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Aggregates of Perylene bisimide stabilized superparamagnetic Fe₃O₄ nanoparticles: An efficient catalyst for the preparation of propargylamines and quinolines *via* C-H activation

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Aggregates of perylene bisimide derivative 3 act as reactors and stabilizers for the preparation of superparamagnetic Fe₃O₄ nanoparticles (NPs) which exhibit excellent catalytic efficiency in i) A³-coupling and aldehyde free coupling reactions for the preparation of propargylamines ii) tandem intramolecular cyclization reaction for the synthesis of quinolines *via* C-H activation.

Metal catalysed functionalization of carbon-hydrogen (C-H) bond for the formation of carbon-carbon (C-C) bond is a fast, economical and eco-friendly approach for development of biologically active compounds and natural products.[1] Till now, many costly transition metal catalysts such as gold, silver, indium complexes have been extensively used in these C-H activation reactions.[2] Though these catalytic systems contribute towards atom economy yet utilization of costly metal as major component of catalytic system remains a big hurdle towards the development of greener and sustainable chemical industry. Thus, during the last few years, enormous efforts have been made to develop recoverable catalytic system having environmentally benign and less expensive metal ions as major component.[3] In this direction, a variety of recoverable hybrid catalytic systems having iron as one of the component have been developed for activation of C-H bonds, however, iron component in these systems has no practical contribution towards efficiency of catalytic system and its role is limited to make the separation easy.[3b] Thus, development of an economical, recoverable and efficient catalytic system for carrying out C-H activation under mild condition is still a challenge.

Recently, we developed supramolecular aggregates of a hexaphenylbenzene derivative which served as reactors and stabilizers for the preparation of ferromagnetic α-Fe₂O₃ nanoparticles (NPs). These *in situ* generated NPs exhibit high catalytic efficiency in Sonogashira cross coupling reactions[4]

where electron rich hexaphenylbenzene moiety played an important role in enhancing the efficiency of NPs by stabilizing the lower oxidation states of iron during the coupling reaction. In continuation of this work, we were then interested to develop supramolecular assemblies for the preparation of magnetic NPs which could be used for selective C-H functionalization. It has been reported that catalytic systems having stronger Lewis acidity exhibit better efficiency in C-H functionalization. Keeping this in mind, we envisaged that if we use an electron deficient perylene bisimide (PBI) as scaffold,[6] it may contribute in enhancing the Lewis acidity of *in situ* generated NPs which could then influence the catalytic efficiency of the system in the reactions involving C-H activation. Thus, we designed and synthesized PBI derivative **3** having imino and hydroxyl groups. The presence of imino and hydroxyl groups is expected to enhance the affinity of derivative **3** toward different metal ions. Interestingly, derivative **3** formed aggregates in mixed aqueous media and exhibited "turn-on" response towards Fe²⁺ ions and during the sensing process, these assemblies served as "not quenched" reactors as well as stabilizers for the generation of superparamagnetic Fe₃O₄ NPs. The preparation of stable Fe₃O₄ NPs is not a simple process as these NPs have strong tendency to form aggregates and undergo degradation when directly exposed to severe environmental conditions.[7] In this context, work being reported in this manuscript presents a facile and simple approach for the preparation of stable Fe₃O₄ NPs (Table S1, ESI†). To our pleasure, these *in situ* generated magnetic Fe₃O₄ NPs worked as recoverable catalyst in i) nearly solvent-free (100 μl of H₂O/THF) one pot reaction of aldehyde, alkyne, amine (A³-coupling) and aldehyde free coupling reaction for preparation of propargylamines ii) tandem reaction of aldehyde, alkyne, amine for preparation of quinoline derivatives. To the best of our knowledge, this is the first report where the same catalytic system has been used for the preparation of propargylamines and quinoline derivatives. The catalytic efficiency of the Fe₃O₄ NPs was found to be better than the other catalytic systems reported in the literature for the

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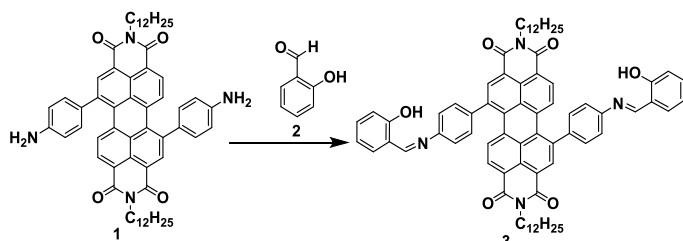
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preparation of propargylamines and quinoline derivatives *via* C-H activation (Table S2, S3 and S4, ESI†).

The condensation of derivative **1**[8] with β-hydroxy salicylaldehyde, **2** furnished derivative **3** in 88% yield (Scheme 1). The structure of derivative **3** was confirmed from its spectroscopic and analytical data (Fig. S32-S34, ESI†).

Scheme 1 Synthesis of PBI based derivative **3**; condition dry THF:MeOH (4:6), 80°C

The photophysical behaviour of derivative **3** in THF and in THF/H_2O mixture with varying amounts of water fraction was studied by UV-vis and fluorescence spectroscopy. It was observed that on increasing the water fraction upto 30%, the absorption and emission bands were red shifted (~5 nm) (Fig. S1-S2, ESI†). These studies indicate the formation of *J*-aggregates. The formation of *J*- aggregates was further confirmed by temperature dependent UV-vis and concentration dependent ^{1}H NMR studies (Fig. S3-S4, ESI†). The scanning electron microscopic (SEM) image of derivative **3** in H_2O/THF (3:7, v/v) showed the presence of spherical aggregates (Fig. S5, ESI†).

The presence of imine and hydroxyl moieties in the derivative **3** prompted us to investigate its sensing behaviour toward different metal ions (Cd^{2+}, Ba^{2+}, Hg^{2+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, Pd^{2+}, Ca^{2+}, Co^{2+}, Ag^+, Cr^{3+} and Al^{3+}) as their perchlorate/chloride/or both perchlorate and chloride salts by UV-Vis and fluorescence spectroscopy in H_2O/THF (3:7, v/v) (Fig. S6A-B, ESI†). On gradual addition of Fe^{2+} ions (0-35 equiv. within 270 minutes) to the solution of **3** (5 µM), a broad absorption band in the near infrared (NIR) region was observed which may be attributed to the intervalence charge transfer (IVCT) transition, thus, indicating the coexistence of Fe^{3+} and Fe^{2+} ions. The appearance of NIR band suggests the formation of Fe_3O_4 NPs[9] (Fig. S7, ESI†).

Upon addition of Fe^{2+} ions (0-35 equiv.) to the solution of derivative **3**, enhancement in the emission intensity of bands at 534 nm (Φ = 0.85) and 575 nm (Φ = 0.42) was observed (Fig. 1A). Further, the excitation spectrum of compound **3** in the presence of Fe^{2+} ions showed broad band in the near NIR region which suggests that Fe_3O_4 NPs are also contributing towards the emission enhancement at 534 nm (Fig. S8, ESI†). Thus, the system being reported here shows Fe_3O_4 NPs induced emission enhancement characteristics. The detection limit of aggregates of **3** for Fe^{2+} ions was found to be 28×10^{-8} M (Fig. S9, ESI†). We also tested the binding behaviour of aggregates of derivative **3** toward other metal ions such as Fe^{3+}, Cd^{2+}, Ba^{2+}, Hg^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Pd^{2+}, Co^{2+}, Ag^+, Cr^{3+}, and Al^{3+} ions but no significant change in fluorescence intensity was observed (Fig. S10A-B, ESI†). However, in case of Fe^{3+} ions 15% enhancement was observed. Thus, aggregates of derivative

3 are more selective towards Fe^{2+} ions as compared to Fe^{3+} ions. This selectivity may be due to more affinity of soft imine moiety towards relatively soft Fe^{2+} ions in comparison to hard Fe^{3+} ions.[10]
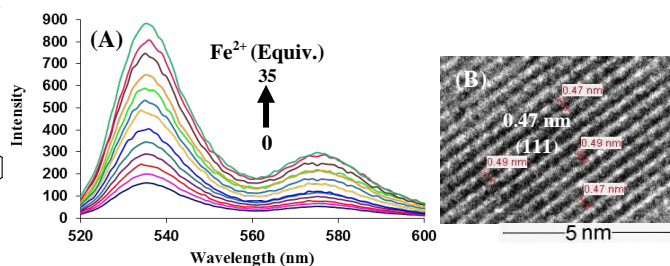

Fig. 1 (A) Fluorescence spectra of compound **3** (5 µM) showing the response to the Fe^{2+} ion (0-35 equiv.) in H_2O/THF (3:7, v/v) mixture buffered with HEPES; pH = 7.05, λ_{ex} = 485 nm. (B) HRTEM image of Fe_3O_4 NPs showing the interplanar spacing.

We also carried out time-resolved fluorescence studies of derivative **3** in the presence and absence of Fe^{2+} ions. In the absence of ferrous ions major fraction of molecules decay through faster pathway while in the presence of ferrous ions, major fraction of molecules decay through slower pathway which suggests the formation of ordered aggregated species (Fig. S11, Table S5, ESI†).

The transmission electron microscopic (TEM) images of derivative **3** in presence of Fe^{2+} ions revealed the presence of nanorods (S12A-B, ESI†). The selected area diffraction pattern[11] (Fig. S12C, ESI†) and high resolution transmission electron microscopic images (Fig. 1B and Fig. S12 D-G, ESI†) confirm the presence of crystalline nanorods of Fe_3O_4 NPs.[12] The powder X-ray diffraction and Raman-scattering studies of the precipitates showed the presence of diffraction peaks corresponding to Fe_3O_4 NPs[12] (Fig. S13 and S14, ESI†). The DLS studies showed the presence of NPs with average size of 20-40 nm (Fig. S15A, ESI†). The POM image of the derivative **3** containing Fe_3O_4 NPs showed ordered morphology (Fig. S15B, ESI†). The magnetic hysteresis measurements indicate the superparamagnetic nature of Fe_3O_4 nanorods (Fig. S16, ESI†).[13]

We believe that upon addition of ferrous ions to the solution of aggregates of derivative **3**, the ferrous ions interact with imine and hydroxyl moieties and get reduced to Fe (0) NPs which were further oxidized to stable Fe_3O_4 NPs by taking up oxygen from water. During this process aggregates of derivative **3** themselves get oxidised. The emission spectrum of derivative **3** obtained in the presence of Fe^{2+} ions has the contribution of oxidised species of aggregates of derivative **3**. To confirm the oxidation of aggregates of derivative **3**, we carried out their fluorescence studies in the presence of *tert*-butyl hydroperoxide, a strong oxidizing agent. The fluorescence spectrum exhibited the emission bands at 534 and 575 nm as observed in the presence of Fe^{2+} ions (Fig. S17, ESI†). This result supports our assumption regarding the formation of oxidised species of aggregates of derivative **3** during the reduction process. To prove the formation of Fe (0) NPs in the reaction, we studied the reaction between aggregates of derivative **3** and $FeCl_2$ under inert atmosphere by UV-Vis-NIR spectroscopy. The UV-Vis-NIR spectrum of the solution showed the presence of bands at
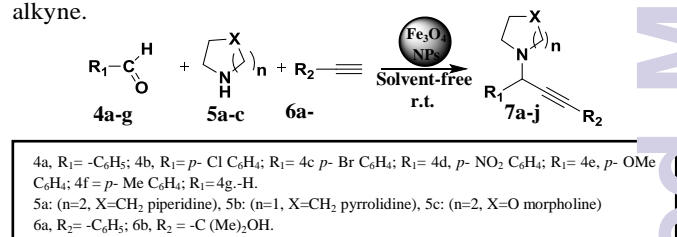
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262 and 357 nm corresponding to Fe (0) NPs[14] (Fig. S18, ESI†). After keeping the sample under air, absorption band corresponding to Fe_3O_4 NPs appeared. This study indicates the oxidation of Fe (0) NPs to Fe_3O_4 NPs. Further, we slowly evaporated the solution of aggregates of derivative **3** containing NPs. After two days, precipitates were observed which were filtered and washed with THF. The ^1H NMR of the residue so obtained after evaporation of THF solution showed the disappearance of signal corresponding to hydroxyl group with upfield shifting of signals corresponding to imino and aromatic protons (Fig. S19 and Table S6, ESI).

Further, we studied the effect of temperature, concentration of aggregates of derivative **3** and presence of additional reducing agent such as sodium hydroxide and methanol[15] on the rate of formation, size and shape of iron NPs. It was observed that at high temperature, higher concentration of aggregates of derivative **3** and in the presence of additional reducing agents, the NPs of bigger size were obtained but there was no change in the shape of NPs (Fig. S20-25, ESI†). These results indicate that under above mentioned conditions, Fe^{2+} ions undergo reduction at faster rate, hence, higher number of reduced NPs are generated which are responsible for furnishing nanorods of bigger size. Interestingly, on switching the solvent from H_2O/THF (3:7, v/v) to THF, the formation of Fe_3O_4 NPs was not observed (Fig. S26, ESI†). This study indicates the importance of aggregates in the formation of NPs.

Having done all this, we then planned to examine the catalytic efficiency of these *in situ* generated Fe_3O_4 NPs in A^3-coupling reaction *via* C-H activation for the preparation of propargylamine derivatives which are important building blocks for the preparation of various nitrogen-containing biologically active compounds and natural products.[16] To elaborate the catalytic efficiency of *in situ* generated Fe_3O_4 NPs, we chose three component coupling reaction between benzaldehyde (1 mmol), piperidine (1.2 mmol) and phenylacetylene (1.2 mmol) as the model reaction. We carried out A^3-coupling of model substrates by using 0.5 mol % of Fe_3O_4 NPs as catalyst in the presence of different solvents such as tetrahydrofuran, acetonitrile, ethanol, and toluene. Interestingly, in the presence of toluene and under solvent-free conditions, desired products were obtained in excellent yields (Table S7, ESI†). Thus, we carried out further reactions either under solvent-free conditions or in toluene. We also studied the model reaction using *in situ* generated nanorods of bigger size (80-100 nm) as catalyst. The reaction was complete in 16 h and desired product was obtained in 82 % yield (Table S8, ESI†). Thus, catalytic efficiency of *in situ* generated Fe_3O_4 nanorods depend on the size of nanorods. Further, we studied the model reaction in presence of bare Fe_3O_4 NPs.[17] The reaction was complete in 24 h to furnish the desired product in 40 % yield (Table S8, ESI†). This result highlights the importance of aggregates of derivative **3** in enhancing the catalytic efficiency of *in situ* generated NPs.

To expand the scope of this A^3-coupling, various aldehydes, alkynes and amines were used as substrates under the optimized reaction conditions (Scheme 2, Table S8). It was found that, aryl aldehydes bearing electron-withdrawing and electron-rich

groups and aliphatic aldehydes reacted smoothly to furnish desired products in excellent yields. The reaction condition also tolerant to nitro functionality. It has been reported that reaction involving nitro benzaldehyde requires much longer time and high temperature to form 1-(1-(4-Nitrophenyl)-3-phenylprop-2-ynyl)piperidine in lower yield.[18] Interestingly, A^3-coupling of 4-nitrobenzaldehyde, piperidine and phenylacetylene in toluene at $50^{\circ}C$ in the presence of Fe_3O_4 NPs went smoothly to give the desired product **(7d)** in moderate yield. Furthermore, the nature of amines affected the rate of A^3-coupling reactions in terms of yield and reaction time. The reactions involving pyrrolidine were faster and furnished the desired products in higher yields in comparison to those of piperidine and morpholine. Furthermore, we also studied the effect of aromatic *vs* aliphatic alkynes and it was found that aromatic alkyne is more reactive than aliphatic alkyne.

4a, R_1= -C_6H_5; 4b, R_1= *p*- Cl C_6H_4; R_1= 4c *p*- Br C_6H_4; R_1= 4d, *p*- NO_2 C_6H_4; R_1= 4e, *p*- OMe C_6H_4; 4f = *p*- Me C_6H_4; R_1=4g.-H.
5a: (n=2, X=CH_2 piperidine), 5b: (n=1, X=CH_2 pyrrolidine), 5c: (n=2, X=O morpholine)
6a, R_2= -C_6H_5; 6b, R_2 = -C $(Me)_2$OH.

Scheme 2. Catalytic activity of *in situ* generated Fe_3O_4 NPs in synthesis of propargylamine synthesis with reaction of various aldehyde, amines and alkynes

All the products were isolated and characterized by ^1H NMR spectroscopy (Fig. S35-S46, ESI). A tentative mechanism is proposed on the basis of our findings (Scheme S1, ESI†). Further, Fe_3O_4 NPs were separated from reaction mixture by simple magnetic decantation (Fig. S27, ESI†) and could be reused for nine times without significant loss of catalytic activity (Fig. S28, ESI†). The efficiency of the *in situ* generated Fe_3O_4 NPs was also tested for model reaction. When the amount of Fe_3O_4 NPs is 0.5 mole %, the yield is 89% in 3.5h against 0% when the reaction is conducted without Fe_3O_4 NPs (Table S9, ESI†). Such an extremely low quantity of catalyst has never been successfully utilized for A^3-coupling reactions at room temperature before the present study.

To evaluate the practical applicability of the *in situ* generated Fe_3O_4 NPs, we also carried out the A^3-coupling reaction of hexaphenylbenzene derivative **4h**, pyrrolidine **5b** and phenylacetylene **6a**. The reaction went smoothly to furnish the desired product **7k** in 58% yield (Scheme 3). This study demonstrates the practical utility of *in situ* generated Fe_3O_4 NPs for carrying out A^3-coupling reactions.
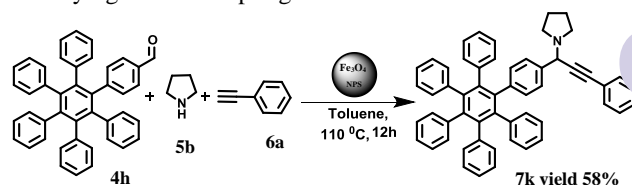
Scheme 3 Synthesis of compound **7k** by A^3-coupling reaction in the presence of *in situ* generated Fe_3O_4 NPs (1 mol%)

In the next part of our work, we planned to examine the catalytic efficiency of *in situ* generated Fe_3O_4 NPs in aldehyde free synthesis of propargylamines using aromatic amines. The

scope of reactions was further explored by using different *p*-substituted N, N-dimethyl aniline derivatives bearing electron donating or electron withdrawing groups (Scheme 4, Table S10). All the products were isolated and characterized by ^{1}H NMR spectroscopy (Fig. S47-S51, ESI†). Furthermore, the *in situ* generated Fe_3O_4 NPs could be reused upto six times in case of reaction involving synthesis of derivative **9a** without significant loss of their catalytic activity (Fig. S29, ESI†). A plausible mechanism for aldehyde free propargylamine synthesis[3b] is given in scheme S2, ESI†.
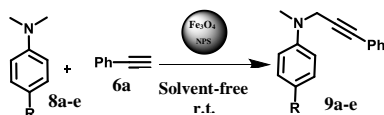
8a/9a, R = -H; 8b/9b, R = -Cl; 8c/9c, R = -Br; 8d/9d, R = -Me; 8e/9e, R = -OMe.

Scheme 4. Catalytic activity of *in situ* generated Fe_3O_4 NPs in synthesis of propargylamine (9a-e) under aldehyde free conditions.

Encouraged by these results, we planned to carry out tandem three component coupling/hydroarylation/dehydrogenation reactions of aldehyde, alkyne and aromatic amine for construction of quinoline derivatives. The quinoline derivatives are important due to their antibacterial, anti inflammatory, antifungal and analgesic properties.[19] Earlier, transition metal mediated synthesis of quinolines has been reported using various transition metals.[20] However, most of these systems suffer from prerequisite of strongly acidic or basic conditions and high reaction temperature. Interestingly, the reaction between benzaldehyde, aniline derivatives **(10a-e)** and phenylacetylene in the presence of *in situ* generated Fe_3O_4 NPs (200 μl, H_2O/THF, 3:7, v/v) in toluene at 110°C resulted in the formation of quinoline derivatives **(11a-e)** (Scheme 5, Table S11).
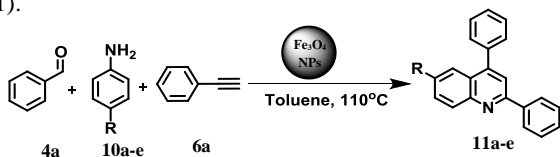
10a/11a, R = -H; 10b/11b, R = -Cl; 10c/11c, R = -Br; 10d/11d, R = -Me; 10e/11e, R = -OMe.

Scheme 5. Catalytic activity of *in situ* generated Fe_3O_4 NPs in quinoline synthesis

In the presence of both electron-withdrawing and electron-donating groups on aniline, the reactions proceeded smoothly to furnish the corresponding products in excellent yields. All the products were isolated and characterized by ^{1}H NMR spectroscopy (Fig. S52-S56, ESI†). The *in situ* generated Fe_3O_4 NPs could be magnetically separated and reused upto five times in case of **11a** without significant loss of their catalytic activity (Fig. S30, ESI†). Based upon these results, we propose that Fe_3O_4 NPs interact with alkyne which on reaction with *in situ* generated imine derivative (I) furnished propargylamine intermediate (II), Intramolecular hydroarylation followed by air oxidation of propargylamine intermediate (III) generated the quinoline derivative (Scheme S3, ESI†). We believe that formation of propargylamine intermediate and hydroarylation/oxidation reaction is a cooperative process. We investigated the reaction between benzaldehyde, 4-chloro-aniline **(10b)** and phenylacetylene **(6a).** We stopped the

reaction after 1.5 h and after usual workup, its ^{1}H NMR recorded (Fig. S31, ESI†). The ^{1}H NMR of the reaction mixture showed the signals corresponding to the quinoline derivative as well as propargylamine derivative which confirms the presence of propargylamine intermediate in the reaction involving synthesis of quinoline derivative **(11b)**.

In conclusion, we utilized aggregates of derivative **3** as reactors and stabilizers for the preparation of Fe_3O_4 NPs at room temperature. Further, *in situ* generated Fe_3O_4 NPs acted as efficient and reusable catalyst for i) one pot A^3-coupling reaction/aldehyde free coupling reaction for preparation of propargylamines ii) for preparation of quinoline derivatives *via* C-H activation.

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