Application of novel nanomagnetic metal–organic frameworks as a catalyst for the synthesis of new pyridines and 1,4-dihydropyridines via a cooperative vinylogous anomic based oxidation

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Herein, a new magnetic metal–organic frameworks based on Fe3O4 (NMMOFs) with porous and high surface area materials were synthesized. Then, NMMOFs were characterized by FT-IR, XRD, SEM, elemental mapping, energy dispersive X-ray (EDS), TG, DTG, VSM, and N2 adsorption–desorption isotherms (BET). Fe3O4@Co(BDC)-NH2 as a magnetic porous catalyst was applied for synthesis of novel fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties as suitable drug candidates under ultrasonic irradiation. The significant advantages of the presented methodology are mild, facile workup, high yields, short reaction times, high thermal stability, and reusability of the described NMMOFs catalyst.

Catalysis under ultrasonic irradiation has been widely applied for the preparation of organic compounds and catalysis1–3. On the other hand, hybrid organic–inorganic catalysts such as metal–organic frameworks (MOFs) as a new class of porous materials have high attention in chemical processes. Porous and magnetic materials have been widely used in biotechnology, magnetic resonance imaging (MRI), catalysis, adsorption, gas separation, and purification, optics, drug delivery, etc.4–6. However, metal–organic frameworks (MOFs) are a widespread strategy for the expansion of new porous materials to reach with the higher surface area. By selecting a suitable plan, reactants and reaction conditions can be correctly controlled by the porosity and structure of desired materials7–13. Magnetic catalysts have been used for the synthesis of a good range of pharmaceutical and chemical compounds, due to their easy removal and convenient separation14–16. The reported catalysts can be easily isolated from the reaction mixture with an external magnetic field17–19. Therefore magnetic metal–organic frameworks (MMOFs) have been used for various purposes due to their exciting properties20–23. The chemistry of magnetic metal–organic frameworks and their corresponding applications comprehensively have been reviewed27–29.

Fused N-heterocycles compounds with pyrazole and pyridines have shown a broad spectrum of biological and agricultural activities such as antitumor, cardiotonic hepatoprotective, antihypertensive, antibronchitic, and antifungal activity30–33. Therefore, research and develop the new strategy are necessary for the synthesis of pyridines with pyrazole moieties. Pyridine derivatives are the central core of natural products such as NADP, clivimine, kedarcidin, and promothiocin A (Fig. 1)34.

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Synthesis of composites of MOF and nano-magnetic Fe₃O₄ is our great research interest. With this aim, we have decided to synthesize nano-magnetic metal–organic frameworks Fe₃O₄@Co(BDC)-NH₂ as a porous and magnetic catalyst under ultrasonic irradiation condition. This nanomagnetic metal–organic frameworks (NMMOFs) was applied in the synthesis of novel fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties by using the corresponding precursors in DMF (5 mL) as solvent under ultrasonic irradiation (Scheme 1).

**Figure 1.** Structure of pyridine as natural products.

**Scheme 1.** Preparation of novel fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties by using Fe₃O₄@Co(BDC)-NH₂ as the catalyst.
Experimental

Materials and methods. All chemicals were purchased from Merck Chemical Company. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. To scrutinize the progress of the reaction silica gel SIL G/UV 254 plates were used. From the model of the BRUKER Ultra shield, NMR spectrometer (δ in ppm) was recorded 1H NMR (400 MHz) and 13C NMR (100 MHz). Recorded on a Büchi B-545 apparatus in open capillary tubes were melting points. The PerkinElmer PE-1600-FTIR device was registered for the infrared spectra of compounds. SEM was performed using a scanning electron microscope for field publishing made by TE-SCAN. Thermal gravimetry (TG), differential thermal gravimetric (DTG) and differential thermal (DTA) were analyzed by a Perkin Elmer (Model: Pyris 1). The analysis 25–1000 °C, temperature increase rate of 10 °C min⁻¹.

General procedure for the synthesis of Fe₃O₄@CH₂CO₂H. Fe₃O₄ was prepared according to the previously reported literature³⁵,³⁶. Then, in a 25 mL round-bottomed flask, a mixture of Fe₃O₄ (1 g), HSCH₂CO₂H (10.0 mmol, 1.38 g), and EtOH (30 mL) were added and refluxed for 24 h. After this time, a dark brown precipitate was appeared, which it is isolated by using a magnet. The obtained Fe₃O₄@CH₂CO₂H (1.95 g) was dried under vacuum²³.

General procedure for the synthesis of Fe₃O₄@Co(BDC)-NH₂. At first, a solution of 45.0 mM of Co(NO₃)₂·6H₂O (2.34 g in 180 mL DMF) (solution I) and 45.0 mM of H₂BDC-NH₂ (1.46 g in 180 mL DMF) (solution II) were prepared respectively. In a 25 mL glass vials, a mixture of Fe₃O₄@CH₂CO₂H (0.5 g) and 10 mL of solution I were sonicated for 20 min. Then, this mixture was separated by a permanent magnet and washed with DMF as step I. Then, a mixture of step I and 10 mL of solution II were sonicated for 45 min. The produced solid was separated by a permanent magnet and washed with EtOH as step II. In continued, two strategies (a mixture of step I and step II) were repeated 18 times, respectively. Finally, Fe₃O₄@Co(BDC)-NH₂ (0.8 g) was dried under vacuum for 2 h (Scheme 2).

General procedure for the synthesis of novel fused pyridines and 1,4-dihydropyridines. In a 10 mL round-bottomed, a mixture of aldehyde (1.0 mmol), pyrimidine (1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione or pyrimidine-2,4,6(1H,3H,5H)-trione) and pyrazole-5-amine (3-methyl-1H-pyrazole-5-amine or 3-methyl-1-phenyl-1H-pyrazole-5-amine or 3-methyl-1-phenyl-1H-pyrazole-5-amine) derivatives] and Fe₃O₄@Co(BDC)-NH₂ (10 mg) as a catalyst were mixed in DMF (5 mL) as solvent under ultrasonic irradiation. After completion of the reaction (monitor by TLC n-hexane/ethyl acetate; 4:6), the catalyst was separated by an external magnet. Finally, the mixture was poured into H₂O and filtered off its precipitate. The obtained residue was washed with warm ethanol and dried at 100 °C (Scheme 1).

Result and discussion

The systematic study of the stereoelectronic effects in target molecules, allows for the design of synthetic strategies based on a numerically driven stereoselective reactions, or highly biased equilibria among isomeric products. To the best of our knowledge, many biological processes involve the oxidation–reduction of substrates by NAD+/NADH, respectively³⁷–⁴¹. The key feature of the oxidation mechanism is hydride transfer from carbon via stereoelectronic interactions. Thus the development of stereoelectronic effects leads to knowledge-based designing
of biomimetic reactions. The obtained results from this research will be supporting the idea of rational designs, syntheses, and applications of tasked-specific catalysts and molecules for the development of stereoelectronic effects in the course of organic synthesis. With this aim, a nanomagnetic metal–organic frameworks (NMMOFs) was designed, characterized and applied for the preparation of pyridines fused with pyrazole and pyrimidine under ultrasonic irradiation.

At first, nanomagnetic metal–organic frameworks (NMMOFs) were synthesized (Scheme 2). Its schematic synthesis is showed in Fig. 2. The synthesized Fe₃O₄@Co(BDC)-NH₂ fully characterized by applying FT-IR, XRD, SEM, elemental mapping, energy dispersive X-ray (EDS), TG, DTG, VSM and N₂ adsorption–desorption isotherms (BET).

FT-IR spectrum of H₂BDC-NH₂, Fe₃O₄, Fe₃O₄@CH₂CO₂H, and Fe₃O₄@Co(BDC)-NH₂ are shown in Figure S1 (see supporting information). The absorption bands at 670 cm⁻¹ linked to the stretching vibrational modes of Fe–O groups in Fe₃O₄. The absorption bands at 1741, 2924, and 3426 cm⁻¹ related to C=O, C–H and, O–H stretching respectively in Fe₃O₄@CH₂CO₂H. Also, the absorption bands at 633 cm⁻¹ and 3318–3448 cm⁻¹ are related to Co–O and N–H stretching respectively, of Fe₃O₄@Co(BDC)-NH₂. Finally, the differences between H₂BC-NH₂, Fe₃O₄, Fe₃O₄@CH₂CO₂H, and Fe₃O₄@Co(BDC)-NH₂ in the FT-IR spectrum were confirmed the synthesis of Fe₃O₄@Co(BDC)-NH₂.

The particle size and shape, as well as the morphology of Fe₃O₄@CH₂CO₂H, Fe₃O₄, MOF-Co(BDC)-NH₂, Co(NO₃)₂·6H₂O and Fe₃O₄@Co(BDC)-NH₂ were studied by XRD (Fig. 3), and SEM (Fig. 4). The comparison XRD pattern of JCPDS (red line), Fe₃O₄ (black line), Co(NO₃)₂·6H₂O (purple line), Simulated XRD (orange line), MOF-Co(BDC)-NH₂ (green line), Fe₃O₄@CH₂CO₂H (brown line) and Fe₃O₄@Co(BDC)-NH₂ (blue line) is assembled according to the literature survey at the range of 5°–80° in Fig. 342. The phase of Co oxide and Fe₃O₄ in Fe₃O₄@Co(BDC)-NH₂ as standard brown line (ICDD Card: 80-1540) of Co and pink standard line (JCP2: 75-449) of Fe₃O₄ in the standard references. Also, Peaks of Fe₃O₄@Co(BDC)-NH₂ exhibited 2θ = 18.3°, 30.2°, 35.6°, 43.3°, 53.6°, 57.3°, 62.8° and 74.2° corresponding to diffraction lines (111), (220), (311), (400), (422), (511), (440) and (533). Then, the averaged interlunar distance and sizes of crystal were calculated by the Scherer equation and Bragg equation, which are determined 0.67 nm (single peak at 12.8 and 17.5–37.5 nm range (Table S1 see in supporting information)43,44.

For comparison, structure and elements in the synthesis of step by step Fe₃O₄@CH₂CO₂H, Fe₃O₄, MOF-Co(BDC)-NH₂ were also studied with energy dispersive X-ray analysis (EDX) analysis (Figure S2 see supporting information). The structures of Fe₃O₄@Co(BDC)-NH₂ and Fe₃O₄@CH₂CO₂H were verified with existence of Fe, Co, N, C, O and Fe and C, O, and S atoms respectively 45. Then, elements dispersed over the surface of the catalyst, and step Fe₃O₄@Co(BDC)-NH₂ was checked out by SEM-elemental mapping (Figure S3 see supporting information). The images in Figure S3 shows that all kinds of elements are well dispersed over the surface of Fe₃O₄@Co(BDC)-NH₂. The difference between EDX analysis and SEM-elemental mapping is confirmed by the structure of Fe₃O₄@Co(BDC)-NH₂.

In another investigation, the particle size and shape, as well as the morphology of Fe₃O₄@Co(BDC)-NH₂ were examined by scanning electron microscope (SEM) (Fig. 4). As shown in Fig. 4, nano-spherical particles of the nanomagnetic metal–organic frameworks (NMMOFs) are in the nanoscale, as the particles are quite overlapped with different crystallite size as observed in SEM Transmission electron microscopy (TEM) images of Fe₃O₄@Co(BDC)-NH₂ catalyst reveal that the particles shape is spherical and the particle size is up to 50 nm (Fig. 5).
Figure 3. Comparison XRD pattern of JCPDS (red line), Fe₃O₄ (black line), Co(NO₃)₂·6H₂O (purple line), Simulated XRD (orange line), MOF-Co(BDC)-NH₂ (green line), Fe₃O₄@CH₂CO₂H (brown line) and Fe₃O₄@Co(BDC)-NH₂ (blue line).

Figure 4. Scanning electron microscope (SEM) images of Fe₃O₄@Co(BDC)-NH₂.
The magnetic measurement of Fe₃O₄, Fe₃O₄@CH₂CO₂H, and Fe₃O₄@Co(BDC)-NH₂ are shown in Fig. 6. Based on Fig. 6, the vibrating sample magnetometer (VSM) of Fe₃O₄, Fe₃O₄@CH₂CO₂H, and Fe₃O₄@Co(BDC)-NH₂ were examined and reduced from 64.4, 60.1 up to 54.3 μg⁻¹ respectively. Therefore, these decreases are the result of coating with its corresponding layers.

In another investigation, the structural and thermal stability of Fe₃O₄@Co(BDC)-NH₂ was also determined using the technique of the thermal gravimetric (TG), derivative thermal gravimetric (DTG), as well as the differential thermal analysis (DTA) (Figure S4 see in supporting information). First stage weight loss is about 100 °C, associated with the removal of possible solvents (organic and water), which was used in the course of catalyst preparation. Then, twice a step of weight loss has occurred at about 300 °C, which is the onset of the structural degradation of the catalyst.

For the determination of surface structural parameters, the N₂ adsorption/desorption technique was used. The results of N₂ adsorption/desorption were plotted in Fig. 7. The obtained surface area based on BET isotherm is 22.35 m² g⁻¹. The total pore volume of the catalyst is 0.02 cm³ g⁻¹. Also, for studying the textural properties of MOF-Co(BDC)-NH₂, the N₂ adsorption–desorption isotherms were used (Fig. 7). The adsorption isotherm is type III and the appearance of hysteresis loop shows the presence of mesopores in the sample. The calculated surface areas based on BET equation and total pore volumes are 86 m² g⁻¹ and 0.36 cm³ g⁻¹ respectively. The pore size distribution of MOF-Co(BDC)-NH₂ based on BJH method is shown (Figure S5 see in supporting information).
anti-bonding orbital of C–H bond ($\pi_{\text{C–H}}$) interacts through C–C double bonds with a vacant lone pair electrons of N atoms of 1,4-dihydropyridine ($H(3\text{-methyl-1H(1,3-dimethylpyrimidine-2,4,6(1\text{-iso-trephetaldehyde, tris-aldehyde, bearing electron-donating and electron-withdrawing groups), pyrimidine novel biological and pharmacological candidate compounds using various aromatic aldehydes (trephetaldehyde, benzaldehyde, 3-methyl-1-phenyl-1,8-dihydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione and 3-methyl-4-phenyl-1,4,8,9-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione. The above mentioned products were obtained by reaction of 4-nitro benzaldehyde (1.0 mmol, 0.151 g), 3-methyl-1-phenyl-1H-pyrazole-5-amine (1.0 mmol, 0.174 g) and pyrimidine-2,4,6(1H,3H,5H)-trione (1.0 mmol, 0.128 g) as a model for the optimization the reaction conditions. The optimized data is listed in Table 1. As shown in Table 1, the best of choice for the synthesis of 3-methyl-1,4-diphenyl-1,8-dihydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione was achieved in the presence of 10 mg Fe$_3$O$_4$@Co(BDC)-NH$_2$ in DMF (5 mL) as solvent under ultrasonic irradiation (entry 4, Table 1). The model reaction was also studied by using several solvents such as H$_2$O, CH$_3$CN, n-hexane, CHCl$_3$, MeOH, EtOH, CH$_2$Cl$_2$, EtOAc (5 mL) and solvent-free condition in the presence of 10 mg Fe$_3$O$_4$@Co(BDC)-NH$_2$. The results of the reaction did not improve (Table 1, entries 6–13). Also, the model reaction was also studied in the magnetic stirrer condition at room temperature under the solvent-free reaction (Table 1, entry 14).

After optimizing the reaction conditions, Fe$_3$O$_4$@Co(BDC)-NH$_2$ (10 mg) is applied to synthesis a good range of novel biological and pharmacological candidate compounds using various aromatic aldehydes (trephetaldehyde, iso-trephaldehyde, tri-aldehyde, bearing electron-donating and electron-withdrawing groups), pyrimidine (1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione, pyrimidine-2,4,6(1H,3H,5H)-trione) and pyrazole-5-amine (3-methyl-1H-pyrazole-5-amine, 3-methyl-1-phenyl-1H-pyrazole-5-amine) derivatives. As shown in Table 2, the obtained results indicated that Fe$_3$O$_4$@Co(BDC)-NH$_2$ is appropriate for the preparation of target molecules in high to excellent yields (65–90%) with in relatively short reaction times (20–40 min). Furthermore, the model reaction is tested by the reaction of 3-methyl-1H-pyrazole-5-amine, and 3-methyl-1H-pyrazole-5-amine to give a mixture of the corresponding pyridine and 1,4-dihydropyridine respectively.

In the proposed mechanism, the aldehyde is activated by Fe$_3$O$_4$@Co(BDC)-NH$_2$. In the initial step, intermediate (I) is produced by the reaction of pyrimidine (R$_1$ = H, Me) and activated aldehyde. In the next step, intermediate (II) is prepared with losing one molecule of H$_2$O. In the third step, pyrazole-5-amine (R$_1$ = H, Ph) derivatives react with intermediate (II) to gives intermediate (IV) after tautomerization. Then, intermediate (IV) gives intermediate (V) after intramolecular cyclization and losing another molecule of H$_2$O. In the last step, the lone pair electrons of N atoms of 1,4-dihydropyridine (VI) interacts through C–C double bonds with a vacant anti-bonding orbital of C–H bond ($\pi_{\text{C–H}}$ $\rightarrow \sigma_{\text{C–H}}^*$ and $\pi_{\text{C–C}}$ $\rightarrow \sigma_{\text{C–C}}$) and weaken it, so that is favoring for hydride transfer and H$_2$ releasing from intermediate VI to generate its corresponding pyridinium salt. The achieved data from the optimization of described reaction under argon and nitrogen atmospheres verified our suggestion for oxidation and aromatization of intermediate VI. On the other hand, 1,4-dihydropyridine (VI) is converted to its corresponding pyridinium intermediate (VII), via a cooperative vinylous anomic base oxidation and releasing a hydrogen molecule (–H$_2$)47–55. Finally, the desired pyridine fused with pyrazole and pyrimidine moiety (B) is obtained via removing a proton from the pyridinium intermediate (VII). When, 3-methyl-1H-pyrazole-5-amine was used instead of 3-methyl-1-phenyl-1H-pyrazole-5-amine after intramolecular cyclization and losing a molecule of water, intermediate (VI) is converted to product (A) (Scheme 3). Interestingly, the 1,4-dihydropyridines (A) did not convert to their corresponding pyridines.

The reusability of Fe$_3$O$_4$@Co(BDC)-NH$_2$ was also investigated. The reaction of 4-nitro benzaldehyde (1.0 mmol, 0.151 g), 3-methyl-1-phenyl-1H-pyrazole-5-amine (1.0 mmol, 0.174 g) and pyrimidine-2,4,6(1H,3H,5H)-trione (1.0 mmol, 0.128 g) was selected as a model reaction under ultrasonic irradiation. The

Figure 7. Nitrogen adsorption–desorption isotherm (BET) of Fe$_3$O$_4$@Co(BDC)-NH$_2$ and MOF-Co(BDC)-NH$_2$. Information}. This plot clearly shows presence of micropores (size < 2 nm) and mesopores (2 < size < 50 nm) in the sample, however the micropores are more abundant.
nanomagnetic metal–organic frameworks (NMMOFs) catalyst was separated by an external magnet, washed with DMF and dried. The results indicated that the catalyst could be utilized for nine runs without any significant loss of its initial catalytic activity, which can be ascribed to the high stability of the synthesized catalyst (Fig. 8). Then, the reused catalyst was also characterized by FT-IR spectrum (Figure S6 see supporting information), N2 adsorption–desorption isotherm (BET) and scanning electron microscope (SEM) images. The obtained spectra are as same as the corresponding spectra of fresh catalyst (Figures S7, S8 see supporting information). Furthermore, to compare the performance of nanomagnetic metal–organic frameworks (NMMOFs) catalyst for the synthesis of desired fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties via a cooperative vinylogous anomeric based oxidation, we have used various organic and inorganic acid catalysts for condensation reaction between 4-nitro benzaldehyde (1.0 mmol, 0.151 g), 3-methyl-1-phenyl-1H-pyrazole-5-amine (1.0 mmol, 0.174 g) and pyrimidine-2,4,6(1H,3H,5H)-trione (1.0 mmol, 0.128 g) and 4-nitrobenzaldehyde (1.0 mmol, 0.151 g).

### Conclusion

In summary, a novel core–shell nanomagnetic metal–organic frameworks Fe3O4@Co(BDC)-NH2 as a new catalyst was prepared and fully characterized. This catalyst was applied for the synthesis of a range of novel fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties with good yields via a cooperative vinylogous anomeric based oxidation mechanism under ultrasonic irradiation. The obtained biological-based compounds are suitable candidates for biological studies. The described catalyst is reusable and easily separated by an external magnet.

### Table 1. Effect of different amounts of catalysts and solvent (5 mL) in the synthesis of novel fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties by using the corresponding precursors under ultrasonic irradiation. Reaction conditions: 3-methyl-1-phenyl-1H-pyrazole-5-amine (1.0 mmol, 0.174 g), pyrimidine-2,4,6(1H,3H,5H)-trione (1.0 mmol, 0.128 g) and 4-nitrobenzaldehyde (1.0 mmol, 0.151 g).

| Entry | Solvent | Cat. (mg) | Sonication (min) | Yield (%) |
|-------|---------|-----------|------------------|-----------|
| 1     | DMF     | –         | 120              | Trace     |
| 2     | DMF     | 5         | 75               | 25        |
| 3     | DMF     | 7.5       | 60               | 45        |
| 4     | DMF     | 10        | 50               | 72        |
| 5     | DMF     | 15        | 50               | 72        |
| 6     | H2O     | 10        | 60               | 35        |
| 7     | n-Hexane| 10        | 60               | 25        |
| 8     | EtOH    | 10        | 60               | Trace     |
| 9     | CH2Cl2  | 10        | 60               | Trace     |
| 10    | CHCl3   | 10        | 60               | 28        |
| 11    | EtOAc   | 10        | 60               | 46        |
| 12    | CH3CN   | 10        | 60               | 54        |
| 13    | MeOH    | 10        | 60               | Trace     |
| 14    | –       | 10        | 60               | 15        |
Table 2. (continued)
Table 2. Synthesis of (a) 3-methyl-1,4-diphenyl-1,8-dihydro-5H-pyrazolo[4,3′,5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione derivatives, (b) 3-Methyl-4-phenyl-1,4,8,9-tetrahydro-5H-pyrazolo[4,3′,5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione derivatives, (c) Bis and tris 3-methyl-1,4-diphenyl-1,8-dihydro-5H-pyrazolo[4,3′,5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione derivatives using Fe₃O₄@Co(BDC)-NH₂ under ultrasonic irradiation.
Scheme 3. Proposed mechanism for the preparation of novel fused pyridines and 1,4-dihydropyridines with pyrazole and pyrimidine moieties via a cooperative vinylogous anomeric based oxidation.
Figure 8. Recyclability of Fe₃O₄@Co(BDC)-NH₂ as a catalyst in the synthesis pyrazolo[4’,3’,5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione.

Table 3. Synthesis of pyrazolo[4’,3’,5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione in the presence of various catalysts under ultrasonic irradiation. *This work.

| Entry | Catalyst                                    | (mol%) | Time (min) | Yield (%) |
|-------|---------------------------------------------|--------|------------|-----------|
| 1     | FeCl₃                                        | 10     | 120        | 25        |
| 2     | [PVI-SO₃H]FeCl₅                              | 10     | 120        | 48        |
| 3     | Fe₂O₃                                       | 10 mg  | 120        | Trace     |
| 4     | NH₄NO₃                                     | 10     | 120        | Trace     |
| 5     | SSA²⁶                                     | 10 mg  | 120        | 35        |
| 6     | Nano-SB-[PSIM]Cl²⁶                         | 10 mg  | 120        | Trace     |
| 7     | NaHSO₄                                     | 10     | 120        | –         |
| 8     | GTBSA²⁶                                   | 10     | 120        | 55        |
| 9     | SBA-15(CH₃)₂[N(CH₂PO₃H)₂]²¹                  | 10 mg  | 120        | 35        |
| 10    | [Py-SO₃H]Cl²⁸                               | 10     | 120        | 35        |
| 11    | p-TSA                                      | 10     | 120        | 25        |
| 12    | Et₃N                                       | 10     | 120        | –         |
| 13    | MIL-100(Cr)/NH₂EtN(CH₂PO₃H)₂²¹             | 10 mg  | 120        | 63        |
| 14    | APVPB²⁸                                    | 10 mg  | 120        | 40        |
| 15    | MHSMPA²⁸                                   | 10     | 120        | 55        |
| 16    | GTMPA²⁸                                    | 10     | 120        | 40        |
| 17    | Co(NO₃)₆·6H₂O                              | 10     | 120        | 36        |
| 18    | H₂BDC-NH₂                                  | 10     | 120        | 42        |
| 19    | Fe₂O₄@Co(BDC)-NH₂                          | 10 mg  | 50         | 72*       |

References
1. Amaniampong, P. N. & Jerome, F. Catalysis under ultrasonic irradiation: A sound synergy. Curr. Opin. Chem. 22, 7–12 (2020).
2. Amaro-Gahete, J. et al. Fast ultrasound-assisted synthesis of highly crystalline MIL-88A particles and their application as ethylene adsorbents. Ultrason. Sonochem. 50, 59–66 (2019).
3. Bigdeli, F., Rouhani, F., Morsali, A. & Ramazani, A. Ultrasonic-assisted synthesis of the nanostructures of a Co(II) metal organic framework as a highly sensitive fluorescence probe of phenol derivatives. Ultrason. Sonochem. 62, 104862 (2020).
4. Ke, F. et al. Facile fabrication of magnetic metal–organic framework nanocomposites for potential targeted drug delivery. J. Mater. Chem. 21, 3843–3848 (2011).

5. Li, J. R., Kupper, R. J. & Zhou, H. C. Selective gas adsorption and separation in metal–organic frameworks. Chem. Soc. Rev. 38, 1477–1504 (2009).

6. Ricco, R., Mallatti, L., Takahashi, M., Hill, A. J. & Falcaro, P. Applications of magnetic metal–organic framework composites. J. Mater. Chem. A 4, 13033–13045 (2013).

7. Hu, X. et al. Magnetic metal–organic frameworks containing abundant carboxyl groups for highly effective enrichment of glycoproteins in breast cancer serum. Talanta 204, 446–454 (2019).

8. Rostamnia, S., Alamgholiloo, H. & Jafari, M. Ethylene diamine post-synthesis modification on open metal site Cr-MOF to access efficient bifunctional catalyst for the Hantzsch condensation reaction. Appl. Organomet. Chem. 32, e4370 (2018).

9. Alamgholiloo, H., Rostamnia, S., Hassankhani, A. & Banuaei, R. Synthesis of a zeoliticimidazolate-zinc metal–organic framework and the combination of its catalytic properties with 2, 2, 2-trifluoroethanol for N-formylation. Synlett 29, 1593–1598 (2018).

10. Alamgholiloo, H. et al. Stepwise post-modification immobilization of palladium Schiff-base complex on to the OMS-Cu (BDC) metal–organic framework for Mizoroki–Heck cross-coupling reaction. Appl. Organomet. Chem. 32, e4539 (2018).

11. Rostamnia, S. & Jafari, M. Metal–organic framework of amine-MIL-53(Al) as active and reusable liquid-phase reaction inducer for multicomponent condensation of Ugi-type reactions. Appl. Organomet. Chem. 3, 1–6 (2016).

12. Rostamnia, S. & Mohsenzad, F. Nanochitecturing of open metal sal Cr-MOFs for oxodiperoxoy molybdenum complexes [MoO(O2)2@En/MIL-100(Cr)] as promising and bifunctional catalyst for selective thetaoxygen. Mol. Catal. 445, 12–20 (2018).

13. Hu, M. L. et al. Taking organic reactions over metal–organic frameworks as heterogeneous catalysis. Microporous Mesoporous Mater. 256, 111–127 (2018).

14. Chen, M. N., Mo, L. P., Cui, Z. S. & Zhang, Z. H. Magnetic nanocatalysts: Synthesis and application in multicomponent reactions. Curr. Opin. Chem. 15, 27–37 (2019).

15. Bai, S. et al. Magnetic biochar catalysts from anaerobic digested sludge: Production, application and environment impact. Environ. Int. 126, 302–308 (2019).

16. Maleki, B., Reiser, O., Esmaeilezhad, E. & Choi, H. J. SO,H-dendrimer functionalized magnetic nanoparticles (Fe3O4@DINH(CH3)2SO2H): Synthesis, characterization and its application as a novel and heterogeneous catalyst for the one-pot synthesis of polyfunctionalizedpyrazin and polyhydroquinolines. Polyhedron 162, 129–141 (2019).

17. Koukabi, N. et al. A magnetic particle-supported sulfonic acid catalyst: Tuning catalytic activity between homogeneous and heterogeneous catalysis. Adv. Synth. Catal. 354, 2001–2008 (2012).

18. Abu-Dief, A. M. & Abdel-Fatah, S. M. Development and functionalization of magnetic nanoparticles as powerful and green catalysts for organic synthesis. Bent Seuf Univ. J. Basic Appl. Sci. 7, 55–67 (2018).

19. Yao, Y. et al. Magnetic recoverable MnFe2O4 and MnFe2O3/graphene hybrid as heterogeneous catalysts of peroxymonosulfate activation for efficient degradation of aqueous organic pollutants. J. Hazard. Mater. 260, 67–70 (2014).

20. Lu, N., He, X., Wang, T., Liu, S. & Hou, X. Magnetic solid-phase extraction using MIL-101(Cr)-based composite dispersed with liquid-liquid microextraction based on solidification of a floating organic droplet for the determination of pyrethroids in environmental water and tea samples. Microchem. J. 137, 449–455 (2018).

21. Gao, G., Di, J. Q., Zhang, H. Y., Mo, L. P. & Zhang, Z. H. A magnetic metal organic framework material as a highly efficient and recyclable liquid catalyst for synthesis of cyclohexene derivatives. J. Catal. https://doi.org/10.1016/j.jcat.2020.04.013 (2020).

22. Safari, M., Yamini, Y., Massomi, M. Y. & Morsali, A. Magnetic metal–organic frameworks for the extraction of trace amounts of heavy metal ions prior to their determination by ICP-AES. Microchem. Acta 184, 1555–1564 (2017).

23. Yamini, Y., Safari, M., Morsali, A. & Safarifard, V. Magnetic frame work composite as an efficient sorbent for magnetic solid-phase extraction of plasticizer compounds. J. Chromatogr. A 1570, 38–46 (2018).

24. Zhang, X. et al. Thermal conversion of an Fe3O4@gemel–organic framework: A new method for an efficient Fe-Co/nanoporous carbon microwave absorbing material. Nanoscale 7, 12932–12942 (2015).

25. Huan, B. et al. Direct epitaxial synthesis of magnetic Fe3O4@UCO-66 composite for efficient removal of arsenate from water. Microporous Mesoporous Mater. 276, 68–75 (2019).

26. Fan, L. et al. Fe-MOF derived guajube pit like Fe3O4/C composite as sulfur host for lithium-sulfur battery. Electrochem. Acta 295, 444–451 (2019).

27. Gao, Y., Liu, G., Gao, M., Huang, X. & Xu, D. Recent advances and applications of magnetic metal–organic frameworks in adsorption and enrichment removal of food and environmental pollutants. Crit. Rev. Anal. Chem. https://doi.org/10.1080/10403739.2019.1653166 (2019).

28. Nadar, S. S. & Rathod, V. K. Magnetic-metal organic framework (magnetic-MOF): A novel platform for enzyme immobilization and nanozyme applications. Int. J. Biol. Macromol. 120, 2293–2302 (2018).

29. Wang, R., Zhang, C., Wang, S. & Zhuy, S. Synthesis and application of magnetic metal–organic frameworks. Prog. Chem. 27, 945–952 (2015).

30. Grivsky, E. M., Lee, S., Sigel, C. W., Duch, D. S. & Nichol, C. A. Synthesis and antitumor activity of 2, 4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d] pyrimidine. J. Med. Chem. 33, 327–329 (1990).

31. Deb, M. L. & Bhuyan, P. J. Synthesis of novel classes of pyrido[2,3-d]-pyrimidines, Pyrano[2,3-d][pyrimidine, and pyridines. Synth. Commun. 36, 3085–3090 (2006).

32. Devi, I., Borah, H. N. & Bhuyan, P. J. Studies on uracils: A facile one-pot synthesis of oxazino[4,5-d]-pyrpyrido[2,3-d]-pyrimidines using microwave irradiation in the solid state. Tetrahedron Lett. 45, 2405–2408 (2004).

33. Lee, H. M., Chiu, P. L., Hu, C. H., Lai, C. L. & Chou, Y. C. Synthesis and structural characterization of metal complexes based on pyrazole/imidazol chloride. J. Organomet. Chem. 690, 403–414 (2005).

34. Allais, C., Grassot, J. M., Rodriguez, J. & Constantieux, T. Metal-free multicomponent synthesis of pyridines. Chem. Rev. 114, 10829–10868 (2014).

35. Tabacchi, G., Vanoni, M. A., Gamba, A. & Fois, E. Does negative hyperconjugation assist enzymatic dehydrogenations. Chem. Phys. Chem. 8, 1283–1288 (2007).

36. Hamasaka, G., Tsuji, H. & Uozumi, Y. Organoborane-catalyzed hydrogenation of unactivated aldehydes with a Hantzsch ester as a synthetic NAD(P)H analogue. Synlett 26, 2037–2041 (2015).

37. He, T. et al. Base-promoted cascade approach to the preparation of reduced knoovegalid adducts using hantsch esters as reducing agent in water. Synlett 27, 1864–1869 (2016).

38. Bai, C. R., Wang, N. X., Xing, Y. & Lan, X. W. Progress on chiral NAD(P)H model compounds. Synlett 13, 402–414 (2017).

39. Zhao, X., Xiao, J. & Tang, W. Enantioselective reduction of 3-substituted quinolines with a cyclopentadiene-based chiral Bronsted acid. Synthesis 49, 3157–3164 (2017).

40. Moradi, S. et al. An efficient catalytic method for the synthesis of pyridine[2,3-d]-pyrimidines as biologically drug candidates by using novel magnetic nanoparticles as a reusable catalyst. Appl. Organomet. Chem. 32, e4043 (2017).

41. Rajabi-Salek, M., Zolfegh, M. A. & Zarei, M. Synthesis of a novel DABCO derived magnetic nanoparticles catalyzed with sulfonic acid tags: Application to the synthesis of diverse spiropyrans. Res. Chem. Intermed. 44, 5255–5269 (2018).

42. Zhang, Y. et al. Tunable chiral metal organic frameworks toward visible light-driven asymmetric catalysis. Sci. Adv. 3(6), e1701162 (2017).
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H.S., M.Z. and S.B.: methodology, validation, investigation, writing the original draft. M.A.Z.: supervision, resources, project administration, funding acquisition, conceptualization, writing—review and editing. S.R.: advisor of project and editing of the manuscript.

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