COMMUNICATION



Sustainable parts-per-million level catalysis with Fe^{III} : Onepot cascade synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in water

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Department of Biotechnology, Ministry of Science and Technology, Grant/Award Number: BT/PR24684/NER/95/810/2017 A silica-supported iron complex has been identified as a highly active and reusable catalyst for the synthesis of medicinally important 2,3-dihydroquinazolin-4(1H)-ones. The catalyst was fully characterized by various spectroscopic analyses such as Fourier-transform infrared spectroscopy (FT-IR), ultraviolet-visible (UV-VIS), scanning electron microscopy (SEM), scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM-EDX), energy-dispersive spectroscopy (EDS) mapping, X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), electron paramagnetic resonance (EPR), inductively coupled plasma atomic emission spectroscopy (ICP-AES), elemental analysis, Brunauer-Emmett-Teller (BET) isotherm and thermogravimetric analysis (TGA) analysis. A diverse library of 2,3-dihydroquinazolin-4(1H)-ones including some new analogues were successfully synthesized in good to excellent yields with parts-per-million (ppm) levels of Fe using water as a solvent. The active catalyst has high turnover number (TON) and turnover frequency (TOF) at the optimized condition, which were 30,087 and 30,087 h⁻¹, respectively. Ppm level catalysis, wide substrate scope, shorter reaction time, reusability of the catalyst, green solvent media and gram-scale synthesis make this protocol eco-friendly and sustainable.

KEYWORDS

2,3-dihydroquinazolin-4(1H)-ones, C2-symmetric, heterogeneous, parts-per-million, recyclability

1 | INTRODUCTION

2,3-Dihydroquinazolin-4(1*H*)-ones are important class of heterocyclic compounds found in a number of biologically active as well as naturally occurring pharmaceutical compounds.^[1,2] Various research groups have developed numerous methodologies for the synthesis of this important scaffold using different homogeneous and heterogeneous catalytic systems.^[2–4] Heterogeneous catalysts possess some advantages over their homogeneous

counterparts such as recyclability, require less amounts of catalyst, and so on. Additionally, the former has many advantages over the later, namely, catalyst can be removed by simple filtration, large surface area and very importantly the metal contamination with the end product is negligible.^[5,6] Recently, there are a large number of heterogeneous catalysts reported by research community that catalysed different types of valuable organic reactions.^[7–12] Literature study showed that quite a good number of methods are available for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones; multicomponent reaction (MCR) of isatoic anhydride, primary amine or ammonium acetate and carbonyl compounds is a familiar one. A vast number of catalytic systems were already reported by different research groups,^[13–22] but these procedures have some drawbacks such as costly reagents or catalysts, tedious process, harsh reaction conditions, elongated time and low product yields. Therefore, efforts are being made for the development of new catalytic system that may overcome these boundaries and gives a new path for the scientific community.

Iron is one the most abundant elements on Earth having low cost and very high strength that make wide application of iron in different aspects. Moreover, like other metals, it has no toxicity issue, and it can be easily stored for long duration without any special care. Due to these advantages, iron has been used as catalyst/raw material in numerous chemical reactions as well as in many industrial processes.^[23-25] In this particular MCR mentioned above, there were a few methods reported in literature, which used iron as homogeneous and heterogeneous catalysts in different solvent media.[26-28] Because the exploration of iron catalyst in this particular reaction is very less, the development of new iron catalysed strategy with extremely low metal content is of noteworthy interest. One of the naturally occurring minerals, silica has been employed in many industrial processes. The polymerization of silica particles gives a silica gel that is used in chemical laboratories in large scale. Silanol groups in their surface, large surface area and particle size make silica useful in catalyst designing mainly as support for the metal.^[29] Due to the various

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advantages, inexpensive nature and easy availability of the silica gel motivated us to use as support in the current study. In organic synthesis, solvent media has a significant role in the reaction mechanism. From green chemistry viewpoint, water is the most suitable solvent to carry out the reactions as it is readily available, economical, innocuous and non-flammable solvent. Furthermore, use of water in organic reactions has many advantages such as improves the reactivities and selectivities, makes the workup procedures simple, enables the recycling of the catalyst and allows mild reaction conditions.^[30] Therefore, development of novel synthetic routes involving silica supported iron catalyst and water as benign solvent for the synthesis of biologically active 2,3-dihydroquinazolin-4(1H)-ones will be of great importance among the scientific community. In the present study, we have developed a simple and convenient method for the synthesis of 2.3-dihydroquinazolin-4(1H)ones through ppm level catalysis with Fe (III). Additionally, we made an attempt to synthesize some novel 2,3-dihydroquinazolin-4(1H)-ones that can be used as ligands and drugs in forthcoming days.

2 | RESULTS AND DISCUSSION

2.1 | Catalyst preparation

The catalyst was synthesized according to the literature reported by Hajipour and Azizi.^[31] as shown in Figure 1. At first, 3-chloropropyl trimethoxysilane reacts with KI in dry acetone under reflux condition to give



[{SiO₂-(acac)}₃Fe^{III}]Cl₃

 $\label{eq:FIGURE1} \begin{array}{l} FIGURE1 & Synthesis of [\{SiO_2-(acac)\}_3Fe^{III}]Cl_3 \ catalyst \end{array}$

3-iodopropyl trimethoxysilane that further reacts with silica gel (60–120 Mesh, preheated at 300°C) in dry toluene for 48 h under reflux temperature. Functionalized silica was then treated with acetyl acetone and K_2CO_3 in CH₃CN under reflux temperature to get SiO₂-acac support. Finally, aqueous solution of FeCl₃·6H₂O was mixed with SiO₂-acac, prepared in the previous step at room temperature and obtained a dark orange precipitate. Then, the solid phase was filtered and washed thoroughly until no more iron leaching was observed. This dark orange solid was the resulting catalyst termed as [{SiO₂-(acac)}₃Fe^{III}]Cl₃.

2.2 | Characterization

In the Fourier-transform infrared spectroscopy (FT-IR) spectrum of silica, an absorption band appearing at 3,780 cm⁻¹ ascribe to Si-OH stretching vibration, which is absent in the modified silica samples and in the final catalyst. The two characteristic peaks at 1,078 and 804 cm⁻¹ are due to the symmetrical and asymmetrical vibrations of Si-O-Si, respectively. The two small bands around 2,892 and 2,828 cm⁻¹ found in the spectrum of SiO₂-silane are due to the asymmetric and symmetric C-H stretching of the alkyl groups. These two peaks were also observed in the catalyst with slight shifting of the vibration bands. A band around 1,635 cm⁻¹ of SiO₂-silane



 $\label{eq:FIGURE2} FIGURE2 \quad \mbox{FT-IR spectra of modified silica samples and} \\ [\{SiO_2\mbox{-}(acac)\}_3Fe^{III}]Cl_3\ catalyst$

can be ascribed to the O-H stretching vibration of the adsorbed water. The peaks appearing at 1,579, 1,521, 1,435, 1,356 and 671 cm⁻¹ of $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ can be correlated to the acetyl acetone ligand coordinated to iron. All these characteristic bands were also found in the FT-IR spectrum of SiO₂-acac (with slight shifting) (Figure 2).^[32-34]

The ultraviolet-visible (UV-VIS) spectra of the silica and modified silica supported catalyst are shown in Figure 3. In the UV spectrum of the catalyst, two absorption bands are observed at 365 and 478 nm clearly confirming the presence of iron in the catalyst.^[35] A band at 265 nm was observed in the spectrum due to the presence of modified silica support in the catalyst.^[36] Because functionalized silica was used as a support in the catalyst. the band is shifted to lower wavelength (blue shift) as compared with silica (283 nm). The content of Fe in the catalyst was investigated by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis. The Fe content of the prepared silica supported catalyst was found to be 4.03×10^{-5} mmol g⁻¹ (0.00023 wt%). The elemental analysis (CHN) of the prepared catalyst was performed and found that carbon, hydrogen and nitrogen contents of the catalyst were 3.70%, 1.692% and 0.00%, respectively.

The morphology of the silica and catalyst was studied by scanning electron microscopy (SEM) shown in Figure 4a,b. The SEM image clearly showed irregular polyhedron morphology of the catalyst. The energy-dispersive X-ray spectroscopy (EDX) spectra of $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ clearly indicated the presence of C, O, Si and Fe (Figure 4c vs. Figure 4d) in the catalyst, which confirmed the immobilization of Fe on the surface of modified SiO₂. The iron concentration was found to be



FIGURE 3 UV–VIS spectra of silica and [{SiO₂-(acac)}₃Fe^{III}] Cl₃ catalyst



740.00

0.00

0.00 1.30k 2.60k 3.90k 5.20k 6.50k 7.80k 9.10k 10.40k11.70k13.00

CPS: 940 DT: 5.6 Lsec: 50.0 0 Cnts 0.000 keV Det: El



different in different areas that were observed when two different areas were selected for EDX analysis. Furthermore, EDS mapping images of the catalyst indicated the presence of uniformly dispersed Fe, C, O and Si in their structure (Figure 5).

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0.00 1.30k 2.60k 3.90k 5.20k 6.50k 7.80k 9.10k 10.40k11.70k13.00k

CPS: 940 DT: 5.6 Lsec: 50.0 0 Cnts 0.000 keV

740.00

370.00

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Further, X-ray diffraction (XRD) pattern analysis of the catalyst provided more evidence for the presence of iron in the modified silica support (Figure 6). A broad peak at around $2\theta = 22.2^{\circ}$ corresponding to the (001) is ascribable to amorphous silica support.^[37] The other characteristic diffraction peaks was found at 2θ values of 35.3° and 62.2°, which are assigned to (311) and (440) planes of iron (III), respectively.^[38]

In order to confirm the elements valence state of all the species in the catalyst, X-ray photoelectron spectroscopy (XPS) analysis was performed. From the survey spectrum of the catalyst, it was confirmed that element carbon was present in the catalyst. The peak appearing at 293.54 eV was assigned to C 1s of carbon species, which was obtained due to the presence of acetyl acetone and propyl moiety in the active catalyst (Figure 7a). The binding energy of Fe $2p_{3/2}$ and $2p_{1/2}$ at 711.42 and 724.85 eV, respectively, in the XPS supported that Fe (III) is present in the prepared catalyst (Figure 7b).^[38,39] The presence of SiO₂ in the catalyst was confirmed by the peak at 103.29 eV assigned to Si 2p (Figure 7d).



FIGURE 5 EDS mapping images of (a) Fe, (b) C, (c) O and (d) Si of the catalyst



FIGURE 6 Powder XRD patterns for (a) SiO₂ and (b) [{SiO₂-(acac)}₃Fe^{III}]Cl₃

Additionally, the XPS peak at 532.5 eV corresponds to the O 1s, clearly indicating the presence of silica bound silanol groups (Figure 7c).

The XRD and XPS data were further supported by electron paramagnetic resonance (EPR) analysis of the catalyst, which was recorded at room temperature (Figure 8). The *g* values of $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ catalyst from the EPR spectrum was found to be 4.31 and 2.00, indicated that iron is present in +3 oxidation state in the silica supported catalyst.^[40]





FIGURE 8 EPR spectrum of Fe in $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$

The N_2 adsorption-desorption isotherms of the silica and all modified samples were calculated by using N_2 adsorption at 77 K shown in Figure 9. All the modified samples showed similar types of isotherm (type IV) as that of silica with typical hysteresis loop, which is a characteristic feature of highly ordered mesoporous materials. The surface area, pore volume and pore diameter of all the samples obtained from N_2 sorption isotherms are compiled in Table 1. Functionalization of silica significantly affected the surface area and pore distribution of modified samples. The Brunauer–Emmett–Teller (BET)





FIGURE 9 N_2 adsorption-desorption isotherms of silica and modified silica samples

surface area decreased from SiO₂ (396.69 m² g⁻¹) to $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ (273.93 m² g⁻¹), which clearly indicates the successful incorporation of iron over modified silica support.^[41] On the other hand, the pore diameter initially decreased from SiO₂ (5.24 nm) to SiO₂-silane (4.01 nm) and then increased to $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ (5.24 nm).

Thermogravimetric analysis (TGA) was applied to investigate the thermal behaviour of the synthesized catalyst from room temperature to 800°C. There are three main weight losses (shown in Figure S1). Firstly, the weight loss (8.74%) at around 100°C–280°C is allocated to physically and hydrogen bonded water on the silica support and decomposition of some organic parts anchored on SiO₂. As the melting point of Fe (acac)₃ is 180°C-181°C, thereafter, it may get decomposed to small fractions. The other two weight losses (5.15% and 4.54%) in the range of 280°C-600°C is related to the modified organic parts that are anchored to SiO₂ surface. Because the first weight loss included organic components of the catalyst, loading of the complex on SiO₂ was calculated by taking the total weight loss (18.43%) that includes the organic components as well as the absorbed water and found to be $0.03847 \text{ mmol g}^{-1}$ on SiO₂ surface.

2.3 | Catalytic application

To show the advantage of the prepared catalyst in organic synthesis, at first, the catalyst was applied for the reaction of isatoic anhydride, aniline and 4-chlorobenzaldehyde affording 2,3-dihydroquinazolin-4(1H)-one. When 20 mg the prepared catalyst was used for the reaction at 100°C, the desired product was obtained in quantitative yield within an hour (Table 2, entry 2). Four other types of iron sources were also employed as catalysts for this reaction, but the yield of the reaction was not satisfactory (Table 2, entries 3–6). The reaction was also carried out with SiO_2 and SiO₂-acac as catalysts; however, no suitable results were obtained (Table 2, entries 7 and 8). Then, some adjustments to the reaction conditions were made to get the optimized result by using the prepared heterogeneous catalyst. At first, different types of solvents were examined for this reaction and found that water gives excellent vield of the product within short period of time (Table 2, entry 2 vs. entries 9-16). The reaction was also performed in the absence of solvent media, but no satisfactory yield was observed, which confirmed the importance of solvent in the reaction (Table 2, entry 17). In absence of the catalyst, the reaction afforded only 30% yield of the desired product (Table 2, entry 1). Further, the amount of the catalyst was optimized and observed that 20 mg of the catalyst (32.24 ppm Fe) was sufficient for quantitative yield of 2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 20 vs. entries 18 and 19). The temperature of the reaction was also investigated and found that 80°C was well enough for the reaction to takes place within an hour (Table 2, entry 20). Finally, the turnover number (TON) and turnover frequency (TOF) of the catalyst were also calculated for the model reaction based on the amount of active Fe used, and they were found to be 30,087 and $30,087 \text{ h}^{-1}$, respectively (Table 3, entry 1).

After obtaining the optimum reaction conditions mentioned above (Table 2, entry 17), we explored the applicability of the system to a wide variety of amines

Catalyst	SiO ₂	SiO ₂ -Silane	[{SiO ₂ -(acac)} ₃ Fe ^{III}]Cl ₃
BET surface area $(m^2 g^{-1}) (A_{BET})$	396.69	332.61	272.93
Total pore volume ^b (cm ³ g ⁻¹) (V _P)	0.519	0.334	0.358
Pore diameter ^c (nm)	5.24	4.01	5.24

 $\begin{array}{ll} \textbf{TABLE 1} & \text{Characterization of} \\ \text{silica and modified silica samples by } N_2 \\ \text{adsorption-desorption measurement} \end{array}$

Abbreviation: BET, Brunauer-Emmett-Teller.

^aThe BET method used in N₂ sorption.

^bSingle-point porevolume at $P/P_0 = 0.994$.

^cAdsorption average pore diameter (by the BET method).

TABLE 2 Optimization of reaction conditions

$\begin{array}{c} \begin{array}{c} O \\ O \\ H \end{array} \\ \end{array} \\ \begin{array}{c} O \\ H \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} O \\ H \end{array} \\ \end{array} \\ \begin{array}{c} O \\ C \\ C \end{array} \\ \begin{array}{c} O \\ C \\ C \end{array} \\ \begin{array}{c} O \\ C \\ \end{array} \\ \begin{array}{c} O \\ C \\$								
Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yield ^a (%)			
1	_	H ₂ O	100	1	30			
2	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	H ₂ O	100	1	98			
3	Fe powder (90)	H ₂ O	100	1	70			
4	FeCl ₃ (5)	H ₂ O	100	1	60			
5	FeCl ₂ (5)	H ₂ O	100	1	50			
6	$Fe(acac)_3(5)$	H ₂ O	100	1	75			
7	SiO ₂ (5)	H ₂ O	100	1	35			
8 ^b	SiO ₂ -(acac)	H ₂ O	100	1	30			
9	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	CH ₃ CN	100	1.5	_			
10	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	EtOH	100	2	20			
11	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	Dry toluene	100	2	20			
12	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	DMSO	100	1.5	_			
13	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	DMF	100	1.5	-			
14	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	DCM	100	1.5	_			
15	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	EtOAc	100	1.5	_			
16	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	THF	100	1.5	trace			
17	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	_	100	1.5	50			
18	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.001612)$	H ₂ O	100	1	80			
19	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.002418)$	H ₂ O	100	1	90			
20	[{SiO ₂ -(acac)} ₃ Fe ^{III}]Cl ₃ (0.003224, 32.24 ppm Fe)	H ₂ O	80	1	97			
21	[{SiO ₂ -(acac)} ₃ Fe ^{III}]Cl ₃ (0.002418)	H ₂ O	80	1	90			
22	$[{SiO_2-(acac)}_3Fe^{III}]Cl_3 (0.003224)$	H ₂ O	70	1	60			

Note. Reaction conditions: isatoic anhydride (1 mmol), aniline (1.2 mmol), 4-chlorobenzaldehyde (1.2 mmol), catalyst (*n* mol% of Fe) and solvent (2 ml) were stirred at different temperature.

^aIsolated yield.

 $^{\rm b}20~{\rm mg}$ of SiO₂-(acac) was used.

TABLE 3TON and TOF of thecatalyst for the model reaction

Entry	[{SiO ₂ -(acac)} ₃ Fe ^{III}]Cl ₃ [#]	Time (h)	Yield ^a (%)	TON ^b	$TOF^{c}(h^{-1})$
1	32.24	1	97	30,087	30,087
2	24.18	1	90	37,221	37,221
3	16.12	1	80	49,628	49,628

Note. Reaction conditions: isatoic anhydride (1 mmol), aniline (1.2 mmol), 4-chlorobenzaldehyde (1.2 mmol), [SiO2-(acac)]3FeIIICl3(*n* ppm) and water (2 ml) were stirred at 80°C.

Abbreviations: TOF, turnover frequency; TON, turnover number.

^aIsolated yield.

^bmmol of product per mmol of catalyst.

^cTON per unit time.

#(0.1 mol% = 1,000 ppm).

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TABLE 4 Synthesis of various disubstituted 2,3-dihydroquinazolin-4(1H)-ones



TABLE 4 (Continued)



Note. Reaction conditions: isatoic anhydrides (1 mmol), anilines (1.2 mmol), benzaldehydes (1.2 mmol), [{SiO₂-(acac)}₃Fe^{III}]Cl₃ (20 mg, 32.24 ppm Fe) in water (2 ml) were stirred at 80°C.

and aldehydes (Table 4). First, the impact of substituted aromatic amine and aldehyde groups were investigated and found that a range of 2,3-dihydroquinazolin-4(1*H*)-ones were formed in good to excellent yields (Table 4, **2a–20**). Furthermore, aliphatic amine was applied in this reaction and gives almost quantitative yields of desired products (Table 4, **2p** and **2q**). We have also investigated propargyl amine with different substituted aromatic aldehydes and gives excellent yield of products in slightly

longer period of time (Table 5, **3a–3e**). These five reactions (Table 5) were performed in gram scale to demonstrate the industrial utility of the methodology. The reaction of isatoic anhydride derivative (5-chloroisatoic anhydride) was also investigated in this study, and moderate yield of 2,3-dihydroquinazolin-4(1*H*)-ones were obtained within 5 h (Table 4, 2r-2v).

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Further, the above methodology was applied for the reaction of isatoic anhydride, ammonium acetate and



TABLE 5 Gram-scale syntheses of various novel 2,3-dihydroquinazolin-4(1H)-ones

Note. Reaction conditions: isatoic anhydride (1.63 mg, 10 mmol), propargyl amine (0.66 mg, 12 mmol), benzaldehydes (12 mmol), $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ (200 mg, 32.24 ppm Fe) in water (20 ml) were stirred at 80°C.

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TABLE 6 Syntheses of monosubstituted 2,3-dihydroquinazolin-4(1H)-ones



Note. Reaction conditions: isatoic anhydrides (1 mmol), NH₄OAc (1.2 mmol), aldehydes (1.2 mmol), [{SiO₂-(acac)}₃Fe^{III}]Cl₃ (20 mg, 32.24 ppm Fe) in water (2 ml) were stirred at 80°C.

different carbonyl derivatives. Substituted benzaldehydes give excellent yields of desired products within 1–2 h (Table 6). Aldehyde containing heterocyclic ring and aliphatic aldehyde also give the desired 2,3-dihydroquinazolin-4(1*H*)-ones within short period of time (Table 6, **4g–4h**). Similarly ketones also gave excellent yields of the products within an hour (Table 6, **4i–4j**).

Finally, the recyclability of the prepared catalyst was investigated by using isatoic anhydride, aniline and 4-chlorobenzaldehyde as the model reaction. After completion of the reaction, the catalyst was recovered by centrifugation, followed by washing with water and acetone to remove the reaction products from the catalyst. Then, the catalyst was dried in oven and directly reused for next run without further purification. The catalyst



TABLE 7Reusability of the $[{SiO_2-(acac)}_3Fe^{III}]Cl_3$ for the synthesis of2,3-dihydroquinazolin-4(1*H*)-ones

Note. Reaction conditions: Isatoic anhydride (1 mmol), aniline (1.2 mmol), 4-chlorobenzaldehyde (1.2 mmol), $[{SiO}_2-(acac)]_3Fe^{III}]Cl_3$ (20 mg, 32.24 ppm Fe) in water (2 ml) were stirred at 80°C. ^bIsolated yield.



FIGURE 10 Structure of [{SiO₂-(acac)}₃Fe^{III}]Cl₃

was reused for five cycles, and the catalytic results are listed in Table 7. The yields were almost identical in all the five cycles, confirming that the catalyst was very active, stable and reusable up to fifth cycle. Further, leaching of the iron species from the support was examined by ICP-AES analysis of reused catalyst. From the ICP-AES analysis, no significant leaching of iron was observed from the catalyst. Further, hot filtration test was

SCHEME 1 Plausible reaction mechanism

performed in which the catalytically active particles were removed from the reaction mixture by filtration after 30 min, and the isolated yields of the reaction was found to be 42%. Then, the filtrate was allowed to continue the reaction without the solid catalyst for additional 3 h. After removal of the catalyst particles, the reaction did not proceed, indicating that no catalytically active Fe remained in the filtrate.

2.4 | Structure of the catalyst

In the last step of the preparation of $[{SiO_2-(acac)}_3Fe^{III}]$ Cl₃, the colour changes from colourless to dark orange, which may be due to the formation of Fe $(acac)_3$. According to the literature reports,^[32,42] the colour and coordination geometry of the Fe (acac)₃ is red and octahedral, respectively. Since in [{SiO₂-(acac)}₃Fe^{III}]Cl₃ catalyst, SiO₂ was used as support that was attached with the Fe^{III}(acac)₃ so the coordination geometry of the catalyst should be octahedral in nature (Figure 10). Again, because the oxidation state of Fe in the catalyst was +3, which was confirmed by XPS, XRD and EPR analyses, Fe must form Fe (acac)₃ in the final catalyst, which was anchored with silica support. Due to the presence of silica support in the catalyst, the colour of the complex changes from red to dark orange.



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TABLE 8 Synthesis of various novel bis-2,3-dihydroquinazolin-4(1H)-ones



Note. Reaction conditions: 3a-3e (1 mmol), piperidine (1 equiv) and Cu(OAc)₂·H₂O (10 mol%) in CH₂Cl₂ were stirred at room temperature.

2.5 | Plausible reaction mechanism

The reaction was initiated by the interaction of carbonyl group of isatoic anhydride with the iron atom of [{SiO₂-(acac)}₃Fe^{III}]Cl₃ through a chemical bond. A vacant site was generated by dissociating one of the oxygen atoms of acetylacetonate ligand from the iron centre, which may be due to the hemilability^[43] of one of the side arms of acetylacetonate that activates the anhydride molecule. After the activation of isatoic anhydride, the iron complex was regenerated. Then, the lone pair of primary amine attacks the carbonyl carbon of the anhydride to produce a reactive intermediate I, which in turn generates intermediate II by the release of one molecule of CO₂. Afterwards, key intermediate III is afforded by the proton transfer reaction. Subsequently, the catalyst activates the carbonyl compound in the similar way and reacts with intermediate III to produce the imine intermediate IV. Finally, nucleophilic attack of amide nitrogen takes place on the electron-deficient imine carbon, followed by a 1,5-proton shift affording the target product 2,3-dihydroquinazolin-4(1H)-one (Scheme 1).^[22,26]

After getting a wide variety of 2,3-dihydroquinazolin-4(1H)-one molecules, we have extended our work for the synthesis of some novel 2,3-dihydroquinazolin-4(1H)-

ones through Glaser coupling reaction using 3a-3e as starting precursors.⁴⁴ As per our expectation, the desired novel 2,3-dihydroquinazolin-4(1H)-one molecules were obtained in moderate to good yields (Table 8, entries **5a–e**). All the five compounds are C₂-symmetric, which was confirmed by NMR spectroscopy. C₂-symmetric molecules have been used in different catalytic reactions as ligands because they limit the numbers of side reaction. Therefore, these molecules are also expected to have wide applicability in different types of organic reactions in near future.

3 | CONCLUSIONS

In summary, we disclosed a methodology for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via one pot multicomponent reaction of isatoic anhydrides, amines or ammonium acetate and carbonyls using ppm level of Fe in H_2O . Highly abundant and inexpensive nature of iron, ppm level catalysis, gram-scale synthesis of novel compounds, aqueous solvent media, short reaction period and reusability of the catalyst up to fifth cycle are the merits and novelty of the current protocol. Furthermore, we designed and successfully executed synthesis of some

novel C_2 symmetric bis-2,3-dihydroquinazolin-4(*1H*)-one derivatives via Glaser coupling. All the five C_2 -symmetric molecules can be used as ligands in different organic reactions in upcoming days. A total of 42 products library were synthesized in the present study, 15 of which were novel analogues that may be used as potential drug candidates in near future.

4 | EXPERIMENTAL

4.1 | Preparation of SiO₂-silane

The catalyst was synthesized according to the literature reported by Hajipour et al.^[31] For preparation of SiO₂-silane, 3-chloropropyl trimethoxysilane reacts with KI in dry acetone under reflux condition to give 3-iodopropyl trimethoxysilane that further reacts with a silica gel (60–120 Mesh, preheated at 300°C) in dry toluene for 48 h under reflux temperature. Then, the solvent was decanted, and the silica was washed thoroughly with toluene, before transferring to a Soxhlet thimble and extracted with dichloromethane for 5 h, yielding SiO₂-silane.

4.2 | Preparation of SiO₂-acac

 SiO_2 -silane was then treated with acetyl acetone and K_2CO_3 in CH₃CN under reflux temperature for 24 h. After cooling, the precipitate was collected by filtration, and the white powder was transferred to a Soxhlet thimble and extracted with dichloromethane for 5 h, which gives pure SiO₂-acac support.

4.3 | Preparation of [${SiO_2}$ -(acac) $_3Fe^{III}$]Cl₃

Aqueous solution of $FeCl_3 \cdot 6H_2O$ was mixed with SiO₂-acac, prepared in the previous step at room temperature and obtained a dark orange precipitate. Then, the solid phase was filtered and washed thoroughly until no more iron leaching was observed. This dark orange solid was the resulting catalyst termed as [{SiO₂-(acac)}₃Fe^{III}]Cl₃.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supporting information of this article.

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AUTHOR CONTRIBUTIONS

Apurba Dutta: Conceptualization; data curation; formal analysis; methodology; software. Priyanka Trivedi: Data curation; formal analysis; methodology. Akshay Kulshrestha : Data curation; formal analysis; methodology. Arvind Kumar: Formal analysis. Vinita Chaturvedi: Formal analysis; methodology. Diganta Sarma: Conceptualization; supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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