by modified Hummer process¹, was dispersed in deionized water (50 mL) and ultrasonicated for 30 min to get a stable ferrofluid. Subsequently, ammonical solution (30 mL, 24 mL water and 6 mL NH₄OH) of FeSO₄ (2.4 g) and Fe₂(SO₄)₃ (7 g) was added into above ferrofluid and again sonicated for 60 min to get GO/Fe₃O₄ nanoparticles. GO/Fe₃O₄ nanoparticles so obtained were filtered, washed with deionized water (3×10 mL), chloroform (3×10 mL) and dried under vacuum. In order to graft L-dopa over GO/Fe₃O₄ nanoparticles, the mixture of GO/Fe₃O₄ (1 g) and L-dopa (0.2 g) was stirred in deionized water (10 mL) at 120 °C for 2 h. Black precipitates of GO/Fe₃O₄/L-dopa were separated magnetically, washed with deionized water (3 × 10 mL) and dried under vacuum. Finally, to immobilization Co(0) nanoparticles onto GO/Fe₃O₄/L-dopa, the aqueous solution of Co(acac)₂ (0.134 g, 1.0 mmol, 3 mL) was added into the dispersed solution of GO/Fe₃O₄/L-dopa (1 g) in ethanol (10 mL), and the reaction mixture was stirred at room temperature for 3 h. Then, aqueous solution of NaBH₄ (1.2 mmol in 5 mL H₂O) was added dropwise into the reaction mixture under continuous stirring. Co@GO/Fe₃O₄/L-dopa so prepared was separated magnetically and washed successively with ethanol (3 × 25 mL) and water (3 × 25 mL). Finally, it was dried under vacuum at room temperature to get Co@GO/Fe₃O₄/L-dopa nanoparticles as dark black powder.

**Characterization of Co@GO/Fe₃O₄/L-dopa**

The novel catalyst, Co@GO/Fe₃O₄/L-dopa was characterized by various techniques such as SEM, HR-TEM, XPS, XRD, TGA, FTIR, VSM, CHN analysis, EDX and ICP-AES studies.
Scanning Electron Microscopy (SEM)

The SEM images of Co@GO/Fe$_3$O$_4$/L-dopa were recorded to get information about the surface morphology. From SEM images (Fig. 1), it was clearly observed that the synthesized catalyst is homogeneous in nature and Co(0) nanoparticles were uniformly deposited over the surface of GO/Fe$_3$O$_4$/L-dopa. Graphene oxide has formed a layered structure on which Fe$_3$O$_4$/L-dopa and cobalt nanoparticles were uniformly spread. Furthermore, Fe$_3$O$_4$/L-dopa and cobalt nanoparticles assume spherical shape, which is responsible for the low tendency of nanoparticles to undergo agglomeration and also accountable for their increased catalytic proficiency.

![SEM images of Co@GO/Fe$_3$O$_4$/L-dopa.](image)

**Fig. 1** SEM images of Co@GO/Fe$_3$O$_4$/L-dopa.
High Resolution Transmission Electron Microscopy (HR-TEM)

HR-TEM was used to get information about morphology, particle size and distribution of cobalt(0) nanoparticles over the GO/Fe₃O₄/L-dopa. In HR-TEM image (Fig. 2a), graphene oxide sheets of micron size are clearly visible. Further, HR-TEM images also reveals uniform coating of cobalt(0) nanoparticles over the GO/Fe₃O₄/L-dopa support (Fig. 2b-d). Moreover, it also deciphered that L-dopa forms a uniform covering over the GO/Fe₃O₄ support and thus responsible for the better anchoring of Co(0) nanoparticles onto the support material, which prevent their leaching.

![HR-TEM images of Co@GO/Fe₃O₄/L-dopa.](image)

Fig. 2 HR-TEM images of Co@GO/Fe₃O₄/L-dopa.
X-Ray Photoelectron Spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS) technique was used to explore the electronic properties of the active species formed on the surface of the catalyst, such as oxidation state and binding energy of the core electrons of the Co metal (Fig. 3). Fig. 3a present the

![XPS spectra](image1.png)

![Co 2p core level spectrum](image2.png)

**Fig. 3** XPS spectra of Co@GO/Fe₃O₄/L-dopa: a) overall survey spectrum; b) Co 2p core level spectrum.
overall survey spectrum of Co@GO/Fe$_3$O$_4$/L-dopa in which peaks corresponding to carbon 1s (284.9 eV), oxygen 1s (532.6 eV) and cobalt 2p (778.5 eV) are clearly seen. Further, Fig. 3b showed typical Co(0) absorptions at 778.5 and 793.4 eV for 2p$_{3/2}$ and 2p$_{1/2}$ respectively, which are consistent with the literature values for Co(0) nanoparticles$^2$.

**X-ray Powder Diffraction (XRD)**

Unambiguous evidence for the presence of cobalt nanoparticles onto the surface of GO/Fe$_3$O$_4$/L-dopa is also provided via X-ray powder diffraction analysis (XRD). XRD spectrum of GO (Fig. 4a) showed diffraction peak at 2$\theta$ = 10.2° which corresponds to the
d-spacing of 8.1 Å resulting from the insertion of the epoxy and hydroxyl groups between the graphite sheets\(^3\). XRD pattern of GO/Fe\(_3\)O\(_4\)/L-dopa (4b) showed diffraction peaks at \(2\theta = 30.2, 35.4, 42.3, 57.3\) and 62.3°, which corresponds to [111], [220], [311], [440] and [511] planes of cubic phase of Fe\(_3\)O\(_4\) lattice\(^4\). Whereas XRD spectrum of Co@GO/Fe\(_3\)O\(_4\)/L-dopa (4c) showed three new peaks at 44.4, 47.5 and 75.6° corresponding to [111], [200] and [220] planes of cubic phase of Co nanoparticles\(^5\). Thus, XRD spectra also aided in providing the information about the nature of cobalt nanoparticles and successful grafting of Fe\(_3\)O\(_4\) onto graphene oxide.

**Thermogravimetric analysis (TGA)**

The thermal stability of the synthesized catalyst was investigated by Thermogravimetric analysis. The TGA was recorded by heating the sample at the rate of 10 °C min\(^{-1}\). The TGA curve of Co@GO/Fe3O4/L-dopa is shown in Fig. 5. It showed an initial weight loss up to 140 °C, which was ascribed to the loss of residual solvent and water trapped onto the surface of the catalyst. Further, no appreciable weight loss up to 389 °C was

![Fig. 5 TGA of Co@GO/Fe3O4/L-dopa.](image)
observed. The major weight loss occurred after 389 °C, which may be due to the desorption of chemisorbed material i.e., L-dopa from the synthesized catalyst.

**Fourier Transform Infrared Spectroscopy (FT-IR)**

The presence of different functional groups in Co@GO/Fe₃O₄/L-dopa was confirmed by FT-IR spectroscopy. FT-IR spectra of GO, GO/Fe₃O₄/L-dopa and Co@GO/Fe₃O₄/L-dopa are shown in Fig. 6. FT-IR spectrum of GO (Fig. 6a) showed bands at 3114, 1721, 1633, 1487, 1007, 870, 609 and 550 cm⁻¹. The band at 3114 cm⁻¹ corresponds to O-H stretching, whereas a band at 1633 and 1487 cm⁻¹ corresponds to the carboxylate group of graphene oxide. Moreover, band at 1007 and 870 cm⁻¹ corresponds to C-O symmetrical stretching and C-O-C asymmetrical stretching of epoxide. FTIR spectrum of GO/Fe₃O₄/L-dopa (Fig. 6b) showed band at 612 cm⁻¹ which correspond to Fe-O stretching vibration of Fe₃O₄, whereas band at 3202, 1587, 1248, 1071 cm⁻¹ are attributed to O-H symmetrical Stretching, C-H bending vibration and C-O symmetrical stretching of L-dopa respectively. However, no significant change occurred in FTIR spectrum of Co@GO/Fe₃O₄/L-dopa (Fig. 6c), although slight decrease in the intensity of bands observed due to the immobilization of Co nanoparticles over the support. Thus, FTIR spectrum clearly indicated the formation of protective layer of L-dopa over the GO/Fe₃O₄ nanoparticles.

**Vibrating Sample Magnetometer (VSM)**

The magnetic property of the synthesized catalyst was investigated using Vibrating Sample Magnetometry (VSM) at room temperature. VSM of GO/Fe₃O₄, GO/Fe₃O₄/L-dopa and Co@GO/Fe₃O₄/L-dopa are shown in Fig. 7. The magnetization curve of GO/Fe₃O₄ showed paramagnetic property with saturation magnetization of about 33.5 emu/g. After grafting of L-dopa on GO/Fe₃O₄, the paramagnetic behavior of GO/Fe₃O₄/L-dopa has decreased from 33.5 emu/g to 27.8 emu/g. The reduction in saturation value arises due to the coating of the non-magnetic material (L-dopa) on the surface of magnetic material (GO/Fe₃O₄) in the synthetic pathway of the novel catalyst. Finally, after the successful immobilization of cobalt nanoparticles over GO/Fe₃O₄/L-dopa, magnetic moment was found to be 25.8 emu/g. It is worth mentioning that the
synthesized catalyst is still magnetic enough to be separated via magnet and assures facile and efficient separation of the catalyst from the reaction mixture. Moreover, the coating of L-dopa over GO/Fe₃O₄ relatively well protects them from oxidation, reinforces the magnetic stability and enables it to disperse rapidly when the magnetic field is removed.

Fig. 6 FTIR spectra: a) GO/Fe₃O₄; b) GO/Fe₃O₄/L-dopa; and c) Co@GO/Fe₃O₄/L-dopa.
Fig. 7 VSM spectra: a) GO/Fe$_3$O$_4$; b) GO/Fe$_3$O$_4$/L-dopa; and c) Co@GO/Fe$_3$O$_4$/L-dopa.

Carbon Hydrogen Nitrogen (CHN) analysis

The successful grafting of L-dopa onto GO/Fe$_3$O$_4$ was further confirmed from the CHN analysis (Fig. 8) and the results showed that catalyst is composed of 1.89% of nitrogen,
1.06% of hydrogen and 10.3% of carbon elements. Thus, CHN study has further established the successful grafting of L-dopa over the GO/Fe$_3$O$_4$ nanoparticles.

**Energy Dispersive X-ray (EDX)**

The elemental composition of Co@GO/Fe$_3$O$_4$/L-dopa was analyzed by the energy dispersive spectrometer (EDX). The results showed that the synthesized catalyst composed of C, O, Fe and Co elements (Fig. 9). This further indicated that L-dopa was successfully incorporated over the GO/Fe$_3$O$_4$ nanoparticles.

![Fig. 9 EDX spectrum of Co@GO/Fe$_3$O$_4$/L-dopa.](image)

**Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)**

In order to evaluate the loading of Co nanoparticles over GO/Fe$_3$O$_4$/L-dopa, the synthesized catalyst was examined using inductively coupled plasma atomic emission spectroscopy (ICP-AES). The results showed that the content of Co nanoparticles loaded onto 0.1 g of GO/Fe$_3$O$_4$/L-dopa is 2.14 wt%.
REFERENCES


4.2 Co@GO/Fe$_3$O$_4$/L-dopa as an inexpensive and water dispersible magnetically recoverable catalyst for the Suzuki coupling in aqueous medium

The Suzuki cross-coupling reaction is one of the most effective tools in organic synthesis for C-C bond formation$^1$. This reaction has been widely used for the synthesis of substituted biaryls, which possess a broad range of applications in the chemical and pharmaceutical industries. Palladium based catalysts are considered as the most competent catalysts for C-C cross coupling reactions, offering high turnover frequency, fast reaction rates and good selectivity in various synthetic protocols$^{2,3}$. The worth of the biaryl motif is demonstrated by its presence in a wide range of biologically active compounds and functional moieties$^4$ (Fig. 1). As a pharmacophore, biaryl moiety is present in numerous medically and industrially important compounds, such as Losartan, Micardis, NCB

![Fig. 1 Some biaryl motifs in medicinally and industrially important compounds.](image-url)
807, Biphenomycin, and Felbinac. Besides, this is an essential part of liquid crystal displays, agrochemicals and also has been incorporated into molecular switches and motors\(^5\).

**Earlier approaches for C-C couplings**

Over a century, synthesis of biaryls via C-C cross-coupling remains a challenging task. Later on, numerous valuable methodologies have been reported for the preparation of biaryls after Ullmann’s first report of copper bronze catalyzed coupling reaction of aryl halides\(^6\text{-}^9\). But, these methodologies suffered from harsh reaction conditions and gave low yields, especially in case of unsymmetrically substituted biaryls.

One of the most significant and useful methodology for the construction of C-C bonds was reported in 1979 by Miyaura, Yamada and Suzuki via cross-coupling reaction between organoboron compounds and organic halides in the presence of catalytic amount of tetrakis(triphenylphosphine)palladium and base\(^10\). After that, several advances have been made in this methodology to explore its utility to the fullest\(^11\). Easy availability, non-toxic and stable nature of boronic acids, broad tolerance to different functional groups, easy handling of products, mild reaction conditions and high regio- and stereoselectivity etc. were the main reasons for the impressive development of this reaction.

Now, palladium catalyzed Suzuki-Miyaura cross-coupling reaction has become a mainstay of modern synthetic organic chemistry for the manufacture of diversified biaryls. In the Suzuki-Miyaura cross-coupling reaction, Pd(II) based catalysts along with phosphine ligands have been used for the synthesis of substituted biaryls\(^12\text{-}^13\). But, phosphine-containing ligands are toxic in nature and sensitive to air and moisture\(^14\). Furthermore, the presence of palladium and ligands as impurities in the products were difficult to separate\(^15\). Thus, the designing of phosphine-free catalysts for the synthesis of substituted biaryls became a topic of enormous interest in modern synthetic organic chemistry\(^14\).

Leadbeater *et al*.\(^16\) showed that substituted biaryls could be prepared successfully in good yield from corresponding aryl halides and phenylboronic acid using palladium acetate as
catalyst and water as solvent. It was also reported that the reaction proceeds equally well using microwave and conventional heating, which indicates that no non-thermal microwave effects are associated with the impressive speed of the reaction (Scheme 1).

**Scheme 1**

\[
\begin{align*}
&\begin{array}{c}
\text{Ph} \quad \text{X} \\
& \quad \text{R}
\end{array} + \\
&\begin{array}{c}
\text{Ph} \quad \text{B(OH)}_2 \\
& \quad \text{R}
\end{array} \\
\xrightarrow{\text{Pd(OAc)}_2, \text{H}_2\text{O}} \\
&\begin{array}{c}
\text{Ph} \quad \text{R}
\end{array}
\end{align*}
\]

Li *et al.*\(^{17}\) have reported Pd(OAc)\(_2\)/DABCO (1,4-diaza-bicyclo[2.2.2]octane) catalyzed Suzuki–Miyaura cross-coupling reaction under milder reaction conditions. Both aryl bromides and aryl chlorides have reacted smoothly with arylboronic acids to form diversely substituted biaryls in moderate to excellent yields (Scheme 2).

**Scheme 2**

\[
\begin{align*}
&\begin{array}{c}
\text{Ph} \quad \text{Cl} \\
& \quad \text{R}
\end{array} + \\
&\begin{array}{c}
\text{Ph} \quad \text{B(OH)}_2 \\
& \quad \text{R}
\end{array} \\
\xrightarrow{\text{Pd(OAc)}_2 (3 \text{ mol}%), \text{DABCO} (6 \text{ mol}%), \text{Cs}_2\text{CO}_3, \text{DMF, 110 }^\circ\text{C}} \\
&\begin{array}{c}
\text{Ph} \quad \text{R}
\end{array}
\end{align*}
\]

Zhou *et al.* have reported atom-efficient cross-coupling reaction of sodium tetraarylborates with aryl iodides and bromides using palladium chloride, sodium carbonate and methanol at room temperature. The reported methodology was atom-efficient, as 4 equiv. of aryl halides coupled effectively with 1 equiv. of sodium tetraarylborates to give 4 equiv. of the corresponding functionalized biaryls in good to excellent yields (Scheme 3).\(^{18}\)

**Scheme 3**

\[
\begin{align*}
&\begin{array}{c}
\text{Ph} \quad \text{BNa} \\
& \quad \text{R}_1 \\
& \quad \text{1 eq}
\end{array} + \\
&\begin{array}{c}
\text{Ph} \quad \text{Br} \\
& \quad \text{R}_2 \\
& \quad \text{4 eq}
\end{array} \\
\xrightarrow{\text{PdCl}_2 (3 \text{ mol}%), \text{Na}_2\text{CO}_3 (3 \text{ mmol}), \text{MeOH, Air, r.t.}} \\
&\begin{array}{c}
\text{Ph} \quad \text{R}_1 \quad \text{R}_2 \\
& \quad \text{4 eq}
\end{array}
\end{align*}
\]
Na$_2$Pd$_2$Cl$_6$ complex with ethyl calix[4]aryl acetate has been reported as an efficient catalyst for Suzuki-Miyaura cross-coupling reaction at room temperature under ambient conditions. Here, the extended hydrophobic host cavities and surface active properties of ethyl calix[4] aryl acetate were responsible for rapid and quantitative coupling (Scheme 4).

**Scheme 4**

Suzuki-Miyaura cross-coupling reaction of aryl bromides or iodides with arylboronic acid has been reported by Liu et al. using Pd(OAc)$_2$ and 4-(benzylthio)-$N,N,N$-trimethylbenzenammonium chloride under mild conditions. The corresponding products were obtained in good to excellent yields (Scheme 5).

**Scheme 5**

Though homogeneous palladium catalysts showed enormous catalytic activity for C-C bond formation, but expensive palladium complexes were often lost at the end of the reaction due to their homogeneous nature. Moreover, separation of palladium compounds from the desired products became the main drawback of this method. Therefore, development of heterogeneous palladium catalysts to carry out C-C cross-coupling became the current impetus in organic synthesis. Different support materials were used for this purpose, such as inorganic supports (silica, titania, zirconia), organic supports (cellulose, starch) etc. Nowadays, magnetic nanoparticles also appeared as a viable and
efficient support materials for the immobilization of homogeneous palladium nanoparticles.

Palladium(0) nanoparticles immobilized on cellulose has been reported as a highly efficient and recyclable catalyst for the Suzuki cross-coupling between phenyl boronic acid and aryl bromides by Jamwal and co-workers. Biaryls and polyaryls were obtained in excellent yields with high turn over numbers (Scheme 6).\textsuperscript{20}

**Scheme 6**

\[
\begin{array}{c}
\text{Br} \\
\text{R} \\
\end{array}
+ \text{ArB(OH)}_2 \xrightarrow{\text{Cell-Pd(0), K}_2\text{CO}_3, \text{TBAB, H}_2\text{O, 100 }^\circ\text{C}}
\begin{array}{c}
\text{Ar} \\
\text{R} \\
\end{array}
\]

Dadras et al. have reported Pd@Fe\textsubscript{3}O\textsubscript{4} catalyzed Suzuki–Miyaura cross-coupling reaction of aryl halides, especially of inactive aryl chlorides with aryl boronic acids in the absence of toxic phosphine ligands in aqueous media (Scheme 7).\textsuperscript{21}

**Scheme 7**

\[
\begin{array}{c}
\text{X} \\
\text{R'} \\
\end{array}
+ \begin{array}{c}
\text{B(OH)}_2 \\
\text{R''} \\
\end{array} \xrightarrow{\text{Pd/Fe}_3\text{O}_4 (0.01 g)} \begin{array}{c}
\text{R} \\
\text{R'} \\
\end{array}
\]

Yinghuai et al. have reported a simplistic method for the preparation of palladium nanoparticles grafted onto the magnetic support derived from phosphate functional groups. The reported catalyst was found to be active for Suzuki cross-coupling and afforded products in good to excellent yields. Furthermore, the catalyst could be easily separated from the reaction mixture via external magnet and reused several times.\textsuperscript{22}

The Pd nanoparticles immobilized onto magnetically retrievable carboxymethylcellulose/Fe\textsubscript{3}O\textsubscript{4} organic/inorganic hybrid were successfully prepared. The existence of the carboxyl and hydroxyl groups within the scaffold of the magnetic hybrid was responsible for the stabilization of Pd NPs and prevents their leaching. This hybrid catalyst was found to be highly effective for the Suzuki–Miyaura reaction of a wide range of aryl halides with arylboronic acids.\textsuperscript{23}
Klimov et al.\textsuperscript{24} have developed palladium catalyst supported onto hydrogen titanate nanotubes (HTN) by impregnation of palladium (II) acetate. The reported catalyst, Pd/HTN showed good to excellent yields of substituted biaryls and its activity decreased by about 10% after five catalytic cycles. This was due to the leaching, agglomeration of palladium NPs and presence of organic and inorganic species on the spent catalyst’s surface.

Palladium(0) nanocluster immobilized onto hydrotalcite has been developed and its efficiency was tested for the Suzuki cross-coupling reaction. The catalyst showed excellent catalytic activity for cross-coupling of iodo- and bromoarenes under mild reaction conditions and afforded desired products upto 90% yields.\textsuperscript{25}

It has been observed that majority of Suzuki cross-coupling reactions were achieved by precious and costlier palladium catalysts. But there were also reports showing the use of inexpensive metals, usually 3d transition metals, for C-C cross-coupling reactions. 3d Transition metal based catalysts represented an attractive alternate to carry out important organic transformations, being naturally more abundant and cost-efficient. As a consequence, the use of inexpensive first-row transition metal catalysts in chemical industries for C-C bond formation has been gaining much momentum recently.

**Iron catalyzed C-C cross-coupling reactions**

Hatakeyama et al. have reported novel iron(II) chloride-diphosphine complex-magnesium bromide catalyzed cross-coupling reaction between lithium arylborates and primary or secondary alkyl halides and afforded desired products in good to excellent yields (Scheme 8).\textsuperscript{26}

**Scheme 8**

\[
\begin{align*}
\text{Br} & \quad \text{B(OH)}_2 \\
\text{R}_1 & \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{FeCl}_2 \text{-diphosphine complex (5 mol\%)} & \quad \text{MgBr}_2 (20 \text{ mol\%}), \text{THF, 40}^\circ \text{C} \\
\text{R}_1 & \quad \text{R}_2
\end{align*}
\]

Hatakeyama et al.\textsuperscript{27} have reported alkyl–alkyl Suzuki-Miyaura cross-coupling of primary and secondary alkyl halides using [Fe(acac)\textsubscript{3}]/Xantphos as a catalyst (Scheme 9). Here,
iso-propylmagnesium chloride (\(^{1}\)PrMgCl) was used as an efficient activator for trialkylboranes. This method was applicable for the facile synthesis of a range of functional molecules, particularly for the synthesis of long-chain fatty acid derivatives.

**Scheme 9**

\[
\text{R}^1-\text{X} + [\text{R}^2/\text{PrB}][\text{MgCl}] \xrightarrow{[\text{Fe(acac)}_3] (3-5 \text{ mol}\%)} \xrightarrow{\text{Xantphos} (6-10 \text{ mol}\%)} \text{THF} \quad \text{R}^1-\text{R}^2
\]

**Rhodium catalyzed C-C cross-coupling reactions**

Gooben *et al.*\(^{28}\) have reported for the first time, [Rh(ethylene)\(_2\)Cl]\(_2\)/KF catalyzed cross-coupling of aromatic carboxylic acid derivatives with triarylboroxines under decarbonylation conditions leading to the formation of unsymmetrical biaryls rather than the expected diaryl ketones.

This decarbonylative Suzuki cross-coupling worked smoothly with aromatic, heteroaromatic and vinylic carboxylic anhydrides, opens up new perspectives for the use of carboxylic acid derivatives as substrates in biaryl synthesis (**Scheme 10**).

**Scheme 10**

\[
\text{Ar}_2\text{COOAr} + [\text{Ar}']_3\text{B} \xrightarrow{[\text{Rh(ethylene)}_2\text{Cl}]_2/\text{KF}} (\text{ArCOBO})_3 \xrightarrow{\text{Ar}'} \text{Ar} - \text{Ar}' + \text{Ar} - \text{Ar}'
\]

Ueura *et al.*\(^{29}\) have reported rhodium-based catalytic system for the Suzuki-Miyaura cross-coupling of arylboron compounds with aryl halides affording the corresponding biaryls in good yields. Furthermore, it was reported that with halide substituted benzonitrile substrates, multiple arylation took place under similar set of conditions (**Scheme 11**).
Scheme 1

\[
\text{PhB(OH)_2 or Ph}_4\text{BNa} + \begin{array}{c}
\text{X} \\
\text{R}
\end{array}
\xrightarrow{\text{NiCat, phosphine ligand}}
\begin{array}{c}
\text{Ph} \\
\text{R}
\end{array}
\]

Nickel catalyzed C-C cross-coupling reactions

Fu et al.\textsuperscript{30} have reported a stereoconvergent amine directed Suzuki cross-coupling of unactivated secondary alkyl chlorides. The nitrogen-directed enantioselective Suzuki reaction complement with the previous reports of couplings directed by carbon-(arenes) and oxygen-based functional groups (\textbf{Scheme 12}).

Scheme 12

\[
\text{ArN} \xrightarrow{\text{R}} \text{R} + \text{(9-BBN)-R}_2 
\xrightarrow{\text{NiBr}_2 (10 \text{ mol%), diglyme, KOr-Bu, n-hexanol}}
\text{ArN} \xrightarrow{\text{R}} \text{R}_2
\]

Hu and coworkers\textsuperscript{31} have developed a Ni-catalyzed Suzuki cross-coupling reactions of aryl chlorides with arylboronic acids in the presence of air- and moisture-stable diaminophosphine oxides as preligands. It has been reported that this methodology tolerates the presence of variety of functional groups and is applicable for both electron-rich and electron-deficient aryl chlorides. It showed higher activity for activated arylboronic acids than deactivated ones (\textbf{Scheme 13}).

Scheme 13

\[
\text{Cl} \xrightarrow{\text{R}} \text{B(OH)_2} 
\xrightarrow{\text{Ni Cat, phosphine ligand, toluene, K}_2\text{CO}_3}
\text{Cl} \xrightarrow{110 ^\circ\text{C}, 18 \text{ h}}
\]
Handa et al. employed *in situ* formed nickel nanoparticles catalyzed Suzuki–Miyaura cross-couplings in water under mild reaction conditions (Scheme 14).32

**Scheme 14**

\[
\begin{array}{c}
\begin{array}{c}
\text{Cat (3 mol%), MeMgBr (3 mol%)} \\
K_3PO_4, \text{TPGS-750-M (0.5 M), 45 }^\circ\text{C}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{Cat (3 mol%), MeMgBr (3 mol%)} \\
K_3PO_4, \text{TPGS-750-M (0.5 M), 45 }^\circ\text{C}
\end{array}
\]

Xing et al. have reported Ni-catalyzed Suzuki–Miyaura coupling of pyrimidin-2-yl phosphates, pivalates and tosylates with arylboronic acids. A broad array of functionalized pyrimidines were synthesized in good yields (Scheme 15).33

**Scheme 15**

A new octahedral nickel(II) complex of 4-chlorobenzoic acid pyridin-2-ylmethylene-hydrazide ligand appeared as an active homogeneous catalyst for the Suzuki–Miyaura cross-coupling reaction of substituted aryl bromides with various arylboronic acids. Besides, the biphenyl and triphenyl derivatives were also obtained in moderate to excellent isolated yields (Scheme 16).34
Zhou et al.\textsuperscript{35} have reported NHC nickel complex $[\text{Ni}_2(\text{iPr}_2\text{Im})_4(\mu-\text{COD})]$ catalyzed Suzuki-Miyaura cross-coupling reaction of perfluorinated arenes with aryl boronate esters. The cross-coupling reactions between different boronate esters and the corresponding boronic acids have worked smoothly. Out of different esters tested, ethyleneglycolato ester showed excellent efficiency for C-C coupling reactions (\textbf{Scheme 17}).

\textbf{Scheme 17}

\textbf{Co catalyzed C-C cross-coupling reactions}

Recently, Co complexes have also emerged as cost-effective alternatives to the precious metals, such as palladium, rhodium, or toxic metals, such as nickel for carrying out Suzuki coupling reaction. Some of the reported protocols of cobalt complexes catalyzed C-C cross-couplings are cited below:
Cobalt catalyzed route for the synthesis of functionalized biaryl and heterobiaryl compounds was reported by Amatore et al.\textsuperscript{36} This protocol utilized inexpensive and environmentally benign cobalt halide salt and the triphenylphosphane ligand for the synthesis of heterocyclic biaryl compounds (Scheme 18).

**Scheme 18**

\[
\begin{align*}
&\text{EtOOC} \text{O} \text{TF} + \begin{array}{c}
\text{\text{R}}
\end{array} \text{Br} \quad \text{CoBr}_2 (20 \text{ mol\%}), \text{PPh}_3 (20 \text{ mol\%}) \\
&\text{DMF:pyridine (6:1)} \\
&\text{or} \quad \text{COOEt} \quad \text{or} \quad \text{COOEt}
\end{align*}
\]

Suzuki cross-coupling of aryl bromides or chlorides with alkyllithium-activated arylboronic pinacolate esters were developed by Asghar et al.\textsuperscript{37} using 10 mol\% of cobalt chloride in the presence of ligand (Scheme 19).

**Scheme 19**

\[
\begin{align*}
&\begin{array}{c}
\text{R}
\end{array} \text{X} + \begin{array}{c}
\text{O} \text{B} \text{O} \text{Li}^+(\text{THF})_2
\end{array} \quad \text{CoCl}_2 (10 \text{ mol\%}), \text{Ligand (10 mol\%)} \\
&\text{THF, 60 °C, 48 h} \\
&\begin{array}{c}
\text{R}
\end{array}
\end{align*}
\]

Kumar et al.\textsuperscript{38} have reported the synthesis of substituted biaryls via cross-coupling of substituted aryl halides with phenyl boronic acid using cost-effective and environmentally friendly cobalt pincer complex (Scheme 20).
From the literature survey, it was clearly depicted that majority of important C-C cross-coupling reactions were usually achieved by precious and costlier second and third row transition metals, especially Pd. In this perspective, 3d transition metal based catalysts represented an attractive alternate to carry out important organic transformations, being naturally more abundant and cost-efficient. 3d Transition metals such as Ni, Rh and Co have been reported to catalyze the C-C cross-coupling reaction. Out of three, Co represented an appropriate substitute to carry out C-C cross-coupling reactions owing to its non-toxic nature and availability. Very few methods were reported in the literature for the Suzuki coupling catalyzed by cobalt. So, keeping in view the importance of Suzuki cross-coupling for the synthesis of diversely substituted biaryls and to avoid tedious workup procedures, herein, Co@GO/Fe₃O₄/L-dopa, magnetically recoverable catalyst system has been developed as a highly active and stable catalyst for the synthesis of biaryls/polyaryls under aqueous medium in ligand-free conditions. The products were obtained in good to excellent yields (Scheme 21).
Results and discussion

Optimization of the reaction conditions

In order to optimize the reaction conditions for the Suzuki cross-coupling, the reaction between 4-bromoacetophenone and phenyl boronic acid was selected as the model reaction. Initially, the Suzuki coupling was carried out with test substrates using Co@GO/Fe$_3$O$_4$/L-dopa as a catalyst in the absence of base (entry 1, Table 1), unfortunately poor results were obtained. This suggests that addition of base is necessary to carry out the Suzuki coupling effectively as evident from the literature. So K$_2$CO$_3$ was selected as the green base, since it is mild, inexpensive and easily available. Further, the test reaction was carried out in the presence of different solvents (water, ethanol, acetonitrile, methanol) keeping 80 °C as the temperature and K$_2$CO$_3$ as base to study the effect of different solvents on the rate of the reaction. The results clearly depicted water as a solvent of choice (entry 2, Table 1), owing to the stability of phenyl boronic acid in aqueous medium. Further, the effect of increased temperature on the model reaction was also investigated in the presence of water and K$_2$CO$_3$. It was observed that on increasing temperature from 80 °C to 100 °C, there occurred significant increase in the yield of the desired product (entry 6, Table 1). Besides, no appreciable increase in the yield of the product was observed on raising the temperature above 100 °C (entry 7, Table 1). Lastly, different bases (K$_2$CO$_3$, Cs$_2$CO$_3$, Na$_2$CO$_3$) at 100 °C temperature were also scrutinized for the Suzuki coupling using Co@GO/Fe$_3$O$_4$/L-dopa as a catalyst, wherein best results were obtained with K$_2$CO$_3$ at 100 °C (entries 6,8,9, Table 1). Thus, the optimized reaction conditions for the Suzuki cross-coupling reaction were water as a green solvent, K$_2$CO$_3$ as base and 100 °C as the temperature. To the best of our knowledge, this is the first kind of report for Suzuki cross-coupling reaction catalyzed by heterogeneous cobalt nanoparticles.
Table 1. Optimization of the reaction conditions for Suzuki cross-coupling using Co@GO/Fe$_3$O$_4$/L-dopa as a catalyst$^a$

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Solvent</th>
<th>Base</th>
<th>Temperature (°C)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>No</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Water</td>
<td>K$_2$CO$_3$</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>K$_2$CO$_3$</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Acetonitrile</td>
<td>K$_2$CO$_3$</td>
<td>80</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>K$_2$CO$_3$</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Water</td>
<td>K$_2$CO$_3$</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>Water</td>
<td>K$_2$CO$_3$</td>
<td>110</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>Water</td>
<td>Cs$_2$CO$_3$</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>Water</td>
<td>Na$_2$CO$_3$</td>
<td>100</td>
<td>63</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 4-bromoacetophenone (1 mmol), phenyl boronic acid (1.2 mmol), base (1.2 eq), Co@GO/Fe$_3$O$_4$/L-dopa (0.1 g), solvent (5 mL) at different temperature.

$^b$Isolated yield.

Further, amount of the catalyst necessary to carry out the reaction efficiently was also optimized. In order to attain maximum conversion, cross-coupling reaction between 4-bromoacetophenone and phenyl boronic acid was carried out in the presence of K$_2$CO$_3$ as base and water as solvent at 100°C under different catalyst loadings (Table 2). It was found that almost same yield of the product was obtained when 0.05 g (1.84 mol% Co) and 0.1 g (3.69 mol% Co) of the catalyst was used (entry 2, Table 2). Thus, 0.05 g (1.84 mol% Co) was selected as the optimum amount of the catalyst.
Table 2. Effect of catalyst loading on the Suzuki cross-coupling reaction between 4-bromoacetophenone and phenyl boronic acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst in gram (mol% Co)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.025 (0.92)</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>0.05 (1.84)</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>0.1 (3.69)</td>
<td>81</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 4-bromoacetophenone (1 mmol), phenyl boronic acid (1.2 mmol), $\text{K}_2\text{CO}_3$ (1.2 eq), water (5 mL) at 100 °C.

$^b$Isolated yield.

The scope of the catalytic system was explored for the cross-coupling reaction between phenyl boronic acid and diversely substituted aryl halides using the above optimized reaction conditions and the results are summarized in the Table 3. The results showed that Suzuki cross-coupling reaction worked smoothly and the desired substituted biaryl compounds were formed in good to excellent yields. It has been observed that presence of electron-withdrawing group on aryl halides enhanced conversion to biaryls as compared to unsubstituted aryl halides, whereas presence of electron-donating group brought about lesser conversion as compared to unsubstituted aryl halides. It is pertinent to mention that both bromo as well as chloro substituted aryl halides reacted smoothly with phenyl boronic acid in the presence of developed catalytic system. Further, bromo substituted aryl halides showed somewhat better yields as compared to their chloro substituted counterparts owing to their better leaving nature. Amino- and hydroxyl group substituted bromobenzenes also gave desired products in satisfactory yields. It has been observed that when the same coupling was tested with the dibromo benzene, double substituted product was obtained. But in case of bromochloro benzene, inspite of double substitution, monosubstitution of bromo group by phenyl group take place, leaving the chloro group intact. Thus, the catalyst showed selectivity in case of different halo substituted benzenes.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Br-Br" /></td>
<td><img src="image2" alt="Product1" /></td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image3" alt="Cl-Cl" /></td>
<td><img src="image4" alt="Product2" /></td>
<td>7.25</td>
<td>62</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image5" alt="H3C-C-Br" /></td>
<td><img src="image6" alt="Product3" /></td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image7" alt="H3C-C-Cl" /></td>
<td><img src="image8" alt="Product4" /></td>
<td>5.5</td>
<td>72</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image9" alt="NC-Br" /></td>
<td><img src="image10" alt="Product5" /></td>
<td>4.5</td>
<td>82(^c)</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image11" alt="NC-Cl" /></td>
<td><img src="image12" alt="Product6" /></td>
<td>4</td>
<td>79(^c)</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image13" alt="NC-Cl" /></td>
<td><img src="image14" alt="Product7" /></td>
<td>5</td>
<td>70(^c)</td>
</tr>
<tr>
<td>8.</td>
<td><img src="image15" alt="Ph-Br" /></td>
<td><img src="image16" alt="Product8" /></td>
<td>4.25</td>
<td>74</td>
</tr>
<tr>
<td>9.</td>
<td><img src="image17" alt="Ph-Cl" /></td>
<td><img src="image18" alt="Product9" /></td>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>10.</td>
<td><img src="image19" alt="HO-Br" /></td>
<td><img src="image20" alt="Product10" /></td>
<td>8</td>
<td>66</td>
</tr>
</tbody>
</table>
11. \[ \text{H}_2\text{N} - \text{Br} \quad \text{H}_2\text{N} - \text{Br} \]
\[ \text{7} \quad 65^\circ \]

12. \[ \text{Br} - \text{Br} \quad \text{Br} - \text{Br} \]
\[ \text{5} \quad 70 \]

13. \[ \text{Br} \quad \text{Br} \]
\[ \text{6.5} \quad 69^\circ \]

14. \[ \text{Cl} \quad \text{Br} \quad \text{Cl} \]
\[ \text{6} \quad 70^\circ \]

\[ ^a\text{Reaction conditions: aryl halides (1 mmol), phenyl boronic acid (1.2 mmol), K}_2\text{CO}_3 (1.2 eq), \text{water (5 mL), Co@GO/Fe}_3\text{O}_4/L\text{-dopa (0.05 g, 1.84 mol\% Co) at 100 °C.} \]

\[ ^b\text{Isolated yield.} \]

\[ ^c\text{Column chromatography yield.} \]

**Recyclability**

Recyclability of the synthesized catalyst was tested for the Suzuki cross-coupling reaction using 4-bromoacetophenone and phenyl boronic acid as substrates (**entry 3, Table 3**). After completion of the reaction, the catalyst was separated via magnet, washed with deionized water (3 × 10 mL), chloroform (3 × 10 mL) and dried under vacuum. Then a fresh reaction was tested with the used catalyst. The amount of the substrates taken for next run was adjusted according to the amount of catalyst recovered from the previous run. No significant decrease in the catalytic activity of the catalyst was observed up to five runs (**Fig. 2**), and hence the catalyst could be used at least five times without any significant change in activity.
Fig. 2 Recyclability of Co@GO/Fe₃O₄/L-dopa. Reaction conditions: 4-bromoacetophenone (1 mmol), phenyl boronic acid (1.2 mmol), K₂CO₃ (1.2 eq), water (5 mL) and Co@GO/Fe₃O₄/L-dopa (0.05g, 1.84 mol% Co) at 100 °C.

Proposed mechanism

The plausible mechanism for the Co@GO/Fe₃O₄/L-dopa catalyzed Suzuki cross-coupling involves oxidative addition followed by transmetallation and reductive elimination. The coupling process initiated with the oxidative addition of aryl halide to the Co(0) species to give intermediate I, which is prone to react with nucleophiles. This step is followed by transmetallation and reductive elimination leading to the formation of corresponding biaryl (III) and the catalyst is regenerated (Fig. 3).
Fig. 3 Proposed mechanism for the Suzuki cross-coupling using Co@GO/Fe₃O₄/L-dopa.

Conclusion

An inexpensive and water dispersible catalytic system, Co@GO/Fe₃O₄/L-dopa has been successfully developed. Here, graphene oxide has provided large surface area and over which magnetic nanoparticles were coated to further enhance the catalytic efficiency, and also for the easy separation of catalyst from the reaction mixture. Further, L-dopa, an excellent interparticle linker has been used to immobilize Co(0) nanoparticles on Fe₃O₄ grafted graphene oxide, and thereby helps in preventing their leaching. The synthesized catalyst has showed excellent catalytic activity for Suzuki cross-coupling reaction and afforded products in satisfactory to good yields. In the reported method, both bromo as well as chloro substituted aryl halides reacted smoothly with the phenyl boronic acid to give desired products. It has been observed that even the presence of amino and hydroxyl groups in aryl halides were fairly tolerated in the proposed method. To the best of our knowledge, this is the first kind of report for Suzuki cross-coupling reaction catalyzed by heterogeneous cobalt nanoparticles.
Experimental

General procedure for the Co@GO/Fe₃O₄/L-dopa catalyzed Suzuki cross-coupling reaction

To a mixture of aryl halide (1 mmol), phenyl boronic acid (1.2 mmol), K₂CO₃ (1.2 eq.), and Co@GO/Fe₃O₄/L-dopa (0.05 g, 1.84 mol% Co) in a round bottom flask (25 mL), double distilled water (5 mL) was added, and the reaction mixture was stirred at 100 °C for an appropriate time (monitored by TLC) (Table 3). After completion of the reaction, the reaction mixture was cooled to room temperature, the catalyst was separated via magnet and washed with EtOAc (3 × 5 mL) followed by double distilled water (3 × 10 mL). It was dried under vacuum for 1 h and could be used in the subsequent reactions. The aqueous layer was diluted with ethyl acetate (15 mL), washed with brine solution (3 × 15 mL) and dried over anhydrous Na₂SO₄. Finally, the product was obtained after removal of the solvent under reduced pressure followed by crystallization from a suitable solvent or passing through column of silica gel and elution with EtOAc-pet. ether (2:98).

The structures of the products were confirmed by ¹H, ¹³C NMR, mass spectral data and comparison with authentic samples obtained commercially or prepared according to the literature methods.
Spectral data of the compounds listed in Table 3

Biphenyl (entry 1)

White solid, M.pt. 69-70 °C (Lit. M.pt. 70-72 °C)\(^{39}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.35-7.37 (t, 2H, J=4 Hz, H\(_{arom}\)), 7.46-7.49 (t, 4H, J=8 Hz, H\(_{arom}\)), 7.62-7.64 (d, 4H, \(J = 8\) Hz, H\(_{arom}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 140.41, 128.92, 128.33, 127.29; ESI-MS: 154 (M\(^+\)).

4-Acetylbiphenyl (entry 3,4)

White solid, M.pt. 115-116 °C (Lit. M.pt. 115-117 °C)\(^{39}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.67 (s, 3H, -COCH\(_3\)), 7.41-7.44 (m, 1H, H\(_{arom}\)), 7.48-7.52 (t, 2H, \(J = 8\) Hz, H\(_{arom}\)), 7.65-7.66 (d, 2H, \(J = 4\) Hz, H\(_{arom}\)), 7.70-7.72 (d, 2H, \(J = 8\) Hz, H\(_{arom}\)), 8.05-8.07 (d, 2H, \(J = 8\) Hz, H\(_{arom}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 26.80, 127.28, 128.24, 128.92, 135.87, 139.89, 145.81, 197.93; ESI-MS: 197 (M+1).

4-Phenylbenzonitrile (entry 5)

White solid, M.pt. 85-86 °C (Lit. M.pt. 85-87 °C)\(^{40}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.44-7.53 (m, 3H, H\(_{arom}\)), 7.61-7.63 (d, 2H, \(J = 8\) Hz, H\(_{arom}\)), 7.70-7.76 (m, 4H, H\(_{arom}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 111.4, 118.89, 127.25, 127.76, 128.69, 129.14, 132.63, 139.18, 145.69; ESI-MS: 179 (M\(^+\)).
Biphenyl-4-carboxaldehyde (entry 6,7)

White solid, M.pt. 56-58 °C (Lit. M.pt. 58-60 °C)\(^{40}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.44-7.47 (t, 1H, J = 8 Hz, H\(_{\text{arom}}\)), 7.51-7.55 (t, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.69-7.71 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.72-7.74 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.97-7.99 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 9.93 (s, 1H, -CHO); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 127.2, 128.1, 128.9, 131.2, 138.5, 140.4, 143.5, 191.9; ESI-MS: 182 (M\(^+\)).

Phenyl-4-biphenyl ketone (entry 8,9)

White solid, M.pt. 97-99 °C (Lit. M.pt. 99-101 °C)\(^{41}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.42-7.46 (m, 1H, H\(_{\text{arom}}\)), 7.50-7.55 (m, 4H, H\(_{\text{arom}}\)), 7.62-7.65 (m, 1H, H\(_{\text{arom}}\)), 7.67-7.69 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.73-7.75 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.86-7.88 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.92-7.94 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 127.29, 128.25, 128.59, 128.93, 131.92, 137.92, 139.89, 137.4, 140.41, 196.29; ESI-MS: 259 (M\(^+\)), 257 (M-1).

4-Phenylphenol (entry 10)

White solid, M.pt. 162-163 °C (Lit. M.pt. 165-166 °C)\(^{20}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 4.93 (s, 1H, OH), 6.93-6.95 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.33-7.35 (m, 1H, J = 8 Hz, H\(_{\text{arom}}\)), 7.42-7.46 (t, 2H, J=8 Hz, H\(_{\text{arom}}\)), 7.50-7.52 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.56-7.58 (d, 2H, J =
8 Hz, H\textsubscript{arom}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 116.4, 127.7, 127.9, 128.3, 129.1, 129.3, 136.5, 157.4; ESI-MS: 170 (M\textsuperscript{+}).

4-Aminobiphenyl (entry 11)

Yellow solid, M.p. 51-52 °C (Lit. M.p. 52-53 °C)\textsuperscript{20}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 4.95 (bs, 2H, NH\textsubscript{2}, exchangeable with D\textsubscript{2}O), 6.80-6.82 (d, 2H, J = 8 Hz, H\textsubscript{arom}), 7.46-7.49 (m, 3H, H\textsubscript{arom}), 7.64-7.72 (m, 4H, H\textsubscript{arom}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 116.86, 126.57, 127.96, 128.58, 128.72, 136.59, 147.25; ESI-MS: 169 (M\textsuperscript{+}).

4-(Phenyl) biphenyl (entry 12)

White solid, M.p. 210-212 °C (Lit. M.p. 212-213 °C)\textsuperscript{20}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.43-7.49 (m, 4H, H\textsubscript{arom}), 7.60-7.62 (m, 2H, H\textsubscript{arom}), 7.71-7.73 (d, 4H, J = 8 Hz, H\textsubscript{arom}), 8.01-8.03 (d, 4H, J = 8 Hz, H\textsubscript{arom}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 122.12, 126.18, 126.39, 126.80, 128.98, 135.62, 140.20, 141.08; ESI-MS: 230 (M\textsuperscript{+}).

1-Phenyl naphthalene (entry 13)

Yellow liquid\textsuperscript{42}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.39-7.64 (m, 4H, H\textsubscript{arom}), 7.62-7.71 (m, 5H, H\textsubscript{arom}), 7.84-7.86 (d, 1H, J = 8 Hz, H\textsubscript{arom}), 7.89-8.11 (d, 1H, J = 8 Hz, H\textsubscript{arom}), 8.14-8.16 (d, 1H, J = 8 Hz, H\textsubscript{arom}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 125.4, 125.9, 126.6,
127.2, 127.5, 127.9, 128.2, 128.5, 129.3, 130.3, 131.9, 134.0, 140.5, 141.0; **ESI-MS**: 204 (M⁺).

3-Chlorobiphenyl (entry 14)

![Chemical structure of 3-Chlorobiphenyl](image)

Colourless liquid⁴³. **H NMR (400 MHz, CDCl₃)**: δ 7.37-7.46 (m, 3H, H\textsubscript{arom}), 7.49-7.53 (m, 3H, H\textsubscript{arom}), 7.61-7.66 (m, 3H, H\textsubscript{arom}); **C NMR (100 MHz, CDCl₃)**: δ 125.78, 127.05, 127.27, 127.53, 128.53, 128.91, 129.20, 135.04, 140.19, 141.70; **ESI-MS**: 189 (M), 191 (M+2).
REFERENCES


201-202

185-200,203-211
Co@GO/Fe₃O₄/L-dopa catalyzed selective C-H bond oxidation of aryl alkanes and secondary alcohols to corresponding carbonyl compounds in an aqueous medium

The synthesis of diversified aldehydes and ketones have become a key reaction in organic syntheses, as these are important synthetic intermediates, especially for the manufacture of carbon-skeletons and preparation of numerous drugs, vitamins and fragrances. Over the past few decades, various methods and reagents have been reported in the literature for the catalytic oxidation of C-H bond of hydrocarbons and secondary alcohols. But the selective oxidation of benzylic C-H bond into the corresponding carbonyl compound is considered as one of the most significant and challenging transformations in the chemical industry. Thus, development of newer methodologies for the preparation of valuable products such as aldehydes and ketones from hydrocarbons, and secondary alcohols under mild conditions is currently gaining much attention. Usually, catalytic oxidation of hydrocarbons is quite complicated, due to the lack of reactivity of hydrocarbons. However, the conversion of arylalkanes into the corresponding carbonyl compounds has been achieved smoothly by the combining effect of catalytic amounts of transition-metal catalysts and peroxide under mild reaction conditions.

Earlier approaches for the C-H bond oxidation of arylalkanes and secondary alcohols

Catalytic oxidation of benzylic C-H bond of hydrocarbons and secondary alcohols is one of the fundamental transformations in organic syntheses and has a wide applications in the production of agrochemicals and medicines. Further, transition metal catalyzed oxidation reactions are particularly attractive, owing to their environmentally benign and economic nature. Several procedures have been reported in the literature employing transition metals (Ru, Co, Cu, Pt, and Rh) as catalysts for the oxidation reactions.

Blackburn et al. have reported the first example of PdCl₂ catalyzed oxidation of secondary alcohols to corresponding ketones using molecular O₂ as an oxidant at room temperature. After that, various efforts have been made to develop a synthetically valuable methods for Pd-catalyzed oxidations.
Nishimura et al.\textsuperscript{19} have reported Pd(OAc)$_2$/pyridine/MS 3\textsuperscript{o}A catalyzed aerobic oxidation of a variety of primary and secondary alcohols in toluene into the corresponding aldehydes and ketones, and obtained products in high yields. Besides, different substituents and protecting groups were found to be compatible with the reported method (Scheme 2).

Scheme 1

\[
\begin{array}{c}
\text{OH} \\
R_1R_2
\end{array}
\begin{array}{c}
+ \frac{1}{2}O_2 \\
\text{PdCl}_2\text{-NaOAc}
\end{array}
\begin{array}{c}
\text{88 °C}
\end{array}
\begin{array}{c}
\text{O} \\
R_1R_2
\end{array}
\begin{array}{c}
+ \\
\text{H}_2\text{O}
\end{array}
\]

CAN/[Ru(tpa)(H$_2$O)$_2$]$^+$ catalyzed benzylic oxidation of arylalkanes in aqueous medium has been reported by Fukuzumi et al.\textsuperscript{20} (Scheme 3).

Scheme 2

\[
\begin{array}{c}
\text{OH} \\
R_1R_2
\end{array}
\begin{array}{c}
\text{Pd(OAc)}_2 (5 \text{ mol}%) \\
\text{base, MS 3 °A, toluene}
\end{array}
\begin{array}{c}
\text{80 °C, O}_2
\end{array}
\begin{array}{c}
\text{O} \\
R_1R_2
\end{array}
\]

Bismuth and picolinic acid were also used as efficient catalysts for the oxidation of alkyl arenes with tert-butyl hydroperoxide in the presence of pyridine by Bonvin et al.\textsuperscript{21}

Co(OAc)$_2$ catalyzed benzylic oxidation of alkyl arenes to corresponding carbonyl compounds in the presence of NaClO/TEMPO was reported successfully by Jin and co-workers\textsuperscript{22} (Scheme 4).

Scheme 4
Ang and his colleagues have developed an efficient copper catalyzed method for the oxidation of benzylic and allylic sp³ C-H compounds using recyclable fluorous ligand and aqueous t-butyldydroperoxide as an oxidant in water (Scheme 5).²³

Scheme 5

Copper (II) phthalocyanine complex was also utilized to catalyze oxidation of alcohols to the corresponding carbonyl compounds in the presence of tetra-n-butyl-ammonium-peroxo-monosulfate (n-Bu₄NHSO₅) as an oxidant under aqueous conditions. Moreover, this catalytic approach does not require any surfactant, organic co-solvents and co-catalysts. Furthermore, the by-product (TBAHSO₄) and catalyst were resourcefully recovered and reused numerous times without any significant lose of catalytic activity²⁴.

Although literature is full of transition metal catalyzed oxidation reactions under homogeneous conditions, yet there were also reports of oxidation reactions carried out in the absence of transition metals, which afforded desired products in good yields. Following are some of the methods reported for the oxidation of hydrocarbons and secondary alcohols to corresponding carbonyl compounds in transition metal-free conditions.

Jain et al.²⁵ have reported selective oxidation of secondary alcohols to corresponding ketones using HBr/H₂O₂ under solvent-free conditions, and obtained products in excellent yields.

An efficient metal-free method for the mild oxidation of primary, secondary, allylic and benzylic alcohols into their corresponding aldehydes and ketones using dimethyl sulfoxide/tosyl chloride was reported by Saadati et al.²⁶

Dip et al.²⁷ have reported trichloroisocyanuric acid catalyzed rapid and selective method for the oxidation of secondary alcohols to corresponding ketones in the presence of pyridine at room temperature.
Khazaei et al. have developed a new protocol for the preparation of aromatic ketones via oxidation of secondary alcohols, and benzhydrol and its derivatives using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as homogenous N-halo reagents under solvent-free conditions. The high yield, high efficiency, short reaction time, simplicity, cleaner reaction profile and cost-effectiveness were the key advantages of this protocol. However, this method was not suitable for oxidation of primary or secondary aliphatic and benzyl alcohols because of low yield and presence of large amount of unreacted starting materials.28

Very few reports of transition metal-free oxidation reactions of hydrocarbons and secondary alcohols were known. After literature survey, it has been found that transition metals represented a best alternative for catalyzing oxidation reactions owing to their high efficiency, environmentally benign nature and non-toxicity. Usually, benzylic C-H bond and secondary alcohol oxidation reactions have been reported by homogeneous transition metals and hence recyclability of these expensive catalysts became one of the most challenging tasks in synthetic organic chemistry. Due to the increasing environmental concerns, several efforts have been made to develop environmentally friendly heterogeneously catalyzed protocols for the oxidation of hydrocarbons and secondary alcohols. Recently, the combining effect of heterogeneous noble transition metal catalysts with environment friendly oxidants, such as hydrogen peroxide, oxygen or tert-butyl hydroperoxide (TBHP) appeared as best alternative to their homogenous counterparts14,15. We are here undergoing few methods reported in the literature for the oxidation of hydrocarbons and secondary alcohols under heterogeneous catalysis conditions.

Albadi et al. have proposed a novel and efficient method for the aerobic oxidation of alcohols using ZnO-supported copper oxide nanocatalyst in the presence of oxygen as the oxidant. The diversely functionalized carbonyl compounds were obtained in good to excellent yields from corresponding primary and secondary alcohols.29

Hazra et al. have reported a simple and efficient protocol for the synthesis of a series of four selective copper (II) catalysts for the oxidation of alcohols. Reaction between Cu(II) salts with new sulfonated Schiff base 2-[(2-hydroxy-3-methoxyphenyl)methylidene
amino]benzenesulfonic acid (1) in the presence of n-heterocycle [pyridine or 2,2’-bipyridine] results in the formation of two mononuclear copper complexes [CuL(H₂O)₂] (2) and [CuL(2,2’-bipy)].DMF.H₂O (3) and two the diphenoxo-bridged dicopper complexes [CuL(py)]₂ (4) and [CuL(EtOH)]₂.2H₂O (5). Out of the series of four copper complexes, diphenoxo-bridged dicopper complexes (4, 5) showed fastest and most proficient copper catalyzed MW-assisted, solvent and additive-free oxidation of secondary alcohols (Scheme 6).³⁰

Scheme 6

Liu et al. have reported a very efficient and novel heterogeneous catalyst, Au/Cr-HT for the aerobic oxidation of alcohols under soluble-base-free conditions. Here, the amalgamation of gold nanoparticles (AuNPs) with chromium-substituted hydrotalcite (Cr-HT) was responsible for the increased efficiency of the catalyst. Moreover, it has been reported that on increasing chromium content of support, the Au-support synergy increases and decreases the size of Au nanoparticles.³¹

Au-Pd bimetal catalysts supported on layered double hydroxide (LDHs) have been developed by Shi et al. The reported bimetallic catalyst showed much higher catalytic efficiency than monometallic catalyst for the oxidation of alcohols in water. Moreover, non-activated aliphatic primary alcohols were also oxidized quantitatively into the corresponding acids (Scheme 7).³²

Scheme 7

Gogoi et al. have developed a novel and greener catalyst, Cu(II) complex grafted onto nanosilica, obtained from rice husk (RH). Here, imines were used as linkers for the
immobilization of Cu(II) complex on nanosilica, which was generated via Schiff-base condensation between 3-aminopropyltriethoxysilane (APTES) functionalized nanosilica and acetamide. The reported catalyst displayed excellent catalytic activity for the controlled oxidation of different primary and secondary alcohols in the presence of t-butyl hydrogen peroxide (TBHP) (Scheme 8).\(^ {33}\)

**Scheme 8**

\[
\begin{align*}
\text{OH} & \quad \text{Cu@imine-SiO}_2 \\
R_1R_2 & \quad \text{CH}_3\text{CN, TBHP, 50 °C} \\
& \quad \rightarrow \quad \text{O} \\
R_1R_2 & \\
\end{align*}
\]

Ceria nanoparticles have been used as efficient catalyst for the oxidation of benzylic C-H bonds by Akhlaghinia and co-worker\(^ {34}\) (Scheme 9). The reported ceria nanoparticles possess several advantages such as high reaction rate, selectivity, recyclability and excellent yield of the products.

**Scheme 9**

\[
\begin{align*}
\text{R} & \quad \text{CeO}_2\text{ NPs, KBrO}_3 \\
\text{H}_2\text{O, 1,4-dioxane, AcOH} & \quad \text{R} \\
& \quad \rightarrow \quad \text{95 °C} \\
\end{align*}
\]

Chen *et al.* have reported a new approach for the selective oxidation of alkyl aromatics using magnetic copper based schiffs base complex\(^ {35}\). The synthesized catalyst appeared as highly efficient and recyclable nanocatalyst and afforded products in good to excellent yields. Moreover, it can be reused for atleast eight times without any significant loss of activity.
Polymeric species \([\text{Cd(im)}_3(\mu,\eta\text{-HL-1kOO’:2kO”O”})]_n\) was employed as an efficient catalyst for the oxidation of alcohols (1-phenylethanol and cyclohexanol) to the corresponding ketones under microwave irradiation by Jlassi et al. (Scheme 10).\(^{36}\)

**Scheme 10**

\[
\begin{array}{cccc}
\text{Me} & \text{H} & \text{OH} & \text{O} \\
\text{Me} & \text{H} & \text{OH} & \text{O} \\
\end{array}
\]

\[\text{[Cd(im)}_3(\mu\text{-HL-1kOO’:2kO”O”})]_n\text{ (15 mmol)} \rightarrow \text{TBHP, MW (25 W), 80 °C} \rightarrow \text{Me} \]

Palladium nanoparticles immobilized on silica gel/polydopamine composite (SiO\(_2\)/PDA) have showed high catalytic efficiency for the aerobic oxidation of primary and secondary alcohols to their corresponding carbonyl compounds. Moreover, recyclability of SiO\(_2\)/PDA/Pd NPs showed no detectable activity loss upto seven runs (Scheme 11).\(^{37}\)

**Scheme 11**

\[
\begin{array}{cccc}
\text{R}_1 \text{R}_2 & \text{OH} & \text{O} & \text{R}_1 \text{R}_2 \\
\text{R}_1 \text{R}_2 & \text{OH} & \text{O} & \text{R}_1 \text{R}_2 \\
\end{array}
\]

\[\text{SiO}_2\text{/PDA/Pd NPs (0.5 mol%)} \rightarrow \text{O}_2, \text{K}_2\text{CO}_3, 80 °C, 12 h \rightarrow \text{O} \]

Literature survey revealed that most extensively used methodologies for the oxidation of alcohols and hydrocarbons are the transition metal catalyzed reactions. Various catalysts such as Pd, Ru, Cu and Au, were reported to catalyze the oxidation reactions under mild reaction conditions. Moreover, use of magnetic nanoparticles as a support for carrying out oxidation reactions has also gained impetus due to their high catalytic activity, and high surface area. Inspite of this, only handful reports of C-H bond oxidation reactions catalyzed by heterogeneous magnetic metal catalysts are known. Thus, development of novel and efficient magnetically separable metal catalysts to carry out oxidation reactions smoothly became the one of the main objective in synthetic chemistry. Herein we report the catalytic efficiency of novel and efficient magnetic catalytic system, Co@GO/Fe\(_3\)O\(_4\)/L-dopa for the oxidation of C-H bond hydrocarbons and secondary alcohols to corresponding carbonyl compounds using mild reaction conditions (Scheme 12).
Results and discussion

Optimization of the reaction conditions

Various experiments were performed to assess the efficiency and the scope of the Co@GO/Fe₃O₄/L-dopa for the oxidation of hydrocarbons and secondary alcohols. The oxidation of anthrone was selected as the model reaction to evaluate catalytic efficiency of different catalysts and their amount for the preparation of corresponding carbonyl compound in the presence of TBHP as an oxidant at 80 ºC under aqueous conditions. The consequent results are presented in Table 1. As clearly depicted from Table 1, the oxidation of anthrone was carried out efficiently by Co@GO/Fe₃O₄/L-dopa (0.05 g) within 0.5 h and the corresponding product was obtained in excellent yield (80%).

Table 1. Optimization of the different catalytic systems for the benzylic C-H bond oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount (g)</th>
<th>Time (h)</th>
<th>Yield b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>Traces</td>
</tr>
<tr>
<td>2.</td>
<td>GO</td>
<td>0.1</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>3.</td>
<td>Fe₃O₄</td>
<td>0.1</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>4.</td>
<td>GO/Fe₃O₄</td>
<td>0.1</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>5.</td>
<td>Co@GO/Fe₃O₄/L-dopa</td>
<td>0.1</td>
<td>0.5</td>
<td>82</td>
</tr>
<tr>
<td>6.</td>
<td><strong>Co@GO/Fe₃O₄/L-dopa</strong></td>
<td><strong>0.05</strong></td>
<td><strong>0.5</strong></td>
<td><strong>80</strong></td>
</tr>
<tr>
<td>7.</td>
<td>Co@GO/Fe₃O₄/L-dopa</td>
<td>0.025</td>
<td>0.5</td>
<td>70</td>
</tr>
</tbody>
</table>

aReaction conditions: anthrone (1 mmol), TBHP (1.2 mmol), catalyst (0.1 g), water (5 mL) at 80 ºC.

bIsolated Yields.
Further, the model reaction was tested under diverse set of conditions in order to optimize the reaction conditions with respect to solvents, oxidants and temperatures. The results are presented in Table 2. Initially, the effect of different solvents such as CH$_2$Cl$_2$, CH$_3$CN, EtOH and H$_2$O on the oxidation of anthrone was tested under similar conditions using oxidant (TBHP) and temperature (80 °C). As depicted from Table 2, the poorest yields were obtained in case of CH$_2$Cl$_2$, CH$_3$CN and EtOH (entries 1-3, Table 2), while quite satisfactory yield was obtained with H$_2$O (entry 4, Table 2). Subsequently, the effect of various oxidants i.e., O$_2$, H$_2$O$_2$ and TBHP on oxidation of anthrone was also investigated and the results revealed that TBHP possess better efficiency as an oxidant (entries 4-6, Table 2). Effect of elevated temperature on model reaction was also studied and it was observed that best yield of corresponding product was obtained at 100 °C. Further, it was observed that increase in temperature lead to the decrease in selectivity of the product formation (entry 8, Table 2). Thus, best possible reaction conditions for the oxidation reaction are TBHP as an oxidant, water as solvent and 100 °C as the optimized reaction temperature.

Table 2. Optimization of different solvents, oxidants and reaction temperatures for benzylic C-H bond oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Oxidant</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>TBHP</td>
<td>80</td>
<td>1.5</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$CN</td>
<td>TBHP</td>
<td>80</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>TBHP</td>
<td>80</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$O</td>
<td>TBHP</td>
<td>80</td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>H$_2$O</td>
<td>O$_2$</td>
<td>80</td>
<td>0.5</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>H$_2$O</td>
<td>H$_2$O$_2$</td>
<td>80</td>
<td>0.5</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>H$_2$O</td>
<td>TBHP</td>
<td>100</td>
<td>0.5</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>H$_2$O</td>
<td>TBHP</td>
<td>120</td>
<td>0.5</td>
<td>89</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: anthrone (1 mmol), oxidant (1.2 mmol), catalyst (0.05 g, 1.84 mol% Co) and solvent (5 mL).

$^b$Isolated yields.
Impressed from above results, a series of different hydrocarbons were also scanned for oxidation to corresponding carbonyl compound using above optimized reaction conditions. As shown in Table 3, the oxidation of several benzylic C-H substrates to the corresponding products using Co@GO/Fe₃O₄/L-dopa proceeded smoothly with good to excellent yields. It is noteworthy to mention that even the unreactive hydrocarbons such as ethyl benzene, p-xylene etc. were also successfully oxidized to corresponding carbonyl compounds in the presence of Co@GO/Fe₃O₄/L-dopa (entries 4, 5, Table 3). In case of p-xylene, both methyl groups were oxidized to aldehydic groups leading to the formation of p-terephthaldehyde as the major product (entry 5, Table 3). Moreover, fluorene and diphenylmethane were also efficiently converted into corresponding ketone derivatives in good to excellent yields.

Further, the activity of the synthesized catalyst was also examined for the oxidation of secondary alcohols to corresponding ketone derivatives. It has been observed experimentally that diversely substituted secondary alcohols were successfully oxidized to corresponding ketones (entries 9-15, Table 3) and afforded products in good to excellent yields. These results showed that Co@GO/Fe₃O₄/L-dopa can facilitate the selective oxidation of hydrocarbons and secondary alcohols; serve as highly efficient catalytic system to carry out the oxidation reactions.

Table 3. Oxidation of hydrocarbons and secondary alcohols using Co@GO/Fe₃O₄/L-dopa as catalyst and TBHP as oxidizing agent under aqueous medium at 100 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate" /></td>
<td><img src="image2.png" alt="Product" /></td>
<td>0.5</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate" /></td>
<td><img src="image4.png" alt="Product" /></td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>11</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>4.25</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>86</td>
</tr>
<tr>
<td>13</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>14</td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>2.5</td>
<td>87</td>
</tr>
<tr>
<td>15</td>
<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>3</td>
<td>86c</td>
</tr>
</tbody>
</table>

^a Reaction conditions: hydrocarbon or secondary alcohol (1 mmol), TBHP (1.2 eq, 0.10 mL), water (5 mL), Co@GO/Fe3O4/L-dopa (0.05 g, 1.84 mol% Co) at 100 °C.

^b Isolated yield.

^c Column chromatography yield.

**Recyclability**

Recyclability of the synthesized catalyst was tested for the oxidation of anthrone using TBHP as an oxidant (entry 1, Table 3). After completion of the reaction, the catalyst was separated via magnet, washed with deionized water (3 × 10 mL), chloroform (3 × 10 mL) and dried under vacuum. Then a fresh reaction was tested with the used catalyst. Amount of the substrates taken for next run was calculated according to the amount of catalyst recovered from the previous run. No significant decrease in the catalytic activity of the catalyst was observed up to five runs (Fig. 1). Thus, it is concluded that the catalyst could be used at least five times without any change in activity.
Fig. 1 Recyclability of Co@GO/Fe₃O₄/L-dopa. Reaction conditions: anthrone (1 mmol), TBHP (1.2 mmol, 0.10 mL), Co@GO/Fe₃O₄/L-dopa (0.05 g, 1.84 mol% Co) and H₂O (5 mL) at 100 °C.

Proposed mechanism

To confirm whether the selective oxidation of hydrocarbons involves a radical mechanism or not, a radical-trapping agent, TEMPO was used. The reaction in case of entry 4, Table 3 has been carried out until the conversion was 50% (45 min), TEMPO (1 mmol) was added and the reaction was allowed to proceed further for 2 h. No significant further conversion was observed, which shows that the selective oxidation of hydrocarbons most likely occurred via radical mechanism (Scheme 13)³⁸.

Scheme 13

A plausible reaction mechanism for the Co@GO/Fe₃O₄/L-dopa catalyzed C-H bond oxidation has been proposed (Fig. 2). Initially, Co(0) on reaction with TBHP form
intermediate (I) and the first type of radical $t$-BuȮ. Intermediate (I) on further reaction with TBHP give tert-butyl peroxide cobalt (II) complex (II). Consequently, $t$-BuȮ reacts with TBHP to generate another radical $t$-BuOOȮ. After that, benzyl radical is produced by the reaction of $t$-BuOOȮ with toluene. The tert-butyl peroxide cobalt(II) complex (II) then reacts with benzyl radical to form the desired product (III) and Co(0) is regenerated back.

**Fig. 2** Proposed mechanism for the Co@GO/Fe₃O₄/L-dopa catalyzed selective oxidation of hydrocarbons.

**Conclusion**

The synthesized catalyst, Co@GO/Fe₃O₄/L-dopa showed excellent catalytic activity for selective oxidation of hydrocarbons and secondary alcohols to the corresponding carbonyl compounds. In the proposed methodology, even the unreactive hydrocarbons such as ethyl benzene, p-xylene etc. were also successfully oxidized to corresponding carbonyl compounds. The products were obtained in good to excellent yields. Moreover, the catalyst is magnetic in nature, can be easily separated from reaction mixture, thus avoids the tedious workup procedure. It is also recyclable upto five runs.
Experimental

General procedure for the Co@GO/Fe₃O₄/L-dopa catalyzed benzylic C-H bond oxidations

To a mixture of hydrocarbon or secondary alcohol (1 mmol), Co@GO/Fe₃O₄/L-dopa (0.05 g, 1.84 mol% Co) and 70% t-BuOOH (0.25 mL, 1.5 mmol) in a round bottom flask (25 mL), water (5 mL) was added, and the reaction mixture was stirred at 100 °C for the appropriate time (Table 3). After completion of the reaction (monitored by TLC), the catalyst was separated using an external magnet and the reaction mixture was diluted with ethyl acetate (3 × 5 mL). The organic layer was washed with water (3 × 25 mL) and dried over anhyd. Na₂SO₄. Finally, the product was obtained after removal of the solvent under reduced pressure followed by crystallization from a suitable solvent or by passing through column of silica gel and elution with EtOAc-pet. ether. The recovered catalyst was washed with EtOAc (3 × 5 mL) followed by double distilled water (3 × 10 mL). It was dried and then reused for the subsequent reaction.

The structures of all the products were confirmed by ¹H, ¹³C NMR, mass spectral data and comparison with authentic samples obtained commercially or prepared according to the literature methods.
Spectral data of the compounds listed in Table 3

**Anthraquinone (entry 1)**

![Anthraquinone structure]

White solid, M.pt. 284-285 °C (Lit. M.pt. 286 °C)\(^{39}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.83-7.85 (m, 4H, H\(_{\text{arom}}\)), 8.34-8.36 (m, 4H, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 127.25, 132.18, 134.15, 139.87, 183.35; \textbf{ESI-MS}: 209 (M+1).

**Fluorenone (entry 2)**

![Fluorenone structure]

White solid, M.pt. 80-81 °C (Lit. M.pt. 80-83 °C)\(^{39}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.29-7.33 (m, 2H, H\(_{\text{arom}}\)), 7.49-7.55 (m, 4H, H\(_{\text{arom}}\)), 7.67-7.69 (d, 2H, \(J = 8\) Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 120.48, 124.55, 129.34, 134.71, 144.57, 194.15; \textbf{ESI-MS}: 181 (M+1).

**Benzophenone (entry 3, 13)**

![Benzophenone structure]

White solid, M.pt. 48-49 °C (Lit. M.pt. 47-51 °C)\(^{39}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.49-7.52 (t, 4H, \(J = 6\) Hz, H\(_{\text{arom}}\)), 7.59-7.63 (t, 2H, \(J = 8\) Hz, H\(_{\text{arom}}\)), 7.82-7.84 (d, 4H, \(J = 8\)Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 128.30, 130.08, 132.45, 137.60, 196.79; \textbf{ESI-MS}: 182 (M\(^+\)).
Acetophenone (entry 4, 9)

Yellow Liquid\(^9\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.60 (s, 3H, COCH\(_3\)), 7.44-7.48 (t, 2H, \(J= 8\) Hz, H\(_{\text{arom}}\)), 7.54-7.58 (t, 1H, \(J= 8\) Hz, H\(_{\text{arom}}\)), 7.95-7.97 (d, 2H, \(J= 8\) Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 27.78, 128.44, 132.79, 136.79, 197.44; ESI-MS: 120 (M\(^+\)).

Teraphthalaldehyde (entry 5)

White Solid, M.pt. 113-114 °C (Lit. M.pt. 114-116 °C)\(^9\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.07 (s, 4H, H\(_{\text{arom}}\)), 10.15 (s, 2H, -CHO); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 130.14, 140.0, 191.53; ESI-MS: 134 (M\(^+\)).

4-Chlorobenzaldehyde (entry 6)

Yellow Solid, M.pt. 46-47 °C (Lit. M.pt. 47-49 °C)\(^9\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.52-7.54 (d, 2H, \(J= 8\) Hz, ArH), 7.83-7.85 (d, 2H, \(J= 8\) Hz, ArH), 10.00 (s, 1H, CHO); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 129.6, 130.9, 134.7, 141, 190.9; ESI-MS: 140 (M\(^+\)), 142 (M+2).
4-Nitrobenzaldehyde (entry 7)

Yellow Solid, M.pt. 101-103 °C (Lit. M.pt. 103-106 °C)\(^{39}\).\(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.07-8.09 (d, 2H, J = 8 Hz, H\text{arom}), 8.35-8.37 (d, 2H, J = 8 Hz, H\text{arom}), 9.62 (s, 1H, -CHO); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 123.63, 129.64, 140.94, 152.56, 191.25; ESI-MS: 151 (M\(^+\)).

4-Aminobenzaldehyde (entry 8)

Yellow solid, M.pt. 66-67 °C (Lit. M.pt. 68-70 °C)\(^{39}\).\(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 3.85 (bs, 2H, NH\(_2\), exchangeable with D\(_2\)O), 6.63-6.66 (d, 2H, J = 8 Hz, H\text{arom}), 7.52-7.55 (d, 2H, J = 12 Hz, H\text{arom}), 8.99 (s, 1H, -CHO); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 116.80, 125.95, 130.58, 155.42, 189.74; ESI-MS: 121 (M\(^+\)).

4-Bromoacetophenone (entry 10)

Pale Yellow Solid, M.pt. 107-108 °C (Lit. M.pt. 108-110 °C)\(^{39}\).\(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.61 (s, 3H, CH\(_3\)), 7.61-7.64 (d, 2H, J = 12 Hz, H\text{arom}), 7.83-7.85 (d, 2H, J = 8Hz, H\text{arom}); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 27.7, 126.2, 130.1, 132.0, 136.3, 197.2; ESI-MS: 197 (M\(^+\)), 199 (M+2).
4-Hydroxyacetophenone (entry 11)

White Solid, M.pt. 107-109 °C (Lit. M.pt. 109-110 °C)\(^{39}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.61 (s, 3H, CH\(_3\)), 4.18 (bs, 1H, OH), 6.95-6.98 (m, 2H, H\(_{\text{arom}}\)), 7.92-7.94 (d, 2H, J = 8Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 27.7, 115.8, 129.2, 131.3, 162.0, 197.2; ESI-MS: 136 (M\(^+\)).

4-Methylacetophenone (entry 12)

White Solid, M.pt. 44-45 °C (Lit. M.pt. 45-49 °C)\(^{39}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.34 (s, 3H, CH\(_3\)), 2.51 (s, 3H, CH\(_3\)), 7.18-7.20 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.79-7.81 (d, 2H, J = 8Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 21.1, 27.7, 128.8, 129.2, 135.8, 143.8, 197.2; ESI-MS: 134 (M\(^+\)).

4-Bromobenzophenone (entry 14)

White Solid, M.pt. 80-81 °C (Lit. M.pt. 79-84 °C)\(^{39}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.50-7.53 (t, 2H, J = 8 Hz, H\(_{\text{arom}}\)), 7.61-7.66 (m, 3H, H\(_{\text{arom}}\)), 7.69-7.72 (d, 2H, J = 12 Hz, H\(_{\text{arom}}\)), 7.79-7.81 (d, 2H, J = 8 Hz, H\(_{\text{arom}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 128.2, 128.9, 129.4, 131.2, 131.7, 131.9, 137.9, 138.3, 196.4; ESI-MS: 259 (M\(^+\)), 261 (M+2).
4-Fluorobenzophenone (entry 15)

Pale Yellow Solid, M.pt. 46-47 °C (Lit. M.pt. 47-49 °C)\textsuperscript{39}. \textbf{\textit{1H NMR (CDCl}_3, 400 MHz)}: \(\delta\ 7.10\text{-}7.13\ (t, 2\text{H}, J = 8\text{ Hz}, \text{H}_{\text{arom}}),\ 7.38\text{-}7.41\ (t, 2\text{H}, J = 8\text{ Hz}, \text{H}_{\text{arom}}),\ 7.46\text{-}7.49\ (m, 1\text{H}, J = 8\text{Hz}, \text{H}_{\text{arom}}),\ 7.65\text{-}7.67\ (m, 2\text{H}, \text{H}_{\text{arom}}),\ 7.70\text{-}7.72\ (d, 2\text{H}, J = 8\text{Hz}, \text{H}_{\text{arom}});\ \textbf{\textit{13C NMR (CDCl}_3, 100 MHz)}: \delta\ 114.3, 128.2, 128.9, 131.8, 137.9, 166.1, 164.0, 196.4; \textbf{ESI-MS:} 200 (M\textsuperscript{+}).
REFERENCES


224-225
212-223, 226-235
4.4 Co@GO/Fe₃O₄/L-dopa catalyzed one-pot multi-component synthesis of 5-substituted-1H-tetrazoles under mild reaction conditions

Nowadays, synthesis of N-heterocyclic compounds, which are the integral part of a wide range of synthetic drugs, bioactive natural products and pharmaceuticals, has been receiving considerable attention in the synthetic organic chemistry. Among the different N-heterocycles, tetrazoles have grabbed a lot of attention due to its varied applicability in different fields (Fig. 1). These compounds possess extensive applications as intermediates for pharmaceuticals, photographic industry, catalysis technology, medicinal chemistry, organometallic chemistry and agriculture sector\(^1\)\(^-\)\(^8\). The high physiological activity of tetrazoles, such as lower toxicity and higher lipophilicity makes them as substances of versatile biochemical and pharmaceutical properties\(^9\). A variety of tetrazole based drugs are also known which possess antihypertensive, antibiotic\(^10\), antiallergic and anticonvulsant\(^11\), anticancer, etc.\(^12\),\(^13\) activities.

![Losartan, Antihypertensive, I-Valsartan](Fig. 1 Some examples of biologically active compounds containing tetrazole motif.)

**Earlier approaches for the synthesis of 5-substituted-1H-tetrazoles**

Different preparative methods for the synthesis of tetrazoles have been intensively developed due to their potential utility in synthetic and medicinal chemistry\(^14\). The conventional method for the synthesis of 5-substituted-1H-tetrazole via [3+2] cycloaddition of nitriles to inorganic azides was first reported by Hantzsch and Vagt\(^15\). Further, Sharpless et al. reported Zn(II) salts catalyzed innovative procedure for the synthesis of 5-substituted-1H-tetrazoles from the corresponding nitriles and NaN\(_3\)\(^16\).
Latterly, Pizzo and co-workers have developed a novel and efficient catalyst, TMSN₃ (TMS=trimethylsilyl) in 50 mole% tetra-n-butylammonium fluoride (TBAF) for the synthesis of tetrazoles from corresponding nitriles. However, reported methods have suffered from several limitations such as strong acidic conditions, cost of synthesis, long reaction times, non-recoverable catalysts, difficult work up, low yields and harsh reaction conditions. Thus, currently the impetus has been shifted for the development of efficient, cost-effective, and eco-sustainable procedures for the preparation of tetrazoles.

Demko et al. have reported ZnBr₂ catalyzed simple protocol for the synthesis of 1H-tetrazoles via cycloaddition of sodium azide to nitriles in water. A variety of aromatic nitriles, substituted vinyl nitriles, activated and unactivated alkyl nitriles, thiocyanates, and cyanamides reacted smoothly with sodium azide to give the corresponding tetrazoles (Scheme 1).

Scheme 1

The synthesis of 5-substituted-1H-tetrazoles was also achieved by reacting different nitriles and trimethylsilyl azide in the presence of copper in DMF/MeOH. It was proposed by Jin et al. that the reaction proceeds through the [3+2] cycloaddition of insitu generated copper azide with the subsequent nitriles (Scheme 2).

Scheme 2

A general and scalable procedure for the microreactor assisted synthesis of 5-substituted-1H-tetrazoles by the addition of HN₃ to organic nitriles was reported by Gutmann et al. The key advantage of this method is the cycloaddition of insitu generated toxic and
explosive HN₃ from NaN₃ and acetic acid to the nitrile in a microreactor coupled to an intensified high-temperature/ high-pressure flow. Tetrazoles were obtained in excellent yields and high purity.¹⁹

Zeolite and sulfated zirconia were used as effective catalysts for the synthesis of 5-substituted-1H-tetrazoles via [2+3] cycloaddition of various nitriles to sodium azide in DMF. This method possesses various advantages such as simple methodology, high yield and easy work-up procedure. Moreover, the catalyst could be recovered by simple filtration and is recyclable.²⁰

CuSO₄·5H₂O catalyzed synthesis of 5-substituted-1H-tetrazoles by cycloaddition of different alkyl and aryl nitriles with sodium azide in DMSO was developed by Akhlaghinia et al. Easy availability of the catalyst, good to excellent yields, short reaction times and simple workup procedure were the key advantages of this method.²¹

Du et al.²² have reported [3+2] cycloaddition of nitriles and sodium azide for the preparation of 5-substituted-1H-tetrazoles using silica supported sulfuric acid as an efficient catalyst. This protocol afforded a series of 5-substituted-1H-tetrazoles from corresponding nitriles with 72-95% yields (Scheme 3).

Scheme 3

```
\begin{align*}
\text{C} & \text{N} + \text{NaN}_3 \xrightarrow{\text{SiO}_2\text{H}_2\text{SO}_4, \text{DMF}} \text{R} \text{R} \\
\text{R} & \text{N}=\text{N} \text{NH}
\end{align*}
```

Copper(II) complex of 4-phenyl-2,2’:6’,2”-terpyridine immobilized on activated multi-walled carbon nanotubes was developed for the synthesis of 5-Substituted-1H-tetrazoles from the corresponding nitriles and NaN₃ by Sharghi et al.²³

Mani et al.²⁴ have reported one-pot convenient synthesis of 5-substituted-1H-tetrazoles from corresponding nitriles and NaN₃ in DMF using AgNO₃ as an efficient catalyst.

Nano-TiCl₄·SiO₂ has also appeared as an efficient catalyst for the synthesis of 5-substituted-1H-tetrazole derivatives. The key advantages of this protocol are the easy synthesis of catalyst, good yields of products and recyclability.²⁵
NiFe$_2$O$_4$ was also reported as a proficient catalyst for the synthesis of 5-substituted 1$H$-tetrazoles via [2+3] cycloaddition of sodium azide with nitriles in dimethylformamide. The chief advantages of this process are simple methodology, high yield, easy work-up and recyclability.$^{26}$

Environmentally benign, microwave-assisted and CuO nanoparticles catalyzed synthesis of 5-substituted-1$H$-tetrazoles via (3+2) cycloaddition reaction between nitriles and NaN$_3$ was successfully reported by Padmaja et al.$^{27}$ The key advantages associated with this methods were its cost effectiveness, mild reaction conditions without any additives, tolerance to various functional groups, reusability and good yields.

A simple metal-free method for the synthesis of 5-substituted-1$H$-tetrazoles has been developed by Yakambram et al. The reaction between various nitriles and sodium azide was catalyzed by urea and acetic acid, which afforded products in good to high yields. It has been reported that the reaction plausibly proceeds through *insitu* formation of urea azide active complex (Scheme 4)$^{28}$

**Scheme 4**

\[
\begin{align*}
R-N & \quad + \quad \text{NaN}_3 & + \quad \text{Urea} & \quad \xrightarrow{\text{Water, DMF, AcOH, 110 °C}} & \quad R-N=N=NH
\end{align*}
\]

An efficient synthetic method has been reported for the selective synthesis of 1,5-disubstituted- tetrazoles and diaryl ureas from corresponding secondary amides in the presence of NaN$_3$ in POCl$_3$ (Scheme 5)$^{29}$

**Scheme 5**

\[
\begin{align*}
\text{Ph}\text{CON} & \quad \text{Ph} & \quad \xrightarrow{\text{POCl}_3, \text{NaN}_3, \text{heat}} & \quad \text{PhN} \quad \text{Ph} & \quad + \quad \text{PhCON} \quad \text{Ph}
\end{align*}
\]

Alibeik *et al.*$^{30}$ have reported a simple and efficient method for the preparation of 5-substituted-1$H$-tetrazoles via one-pot three component reaction of different aldehydes,
hydroxylamine and sodium azide using nanostructured heterogeneous catalyst, Cu-MCM-41 (Scheme 6).

**Scheme 6**

\[
\begin{align*}
&\text{H}_2\text{C}=\text{O} + \text{NaN}_3 + \text{NH}_2\text{OH.HCl} \quad \text{Cu-MCM-41 (30 mg)} \quad \text{DMF, 140 °C} \\
&\rightarrow \text{HN} = \text{N} \\
\end{align*}
\]

Nano-sized Cu$_2$O doped on melamine-formaldehyde resin (nano-Cu$_2$O–MFR) was used for the one-pot three-component synthesis of 5-substituted 1H-tetrazole derivatives from corresponding aldehydes. Here, tetrabutylammonium azide (TBAA) was used as an azide source and afforded the desired products in good to excellent yields. The reported catalyst was economical and stable which could be easily prepared and recycled without any significant decrease in its activity (Scheme 7).\(^{31}\)

**Scheme 7**

\[
\begin{align*}
&\text{R} \quad \text{H}_2\text{C}=\text{O} + \text{NH}_2\text{OH.HCl} + \text{Nano-Cu}_2\text{O-MFR (0.096 mol%)} \\
&\quad \text{DMF, 100 °C} \\
&\rightarrow \text{R} \quad \text{HN} = \text{N} \\
\end{align*}
\]

A non-toxic, cost-effective and reusable ceric ammonium sulphate was used for the synthesis of diverse array of 5-substituted-1H-tetrazoles from the corresponding aldehyde, sodium azide and hydroxylamine hydrochloride by Mitra et al. (Scheme 8).\(^{32}\)

**Scheme 8**

\[
\begin{align*}
&\text{R} \quad \text{H}_2\text{C}=\text{O} + \text{NH}_2\text{OH} + \text{NaN}_3 \quad \text{(NH}_4)_2\text{Ce(SO}_4)\text{4.2H}_2\text{O} \\
&\quad \text{DMF, reflux} \\
&\rightarrow \text{R} \quad \text{HN} = \text{N} \\
\end{align*}
\]

Different methods were reported in the literature for the synthesis of 5-substituted-1H-tetrazoles. Majority of the methods reported involves cycloaddition of nitriles to azides for the preparation of 5-substituted-1H-tetrazoles. But, nitriles are toxic in nature,
moreover, these methods require harsh reaction conditions, expensive reagents, possess low yields, unrecoverable catalysts and further in some cases, there is *insitu* generation of highly toxic and explosive hydrazoic acid. A more convenient scheme for the synthesis of 5-substituted-1H-tetrazole derivatives is the one-pot three-component synthesis from corresponding aldehydes, hydroxylamine and sodium azide. A very few examples of this method are reported in literature. But low yields, unrecoverable catalysts, tedious workup procedures etc. are still some of the limitations associated with the already reported methods. Different attempts have been made constantly for the development of more efficient and cost-effective protocols for the synthesis of 5-substituted-1H-tetrazoles accompanied with higher yields and milder reaction conditions.

Keeping in view the importance of 5-substituted-1H-tetrazoles, herein, we report the one-pot multi-component reaction of aldehydes, hydroxylamine and sodium azide to yield corresponding 5-substituted-1H-tetrazoles using Co@GO/Fe₃O₄/L-dopa as magnetically recyclable heterogeneous catalyst (Scheme 9). The desired products were obtained in good to excellent yields, with no pre-requisite of inert or anhydrous reaction conditions. Also, being magnetic in nature, catalyst can be easily separated from the reaction mixture and thus, avoids the tedious workup procedure.

**Scheme 9**

![Scheme 9](image)

**Results and discussion**

**Optimization of the reaction conditions**

To obtain best possible reaction conditions for the synthesis of 5-substituted-1H-tetrazoles, the reaction between benzaldehyde, hydroxylamine hydrochloride and sodium azide in the presence of Co@GO/Fe₃O₄/L-dopa was selected as the model reaction. The model reaction was optimized with respect to different parameters such as solvent, temperature and catalyst loading. To explore the effect of temperature, firstly, the model
reaction was tested at room temperature, but the yield of the corresponding product was very poor (entry 1, Table 1). Then, model reaction was performed at higher temperatures such as 80, 100 and 120 °C in the presence of the Co@GO/Fe₃O₄/L-dopa using water as solvent, and the best results were obtained at 100 °C (entry 2-4, Table 1). The effect of different solvents was also investigated on the model reaction by performing reaction at 100 °C in the presence of 0.1 g catalyst in various solvents (entries 3.5-7, Table 1). Among the various solvents tested, H₂O has appeared as the best solvent (entry 3, Table 1) in terms of the time and yield of the desired product. Finally, the experiments were also performed to select minimum amount of the catalyst required to get the desired product in quantitative yield. For this purpose, the model reaction was carried out in the presence of various amounts of the catalyst and according to the obtained results (entries 3.8-9, Table 1), 0.1 g of the catalyst was chosen as the best catalyst amount to get corresponding tetrazoles in good yield. Thus, the optimized reaction conditions for the synthesis of 5-substituted-1H-tetrazoles are 0.1g as amount of the catalyst, water as the solvent and 100 °C as a suitable temperature.

Table 1. Screening of the various reaction parameters for the synthesis of 5-substituted-1H-tetrazoles

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Temperature (°C)</th>
<th>Amount of catalyst (g)</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R.T.</td>
<td>0.1</td>
<td>H₂O</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>0.1</td>
<td>H₂O</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>0.1</td>
<td>H₂O</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>0.1</td>
<td>H₂O</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>0.1</td>
<td>EtOH</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>0.1</td>
<td>CH₃CN</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>0.1</td>
<td>DMF</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>0.05</td>
<td>H₂O</td>
<td>35</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>0.2</td>
<td>H₂O</td>
<td>20</td>
<td>93</td>
</tr>
</tbody>
</table>

aReaction conditions: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), sodium azide (1 mmol), Co@GO/Fe₃O₄/L-dopa, solvent (5 mL) at different temperature.

bIsolated yields.
With these optimized reaction conditions in hand, the generality of the developed protocol for the synthesis of 5-substituted-1$H$-tetrazoles was explored and the results are summarized in Table 2. As depicted in Table 2, this protocol works smoothly for a wide variety of electron-rich as well as electron deficient aromatic aldehydes. The better results were observed for aldehydes having electron-withdrawing substituents. Steric hindrance also played important role on the yield of desired products as evident from reaction of 2-nitrobenzaldehyde and 4-nitrobenzaldehyde (entries 4,7, Table 2); 4-chlorobenzaldehyde and 2-chlorobenzaldehyde (entries 5,8, Table 2). In both the cases, para substituted aldehydes gave better yields than their ortho substituted counterparts. It has been observed that aldehydes containing electron-donating group gave lower yield due to decrease in electrophilicity of carbonyl carbon of aldehydes. In case of 2-hydroxy and 4-hydroxybenzaldehyde (entries 9,10, Table 2), 2-hydroxybenzaldehyde gave better yield than 4-hydroxybenzaldehyde due to the increase in electrophilicity of carbonyl carbon of aldehyde by H-bonding, whereas at 4-position it shows only electron donating property.

**Table 2. Co@GO/Fe$_3$O$_4$/L-dopa catalyzed synthesis of 5-substituted-1$H$-tetrazoles**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substrate</th>
<th>Product</th>
<th>Time</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="benzaldehyde" /></td>
<td><img src="image2.png" alt="tetrazole" /></td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="benzaldehyde" /></td>
<td><img src="image4.png" alt="tetrazole" /></td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="benzaldehyde" /></td>
<td><img src="image6.png" alt="tetrazole" /></td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="benzaldehyde" /></td>
<td><img src="image8.png" alt="tetrazole" /></td>
<td>15</td>
<td>93</td>
</tr>
</tbody>
</table>
Recyclability

Recyclability of the synthesized catalyst was tested for the synthesis of 5-phenyl-1H-tetrazole from benzaldehyde, sodium azide and hydroxylamine (entry 1, Table 2). After completion of the reaction, the catalyst was separated via magnet, washed with deionized water (3 × 10 mL), chloroform (3 × 10 mL) and dried under vacuum. Then a fresh reaction was tested with the used catalyst. Amount of reactants taken for further run was adjusted according to the amount of the catalyst recovered from previous runs. No significant decrease in the catalytic activity of the catalyst was observed up to five runs (Fig. 2).
**Fig. 2** Recyclability of Co@GO/Fe$_3$O$_4$/L-dopa. Reaction conditions: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), sodium azide (1 mmol), Co@GO/Fe$_3$O$_4$/L-dopa (0.1 g, 3.68 mol% Co), H$_2$O (5 mL) at 100 °C.

**Proposed mechanism**

A plausible mechanism has been proposed for the synthesis of tetrazoles from corresponding aldehydes, hydroxylamine hydrochloride and azide in the presence of Co@GO/Fe$_3$O$_4$/L-dopa (Fig. 3). Initially, Co(0) nanoparticles interacts with the lone pair of oxygen atom of aldehydes and increases the electrophilicity of carbonyl carbon of the aldehyde. Subsequently, hydroxylamine attacks the carbonyl carbon of aldehyde and form oxime [II] via the formation of intermediate [I], which on expulsion of water molecule form nitrile [III]. Afterthat, Co(0) attaches with p-electron cloud of the intermediate nitrile moiety [III], which in turn reacts with NaN$_3$ for transformation into respective tetrazole [IV] and Co(0) is regenerated back.
Fig. 3  Proposed mechanism for the synthesis of 5-substituted-1H-tetrazoles in the presence of Co@GO/Fe₃O₄/L-dopa.

**Conclusion**

In conclusion, we have developed an efficient and environmentally benign procedure for the one-pot multi-component synthesis of 5-substituted-1H-tetrazoles from corresponding aldehydes, hydroxylamine hydrochloride and sodium azide in the presence of Co@GO/Fe₃O₄/L-dopa as magnetically recyclable heterogeneous catalyst. The products were obtained in good to excellent yields, with no pre-requisite of inert or anhydrous reaction conditions. The key advantages of the proposed method include simple work-up procedure, replacement of toxic and expensive nitrile precursors by aldehydes, different functional group tolerance, mild reaction conditions and no *in situ* generation of toxic substances.
Experimental

General procedure for the Co@GO/Fe₃O₄/L-dopa catalyzed one-pot synthesis of 5-substituted-1H-tetrazoles

To a mixture of aldehyde (1 mmol), sodium azide (1 mmol), hydroxylamine hydrochloride (1 mmol) and Co@GO/Fe₃O₄/L-dopa (0.1 g) in a round bottom flask (25 mL), water (5 mL) was added, and the reaction mixture was stirred at 100 °C for an appropriate time. After completion of the reaction as monitored by TLC, reaction mixture was cooled to room temperature and the catalyst was separated with the help of external magnet. The catalyst was washed with distilled water (2 × 10 mL) and dried under vacuum for further use. The aqueous layer so obtained was diluted with ethyl acetate and washed with brine solution (3 × 10 mL) and dried over anhyd. Na₂SO₄. Finally, product was obtained after removal of the solvent under reduced pressure, followed by crystallization from ethanol.

The structures of the products were confirmed by ¹H, ¹³C NMR, mass spectral data and comparison with authentic samples obtained commercially or prepared according to the literature methods.
Spectral data of the compounds listed in Table 2

5-Phenyl-1\textit{H}-tetrazole (entry 1)

![Structure](image)

White solid, M.pt. 217-218 °C (Lit. M.pt. 218-219 °C). $^1\text{H}$ NMR (400 MHz, CDCl$_3$): $\delta$ 7.60-7.61 (d, 3H, J= 4 Hz, Ar-H), 8.04-8.06 (m, 2H, ArH); $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$): 125.3, 128.8, 129.6, 151; MS (ESI): 145 [M-1].

5-(4-Methylphenyl)-1\textit{H}-tetrazole (entry 2)

![Structure](image)

White solid, M.pt. 250-251 °C (Lit. M.pt. 251-252). $^1\text{H}$ NMR (400 MHz, CDCl$_3$): $\delta$ 2.30 (s, 3H, CH$_3$), 7.19-7.21 (d, 2H, J= 8 Hz, Ar-H), 7.46-7.48 (d, 2H, J=8 Hz, ArH; $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$): 21.1, 125.2, 128.3, 138.5, 151; MS (ESI): 159 [M-1].

5-(4-Methoxyphenyl)-1\textit{H}-tetrazole (entry 3)

![Structure](image)

White solid, M.pt. 230-231 °C (Lit. M.pt. 231-232 °C). $^1\text{H}$ NMR (400 MHz, CDCl$_3$): $\delta$ 3.93 (s, 3H, OCH$_3$), 7.25-7.27 (d, J= 8Hz, 2H, ArH), 7.68-7.70 (d, J= 8 Hz, 2H, ArH); $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$): 56, 113.1, 119.9, 125.6, 151, 160.4; MS (ESI): 175 [M-1].
5-(4-Nitrophenyl)-1H-tetrazole (entry 4)

Yellow solid, M.pt. 217-218 °C (Lit. M.pt. 218-220)\(^3\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.77-7.99 (d, 2H, J= 8Hz, ArH), 8.26-8.28 (d, 2H, J= 8 Hz, ArH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 124.1, 126.6, 128.5, 148.2, 151; MS (ESI): 190 [M-1].

5-(4-Chlorophenyl)-1H-tetrazole (entry 5)

White solid, M.pt. 251-252 °C (Lit. M.pt. 252-253)\(^3\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.34-7.36 (d, 2H, J= 8 Hz, ArH), 7.50-7.52 (d, 2H, J= 8 Hz, ArH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 127.8, 128.2, 129, 136.7, 151; MS (ESI): 179 [M-1], 181 [M+1].

5-(4-Bromophenyl)-1H-tetrazole (entry 6)

White solid, M.pt. 264-265 °C (Lit. M.pt. 265-266)\(^3\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.54-7.56 (d, 2H, J= 8 Hz, ArH), 7.60-7.62 (d, 2H, J = 8 Hz, ArH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 121.6, 128.6, 129.5, 131.6, 146.3, 154.7; MS (ESI): 222 [M-1], 224 [M+1].

5-(2-Nitrophenyl)-1H-tetrazole (entry 7)
Yellow solid, M.pt. 155-156 °C (Lit. M.P. 154-156)\textsuperscript{36}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.53-7.56 (t, 1H, J = 8 Hz, ArH), 7.88-7.90 (d, 1H, J= 8 Hz, ArH), 8.18-8.20 (d, 2H, J=8 Hz, ArH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 123.5, 127.8, 129.1, 138.6, 147.9, 150.6; MS (ESI): 190 [M-1].

5-(2-Chlorophenyl)-1H-tetrazole (entry 8)

White solid, M.pt. 137-138 °C (Lit. M.pt. 137-139)\textsuperscript{33}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.33-7.38 (m, 2H, ArH), 7.46-7.48 (d, 1H, J= 8 Hz, ArH), 7.64-7.66 (d, 1H, J= 8 Hz, ArH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 124.5, 126.1, 127.2, 128.9, 130.7, 132.5, 141.3; MS (ESI): 179 [M-1], 181 [M+1].

5-(2-Hydroxyphenyl)-1H-tetrazole (entry 9)

White solid, M.pt. 223-224 °C (Lit. M.pt. 224-225)\textsuperscript{37}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.93-6.97 (t, 1H, J=8 Hz, ArH), 7.00-7.03 (t, 1H, J= 8 Hz, ArH), 7.20-7.23 (t, 1H, J=8 Hz, ArH), 7.43-7.45 (d, 1H, J=8 Hz, ArH), 9.79 (bs, 1H, OH, exchangeable with D\textsubscript{2}O); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 110.3, 118.8, 120.4, 128.7, 130, 146.1, 157.5; MS (ESI): 161 [M-1].

5-(4-Hydroxyphenyl)-1H-tetrazole (entry 10)
White solid, M.pt. 232-233 °C (Lit. M.pt. 234-235)\textsuperscript{34}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.94-6.96 (d, 2H, J= 8, ArH), 7.48-7.50 (d, 2H, J=8 Hz, ArH), 9.49 (bs, 1H, OH, exchangeable with D\textsubscript{2}O); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 114.4, 117.7, 125.9, 151, 160.4; MS (ESI): 161 [M-1].
REFERENCES


244-245

236-243, 246-254
Chapter 2, Section 2.2, Table 3, entry 4, $^1$H NMR
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Chapter 2, Section 2.2, Table 3, entry 5, Mass spectra
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Chapter 2, Section 2.3, Table 3, entry 5, Mass spectra
Chapter 2, Section 2.3, Table 3, entry 6, $^1$H NMR

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Chapter 2, Section 2.3, Table 3, entry 6, $^{13}$C NMR

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![Carbon-13 NMR Spectrogram](image)
Chapter 4, Section 4.2, Table 3, entry 3, Mass spectra
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Chapter 4, Section 4.4, Table 2, entry 4, $^1$H NMR

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