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Cobalt ferrite nanoparticles: a magnetically separable and reusable catalyst for Petasis-Borono–Mannich reaction

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Magnetically separable cobalt ferrite nanoparticles ($CoFe_2O_4$, NPS) have been demonstrated for the first time as an efficient catalyst in Petasis-Borono–Mannich (PBM) reaction between salicylaldehydes, sec. amines and aryl boronic acids to furnish alkylaminophenols in high yields. Relatively shorter reaction times, easy purification of the products and reusability of the catalyst for five consecutive runs without appreciable loss in it's activity are the noteworthy features of the developed protocol.

Introduction

The emerging trend of high through put screening of drug candidates in pharmaceutical industries has evoked the concept of multicomponent reactions (MCRs) in the field of organic synthesis.[1,2] MCRs, apart from their exceptional synthetic efficiency and easy access in creation of libraries of structurally related as well as structurally diverse compounds, in real sense represent environmental friendly processes due to high atom efficiency, reduction of energy consumption, waste generation, *etc.* Especially the last decade has witnessed tremendous developments in multicomponent reactions as well as combinatorial synthesis.[3] Amongst a variety of multicomponent reactions available at the disposal of chemists, Petasis-Borono–Mannich (PBM) reaction involving a three component condensation between an aldehyde, secondary amine, and boronic acid has received a great deal of attention.[4] This is because, PBM reaction with variation in all the three components of this reaction serves as a useful tool in the synthesis of structurally diverse and synthetically useful class of compounds such as amino acids,[5–8] amino alcohols,[9,10] heterocycles, 2-hydroxy morpholines,[11] alkylaminophenols,[12] *etc.* In Petasis-Borono–Mannich reaction, commonly used aldehyde component is either glyoxylic acid or salicylaldehyde while cyclic or acyclic secondary amines like morpholine, pyrrolidine, piperidine, protected piperazine, α-methylbenzylamine as well as dibenzylamine serve as the most preferred amine components. On the other hand, alkenyl as well as aryl boronic acids are used as the third component. Among the synthetically useful compounds prepared using PBM reaction, alkylaminophenols constitute an attractive class of compounds useful in the field of agrochemicals as well as pharmaceuticals.[13] The first synthesis of this class of compounds was reported by Petasis *et al.* by the reaction between salicylaldehyde, secondary amine and phenyl boronic acid.[13] This catalyst-free synthesis operable at ambient temperature suffered from the drawbacks as regards to low to moderate yields and very long reaction times (24–36 h). Subsequently various attempts were made to expedite the rate of reaction mainly by increase in the reaction temperature in different solvents[14–16] or by microwave dielectric heating technique.[17] These thermally assisted protocols also suffered from the drawbacks of long reaction time (12–15 h). During the literature survey, it was interesting to note that, there are no reports on the use of any catalyst for PBM reaction. These important observations coupled with our interest in the development of mechanistic approaches in making chemistry green, simple and easily adaptable,[18–22] prompted us to develop a catalyst based protocol for the synthesis of alkylaminophenols using PBM reaction.

Development of clean synthetic procedures using heterogeneous catalysts has been the area of active research from "Green Chemistry" point of view.[23] This is because, compared to homogeneous catalysts, heterogeneous catalysts are known to offer advantages such as higher efficiency, mild reaction conditions, simple experimental procedures, minimal waste generation and possibility of reuse of the catalyst.[24,25] One important development in the field of heterogeneous catalysis involves the use of nanocatalysts. This is because; nanocatalysts while retaining their intrinsic properties are known to offer advantages as regards improvement in reactivity, selectivity as well as yields. However, the use of nanocatalysts also suffers from the drawback as regards difficulties in recovery of the catalyst for it's possible reuse. A rational solution that has emerged to overcome this drawback is the use of magnetically separable catalysts. In recent years, use of magnetically separable spinel ferrite nanoparticles as catalyst has received a great

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deal of attention.[26–28] Spinel ferrites have been explored by us[29] as well as by others, as heterogeneous, reusable catalysts in various organic transformations.[30,31]

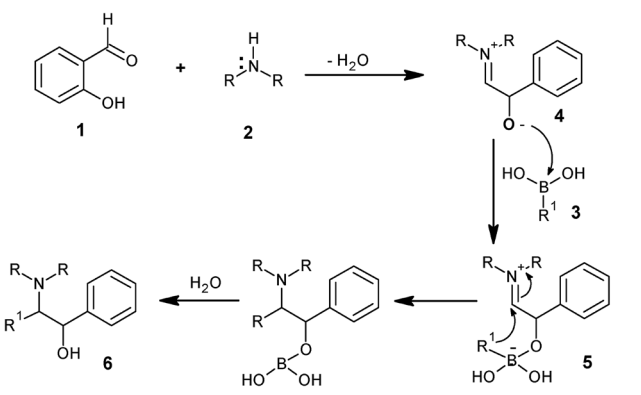
From the mechanistic view point, three component PBM reaction between salicylaldehyde, **1**, sec. amine, **2**, and boronic acid, **3**, is known to proceed *via* formation of iminium intermediate, **4**, which subsequently reacts with boronic acid to form product **6**, *via* a transient intermediate **5**. In this reaction, presence of hydroxyl groups in solvent as well as reactants is known to play a significant role in activating boronic acid.[15,16] Based upon these observations, we reasoned that, spinel ferrites being associated with acidic as well as basic sites in them and as they carry hydroxyl groups on their surface, may be useful in promoting PBM reaction.[32] Thus, we planned to examine the feasibility of using spinel ferrite as catalyst in the synthesis of alkylaminophenols.

Results and discussion

Four representative spinel ferrites *viz.* Fe_3O_4, $NiFe_2O_4$, $CoFe_2O_4$ and $CuFe_2O_4$ were prepared using metal chlorides as starting materials by controlled co-precipitation method as described by us earlier[29] and, the prepared ferrites were examined as catalysts in the synthesis of alkylaminophenols, **6**, by three component condensation between salicylaldehyde, sec. amine and aryl boronic acid following PBM reaction (Scheme 1).

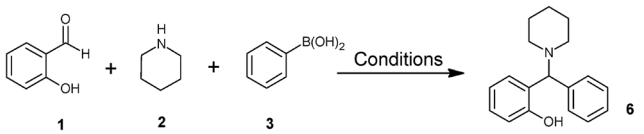
To begin with, a prototype reaction was performed. Thus, to a well stirred solution of salicylaldehyde (1 mmol), phenyl boronic acid (1.2 mmol) and piperidine (1.2 mmol) in acetonitrile (5 mL) was added simple ferrite, Fe_3O_4 (20 mol%) as the catalyst and stirring was continued at ambient temperature. During monitoring of the reaction by TLC, we did not notice any appreciable change in initial hours (4–6 h). However, upon stirring the reaction mixture overnight, formation of desired product was noticed. After routine work-up followed by chromatographic separation, resultant product in moderate yield (52%) was identified to be desired **6a** (NMR). In an attempt to explore the potential of other ferrites as catalysts, the same reaction was repeated using other metal ferrites. However, with the choice of all these ferrites, desired product **6a** was obtained in nearly same yield (52–58%) (Table 1, entry 2–4). In an attempt to improve the yield of **6a**, the model reactions were then repeated at 50 °C as well as under reflux condition (80 °C). Heating the reaction mixture to 50 °C for longer time was although not much beneficial, an appreciable increase in the yield of desired product, **6a**, was noticed upon refluxing the reaction mixture for 2–3 h. Most interestingly, only a marginal difference in the yield of desired **6a** was observed under the influence of all the screened ferrites as catalysts (Table 1). On the basis of this particular observation, choice of ferrite for optimization of the reaction conditions was slightly difficult for us. However, based upon the parameter of easiness of separation of the catalyst by application of external magnet, we decided to choose $CoFe_2O_4$ as the catalyst for subsequent studies. Further optimization of the reaction conditions with respect to effect of catalyst loading revealed that 15 mol% $CoFe_2O_4$ catalyst is sufficient enough for the synthesis of desired alkylaminophenol in excellent yield (Table 1, entry 9). It is well known that, PBM reaction is highly dependent upon the nature of the solvent used and use of water has been demonstrated to be highly useful to obtain alkylaminophenols, **6**, in excellent yield.[15] Thus, the reaction was repeated in water medium. However, the reaction required relatively longer reaction time to obtain desired product **6a** (Table 1, entry 12). So as to examine the role of the catalyst in this MCR, the reaction was finally performed at 80 °C under catalyst-free condition. However, it required long reaction time and furnished desired **6a** in lower yield (Table 1, entry 13).

During the studies on optimization of the reaction conditions, as $CoFe_2O_4$ was found to be the best suited catalyst, we next carried out full characterization of $CoFe_2O_4$. Powder XRD



Scheme 1 Spinel ferrite catalyzed synthesis of alkylaminophenols.

Table 1 Screening of ferrite catalyst for the synthesis of 6a and optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)
1	Fe_3O_4 (20)	RT	24	52
2	$NiFe_2O_4$ (20)	RT	24	55
3	$CuFe_2O_4$ (20)	RT	24	56
4	$CoFe_2O_4$ (20)	RT	24	58
5	Fe_3O_4 (20)	50, 80	8, 3	65, 85
6	$NiFe_2O_4$ (20)	50, 80	8, 2	68, 85
7	$CuFe_2O_4$ (20)	50, 80	8, 2	63, 88
8	$CoFe_2O_4$ (20)	50, 80	8, 2	72, 90
9	$CoFe_2O_4$ (15)	80	2	90
10	$CoFe_2O_4$ (10)	80	4	85
11	$CoFe_2O_4$ (5)	80	6	70
12	$CoFe_2O_4$ (15)	80	4	80[c]
13	—	80	4	62

[a] Reaction conditions: salicylaldehyde (1 mmol), piperidine (1.2 mmol), phenyl boronic acid (1.2 mmol), acetonitrile (5 mL), catalyst. [b] Isolated yield. [c] Using water (5 mL) as the reaction medium.

pattern for cobalt ferrite is displayed in Fig. 1. According to spinel structure; the planes that diffract X-rays are (220), (311), (400), (422), (511) and (440). For spinel ferrites, (311) plane line is the most intense line and the observed reflections in the present case are quite similar to these. All the detectable peaks are indexed as $CoFe_2O_4$ with an inverse spinel structure and are in good agreement with the standard data (JCPDS no. 22-1086). The absence of extra-lines in the present pattern confirms single phase formation of cobalt ferrite. The crystallite size of the sample was calculated from corrected FWHM value of (311) reflection using Scherrer's equation and that was found to be ~40 nm. Fig. 2(A) depicts the TEM image of the cobalt ferrite sample with particle size ranging from 30 to 60 nm. Fig. 3 shows hysteresis loops of the catalyst and confirms the ferrimagnetic behavior of cobalt ferrite nanoparticles with saturation magnetization value (M_s) of 70 emu g^{-1}, which allows easy separation of catalyst for possible reuse. The IR spectrum (Fig. 4) of cobalt ferrite sample apart from peak due to hydroxyl group (3411 cm^{-1}) showed two characteristic peaks at 583 cm^{-1} and 464 cm^{-1} for octahedral and tetrahedral metal–oxygen stretching in spinel ferrites. The composition of catalyst was confirmed from the EDAX spectrum (Fig. 5).

After adequate characterization of the catalyst, scope as well as general applicability of the protocol towards the synthesis of structurally diverse alkylaminophenols was examined under the established reaction conditions. In this regard, a range of aryl boronic acids were allowed to react with *in situ* generated imines by the reaction between salicylaldehydes with various

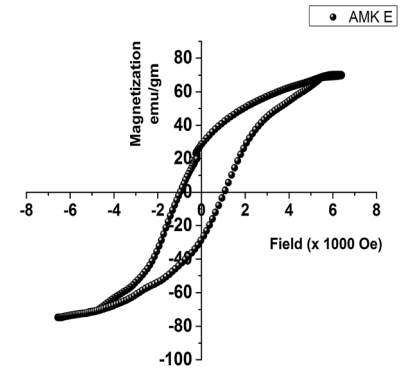


Fig. 3 The hysteresis loop for $CoFe_2O_4$.

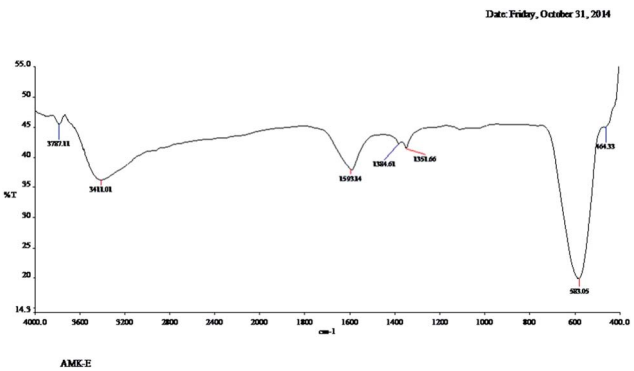


Fig. 4 The IR spectrum of $CoFe_2O_4$.

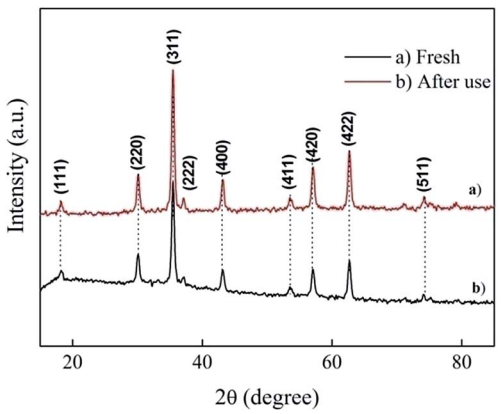


Fig. 1 XRD pattern of $CoFe_2O_4$.

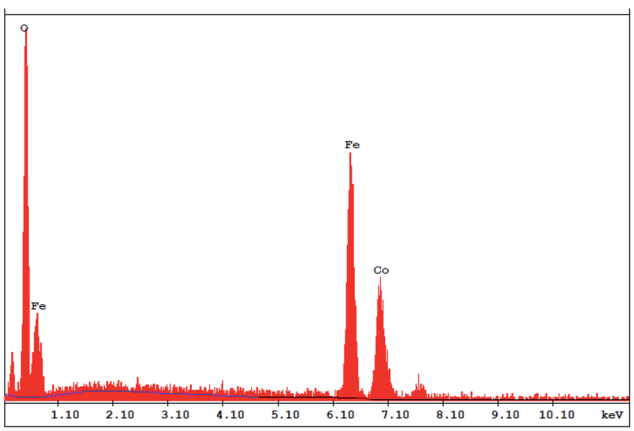


Fig. 5 The EDAX spectrum of $CoFe_2O_4$.

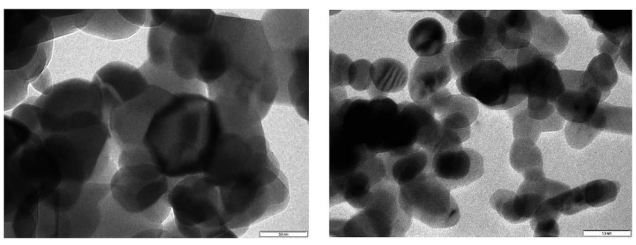


Fig. 2 TEM image of $CoFe_2O_4$: (A) before use and (B) after fifth cycle.

secondary amines. In most of the cases, the reaction proceeded smoothly. The presence of electron-donating or electron-withdrawing group on salicylaldehyde was less significant while secondary amines like piperidine, morpholine, pyrrolidine, as well as dibenzylamine underwent reactions with phenyl boronic acid with equal ease. On the other hand, irrespective of nature of functional group on salicylaldehyde and secondary amine, aryl boronic acids with electron donating group reacted more smoothly than those possessing electron-withdrawing

Table 2 Cobalt ferrite catalyzed synthesis of alkylaminophenols by PBM reaction[a]

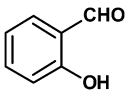
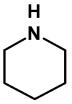
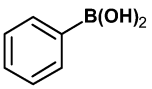
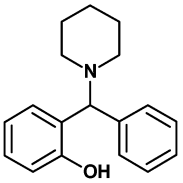
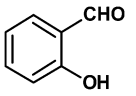
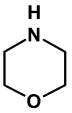
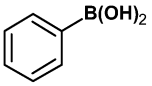
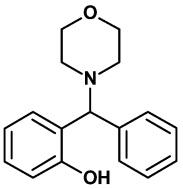
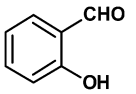
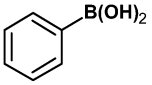
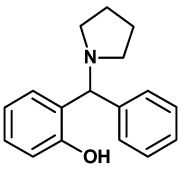
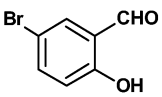
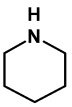
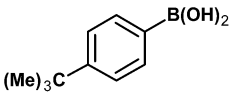
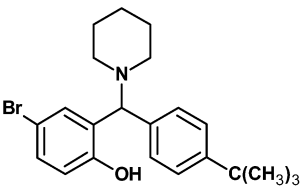
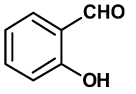
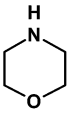
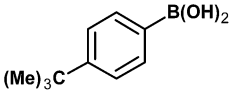
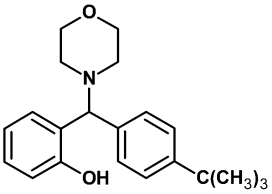
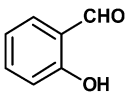
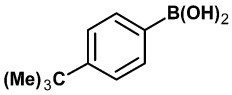
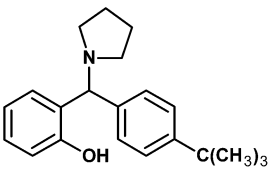
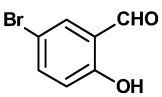
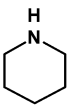
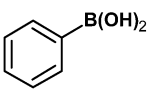
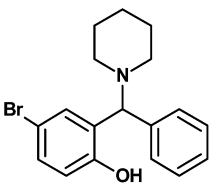
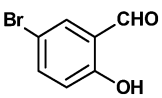
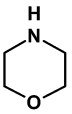
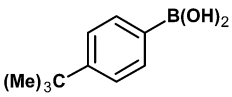
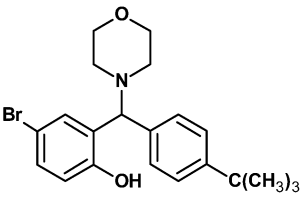
Entry	Aldehyde (1)	Amine (2)	Boronic acid (3)	Product (6)	Time (h)	Yield[b] (%)
a					2	90
b					2.5	88
c					3	83
d					2	90
e					2.5	90
f					3	88
g					3.5	78
h					2.5	89

Table 2 (*Contd.*)

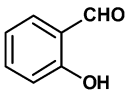
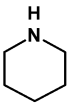
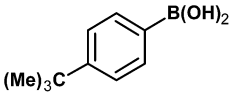
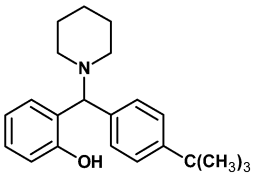
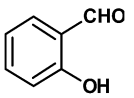
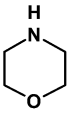
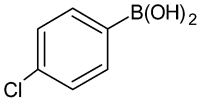
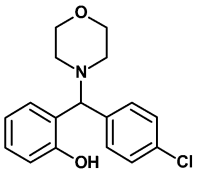
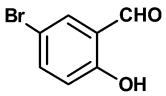
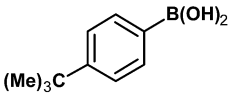
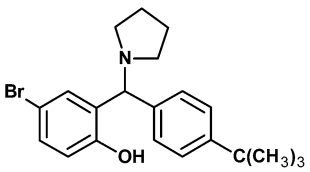
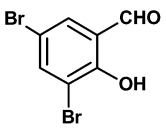
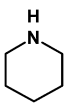
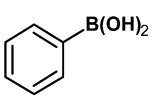
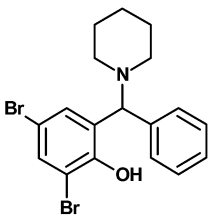
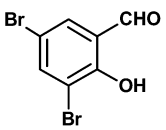
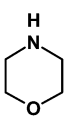
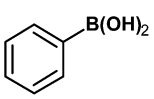
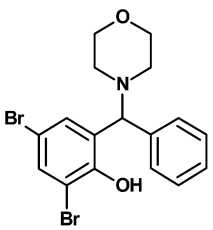
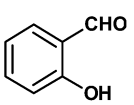
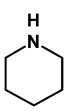
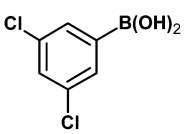
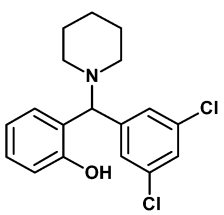
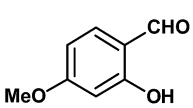
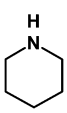
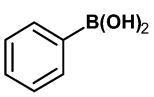
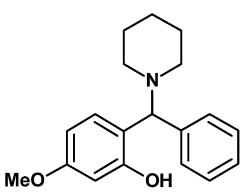
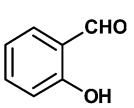
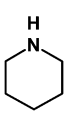
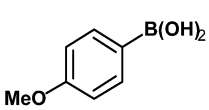
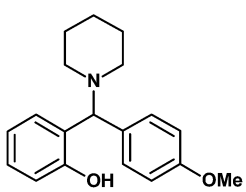
Entry	Aldehyde (1)	Amine (2)	Boronic acid (3)	Product (6)	Time (h)	Yield[b] (%)
i					2	93
j					4.5	75
k					2.5	83
l					3.5	87
m					3.5	85
n					4	80
o					4	75
p					3	85

Table 2 (*Contd.*)

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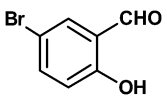
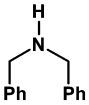
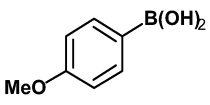
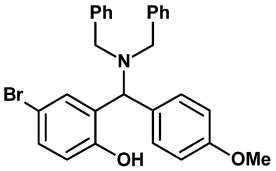
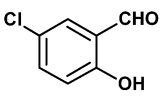
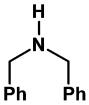
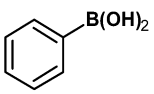
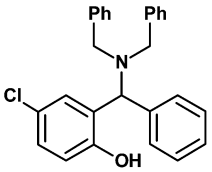
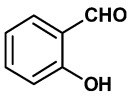
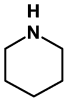
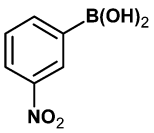
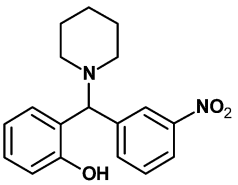
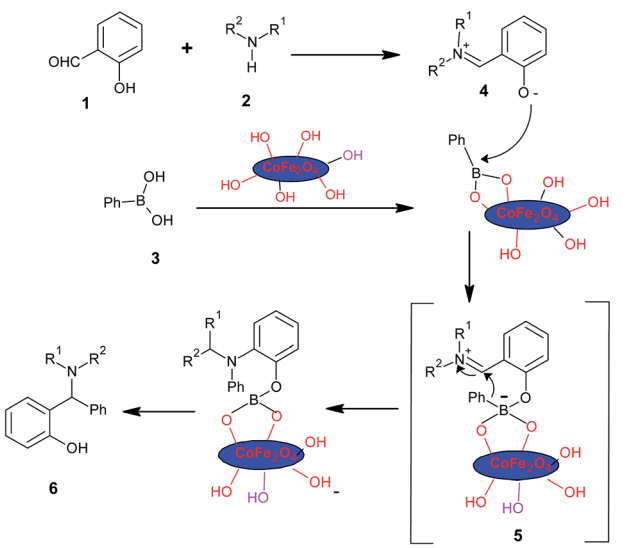
q					3	86
r					4	80
s					6	72

[a] Reaction conditions: aldehyde (1 mmol), sec. amine (1.2 mmol), boronic acid (1.2 mmol), acetonitrile (5 mL), $CoFe_2O_4$ (15 mol%), 80 °C. [b] Isolated yields.

group. Furthermore, the reactions failed to furnish desired product with the choice of sec. amines devoid of α-methylene group *e.g.* *N*-methyl aniline. The results are summarized in Table 2. The plausible reaction mechanism explaining the role of cobalt ferrite in the synthesis of alkylaminophenols is depicted in Scheme 2.

In heterogeneously catalysed reactions, separation of the catalyst from the reaction mixture for it's possible reuse is an important aspect in the context of green chemistry. So we turned our attention towards reusability of the catalyst. Owing to ferrimagnetic behaviour of cobalt ferrite nanoparticles, the catalyst was separated by applying external magnet (Fig. 6). It was washed repeatedly with acetonitrile, acetone (3 × 5 mL), dried in oven for 3 hours at 100 °C and then reused. It was observed that, catalyst could be recycled efficiently for five consecutive cycles without any appreciable change in its activity (Fig. 7). The stability of the catalyst recovered after fifth cycle was confirmed by comparison of XRD of the catalyst employed for the reaction and that recovered after fifth cycle (Fig. 1(a) and (b)). It was observed that, there is no appreciable change in the structure of the catalyst. On the other hand, TEM image of the catalyst recovered after fifth cycle depicts that Fig. 2(B), the particle size of recycled catalyst has remained nearly same. The leaching behavior of the catalyst was then tested. Thus, upon



Scheme 2 Plausible mechanism for the synthesis of alkylaminophenols.

Fig. 6 Easy separation of the catalyst by application of external magnet.

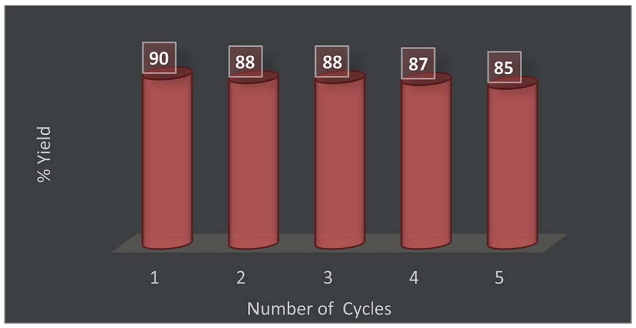


Fig. 7 Reusability of catalyst $CoFe_2O_4$.

completion of the model reaction performed between salicylaldehyde, morpholine and phenyl boronic acid, catalyst was separated using external magnet and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water, dried over anhydrous sodium sulfate and solvent was removed under vacuum. The catalyst obtained was then analyzed through AAS analysis. Absence of Fe as well as Ni confirmed that catalyst does not leach.

Conclusion

In conclusion, we have demonstrated for the first time the use of cobalt ferrite nanoparticles as the catalyst in three component Petasis-Borono–Mannich reaction between aryl boronic acids, salicylaldehydes and secondary amines to prepare alkylaminophenols. Shorter reaction times, excellent yields and reusability of the catalyst for five consecutive runs without appreciable loss in its activity, are the main merits of this environmental friendly protocol. Further studies on the application of this catalyst in PBM and related reactions are currently underway in our laboratory.

Experimental

All the chemicals were purchased from Aldrich or S.D. Fine Chemicals, Mumbai. ^{1}H and ^{13}C NMR spectra were recorded using Bruker Avance-II spectrometer. X-ray powder diffraction was performed on PHILIPS (PW3710) X-ray diffractometer with Cu Kα_1 radiation ($\lambda = 1.5424$ A.U.). TEM studies were performed using Philips CM 200 with operating voltage: 20–200 kV. Hysteresis loop of cobalt ferrite nanoparticles was obtained using vibrating sample magnetometer (VSM) while EDAX spectra were recorded using Genesis XM-2i EDX system. IR spectra were recorded as KBr pellets on a Perkin Elmer Spectrum 1 spectrometer.

General procedure for the preparation of alkylaminophenols

To a well stirred solution of salicylaldehyde (1 mmol), secondary amine (1.2 mmol) and aryl boronic acid (1.2 mmol) in acetonitrile (5 mL) was added cobalt ferrite nanoparticles (15 mol%, 0.035 g). The reaction mixture was heated under reflux until completion of the reaction (TLC). The catalyst was separated by using external magnet and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water, dried over anhydrous sodium sulfate and solvent was removed under vacuum. The resultant residue was chromatographed over silica-gel. Elution with hexane–ethyl acetate (95 : 5%, v/v) furnished pure alkylaminophenols in acceptable yields.

Spectral data of all the synthesized compounds is summarized below

2-[Phenyl(piperidin-1-yl)methyl]phenol, 6a. White solid; mp 88 °C; IR (KBr): 3430, 3060, 2945, 2857, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.49 (s, 2H), 1.64–1.69 (m, 4H), 2.45 (s, 4H), 4.52 (s, 1H), 6.71 (t, 1H, $J = 6$ Hz, ArH), 6.90 (d, 2H, $J = 8$ Hz, ArH), 7.11–7.16 (m, 1H, ArH), 7.31–7.36 (m, 3H, ArH), 7.43 (d, 2H, $J = 6.6$ Hz), 12.42 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.07, 26.02, 52.52, 76.52, 116.96, 119.01, 125.44, 127.86, 128.37, 128.68, 128.84, 129.17, 139.28, 157.14 ppm.

2-[Morpholin-4-yl(phenyl)methyl]phenol, 6b. White solid; mp 115–117 °C; IR (KBr): 3355, 3008, 2853, 1605, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45–2.62 (m, 4H), 3.77 (s, 4H), 4.43 (s, 1H), 6.75 (t, 1H, $J = 7.5$ Hz, ArH), 6.90 (d, 1H, $J = 7.8$ Hz, ArH), 6.97 (d, 1H, $J = 7.2$ Hz, ArH), 7.15 (t, 1H, $J = 7.2$ Hz, ArH), 7.28–7.35 (m, 3H, ArHs), 7.45 (d, 2H, $J = 6.6$ Hz, ArHs), 11.78 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.25, 66.91, 76.87, 117.05, 119.61, 124.80, 128.13, 128.55, 128.71, 128.94, 129.40, 139.27, 156.11 ppm.

2-[Phenyl(pyrrolidin-1-yl)methyl]phenol, 6c. Yellow sticky mass; IR (KBr): 3450, 3060, 2830, 1603, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.85–1.89 (m, 4H), 2.52–2.56 (m, 2H), 2.68 (s, 2H), 4.43 (s, 1H), 6.72–6.77 (m, 1H, ArH), 6.90 (d, 2H, $J = 9$ Hz, ArHs), 7.0 (d, 1H, $J = 9$ Hz, ArH), 7.14 (m, 1H, ArH), 7.25–7.29 (m, 1H, ArH), 7.31–7.35 (m, 2H, ArHs), 7.50–7.53 (m, 2H, ArHs), 10.95 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.49, 53.22, 75.74, 116.90, 119.18, 126.69, 127.71, 127.80, 128.32, 128.38, 128.74, 134.50, 142.12, 156.65 ppm.

4-Bromo-2-[(4-*t*-butylphenyl)(piperidin-1-yl)methyl]phenol, 6d. White solid; mp 142–144 °C; IR (KBr): 3428, 3070, 2945, 2859, 1602, 603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 9H), 1.48 (m, 2H), 1.64–1.67 (m, 4H), 2.41 (s, 4H), 4.39 (s, 1H), 6.74 (d, 1H, $J = 8.7$ Hz, ArH), 7.01 (d, 1H, $J = 2.4$ Hz, ArH), 7.19 (dd, 1H, $J = 8.7$ and 2.4 Hz, ArH), 7.28–7.35 (m, 4H, ArHs), 12.74 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.03, 26.02, 31.27, 34.50, 52.46, 75.69, 110.54, 118.66, 125.67, 127.91, 128.33, 130.97, 131.68, 135.58, 151.03, 156.48 ppm.

2-[(4-*t*-Butylphenyl)morpholino]methylphenol, 6e. White solid; mp 125–127 °C; IR (KBr): 3360, 3008, 2855, 1605, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9H), 2.45–2.51 (m, 2H), 2.60 (s, 2H), 3.75–3.79 (m, 4H), 4.41 (s, 1H), 6.71–6.77 (m, 1H, ArH), 6.86–6.98 (m, 1H, ArH), 6.95–6.98 (m, 1H, ArH), 7.11–7.17 (m, 1H, ArH), 7.31–7.37 (m, 4H, ArHs), 11.73 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.26, 34.48, 52.21, 66.94, 76.46, 116.95, 119.48, 125.03, 125.75, 128.20, 128.56, 129.39, 136.06, 151.01, 156.21 ppm.

2-(4-*t*-Butylphenyl)(pyrrolidin-1-yl)methylphenol, 6f. White solid; mp 138–140 °C; IR (KBr): 3445, 3062, 2828, 1603, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9H), 1.85 (s, 4H),

2.53 (s, 2H), 2.66 (s, 2H), 4.38 (s, 1H), 6.73 (t, 1H, J = 7.2 Hz, ArH), 6.87 (d, 1H, J = 7.8 Hz, ArH), 6.96–6.99 (m, 1H, ArH), 7.09–7.14 (m, 1H, ArH), 7.30 (t, 2H, J = 8.4 Hz, ArHs), 7.41 (d, 2H, J = 8.4 Hz, ArHs), 12.31 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.46, 31.30, 34.43, 53.18, 75.29, 116.78, 119.04, 125.52, 126.91, 127.39, 128.22, 128.27, 138.97, 150.43, 156.70 ppm.

4-Bromo-2-(phenyl)(piperidin-1-yl)methylphenol, 6g. Pale yellow sticky mass, IR (KBr): 3440, 3015, 2945, 2860, 1610, 608 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27–1.35 (m, 2H), 1.49–1.65 (m, 6H), 2.41 (s, 2H), 4.43 (s, 1H), 6.75 (d, 1H, J = 8.7 Hz, ArH), 7.0–7.01 (d, 1H, J = 8.7, ArH), 7.18–7.22 (dd, 1H, J = 8.5 & 2.4 Hz, ArH), 7.31–7.37 (m, 3H, ArHs), 7.55–7.63 (m, 1H, ArH), 7.68–7.72 (m, 1H, ArH), 12.74 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.00, 26.00, 52.46, 76.03, 110.62, 118.76, 120.50, 127.60, 128.15, 128.60, 128.84, 129.14, 131.10, 131.67, 135.39, 138.68, 156.43 ppm.

4-Bromo-2-(4-*t*-butylphenyl)(morpholino)methylphenol, 6h. White solid; mp 168–170 °C; IR (KBr): 3350, 3008, 2857, 1605, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 9H, 3 × CH_3), 2.42–2.49 (m, 2H), 2.58 (s, 2H), 3.75–3.78 (m, 4H), 4.34 (s, 1H), 6.76 (d, 1H, J = 8.7 Hz, ArH), 7.08 (d, 1H, J = 2.4 Hz, ArH), 7.20–7.24 (dd, 1H, J = 8.7 & 2.4 Hz, ArH), 7.28–7.36 (m, 4H, ArHs), 11.88 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.22, 34.53, 52.18, 66.83, 75.98, 111.13, 118.86, 125.92, 128.16, 131.37, 131.91, 135.31, 151.44, 155.48 ppm.

2-(4-*t*-Butylphenyl)(piperidin-1-yl)methylphenol, 6i. White solid; mp 93–95 °C; IR (KBr): 3415, 3045, 2945, 2855, 1610, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9H, 3 × CH_3), 1.64 (m, 2H), 1.66 (s, 4H), 2.44 (s, 4H), 4.46 (s, 1H), 6.68–6.73 (t, 1H, J = 7.5 Hz, ArH), 6.85–6.93 (m, 2H, ArHs), 7.09–7.28 (m, 1H, ArH), 7.32 (s, 4H, ArHs), 12.62 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14, 26.10, 31.31, 34.47, 52.52, 76.09, 116.77, 118.98, 125.51, 125.84, 128.19, 128.41, 129.19, 136.28, 150.60, 157.17 ppm.

2-(4-Chlorophenyl)(morpholino)methylphenol, 6j. White solid; mp 108–110 °C; IR (KBr): 3355, 3010, 2857, 1605, 1110, 605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.43–2.49 (m, 2H), 2.60 (s, 2H), 3.74–3.78 (m, 4H), 4.40 (s, 1H), 6.75 (t, 1H, J = 7.2 Hz), 6.89–6.96 (m, 2H, ArHs), 7.13–7.18 (m, 1H, ArH), 7.29 (d, 2H, J = 8.4 Hz, ArHs), 7.40 (d, 2H, J = 8.4 Hz, ArHs), 11.58 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.24, 66.80, 76.10, 117.24, 119.81, 124.38, 128.97, 129.16, 129.26, 129.87, 134.01, 137.86, 155.95 ppm.

4-Bromo-2-(4-*t*-butylphenyl)(pyrrolidin-1-yl)methylphenol, 6k. Mp 132–133 °C; IR (KBr): 3445, 3062, 2828, 1603, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 9H, 3 × CH_3), 1.85–1.87 (m, 4H), 2.52–2.65 (m, 4H), 4.32 (s, 1H), 6.76 (d, 1H, J = 8.7 Hz, ArH), 7.1 (d, 1H, J = 2.4 Hz, ArH), 7.18 (dd, 1H, J = 6 and 2.4 Hz, ArH) 7.29 (t, 1H, J = 2.4 Hz, ArH), 7.31 (d, 1H, J = 2.1 Hz, ArH), 7.35–7.38 (d, 2H, J = 6.3 Hz, ArHs), 12.35 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.42, 31.28, 34.49, 53.19, 74.70, 110.70, 118.70, 125.69, 127.37, 128.70, 130.89, 131.04, 138.09, 150.89, 155.92 ppm.

2,4-Dibromo-2-(phenyl)(piperidin-1-yl)methylphenol, 6l. White solid; mp 118–120 °C; IR (KBr): 3750, 3066, 2940, 2849, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (m, 2H), 1.65–1.68 (m, 4H), 2.44 (m, 4H), 4.49 (s, 1H), 6.98 (d, 1H, J = 2.4 Hz, ArH), 7.34 (s, 5H, ArHs), 7.53 (d, 1H, J = 2.1 Hz, ArH), 8.2 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.83, 25.80, 52.28, 75.85, 110.20, 111.72, 127.85, 128.06, 128.55, 128.83, 129.00, 130.94, 133.84, 137.52, 155.92 ppm.

2,4-Dibromo-6-[morpholin-4-yl(phenyl)methyl]phenol, 6m. White solid; mp 167–170 °C; IR (KBr): 3365, 3007, 2850, 1603, 1110, 610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.44–2.51 (m, 2H), 2.58 (s, 2H), 3.72–3.84 (m, 4H), 4.40 (s, 1H), 7.04 (d, 1H, J = 2.4 Hz, ArH), 7.32–7.37 (m, 2H, ArHs), 7.53 (s, 3H, ArHs), 7.54 (s, 1H, ArH), 13.02 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.95, 66.66, 76.25, 111.00, 111.73, 127.44, 128.46, 128.78, 129.24, 131.13, 134.18, 137.65, 152.60 ppm.

2-(3,5-Dichlorophenyl)(piperidin-1-yl)methylphenol, 6n. White solid; mp 127–129 °C; IR (KBr): 3450, 3012, 2850, 1608, 1110, 610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.51 (s, 2H), 1.68 (s, 4H), 2.42 (s, 4H), 4.37 (s, 1H), 6.71–6.76 (m, 1H, ArH), 6.88 (d, 2H, J = 7.8 Hz, ArHs), 7.13–7.26 (m, 1H, ArH), 7.27 (s, 1H, ArH), 7.33 (s, 2H, ArHs), 12.50 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.99, 25.98, 52.75, 75.88, 117.30, 119.36, 124.27, 126.93, 128.10, 128.90, 128.95, 135.25, 143.24, 156.73 ppm.

5-Methoxy-2-[phenyl(piperidin-1-yl)methyl]phenol, 6o. Sticky oil; IR (KBr): 3450, 3010, 2855, 1600, 1238, 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 2H), 1.64–1.67 (m, 4H), 2.42 (s, 4H), 3.76 (s, 3H), 4.48 (s, 1H), 6.28 (dd, 1H, J = 8.4 and 2.7 Hz, ArH), 6.44–6.45 (d, 1H, J = 2.4 Hz, ArH), 6.77 (d, 1H, J = 8.4 Hz, ArH), 7.27–7.30 (m, 1H, ArH), 7.32–7.35 (m, 4H, ArHs), 7.37–7.40 (m, 2H, ArHs), 12.50 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14, 26.10, 52.32, 55.13, 75.80, 102.10, 105.18, 117.87, 127.70, 128.57, 128.86, 129.75, 139.44, 158.45, 160.09 ppm.

2-(4-Methoxyphenyl)(piperidine-1-yl)methylphenol; 6p. Sticky solid; IR (KBr): 3450, 3008, 2857, 1605, 1240, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (s, 2H), 1.65 (s, 2H), 1.66 (s, 2H), 2.43 (s, 4H), 3.79 (s, 3H), 4.49 (s, 1H), 6.72 (t, 1H, J = 7.2 Hz, ArH), 6.85–6.92 (m, 4H, ArHs), 7.10–7.16 (m, 1H, ArH), 7.32–7.35 (m, 2H, ArHs), 12.73 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.39, 21.37, 47.58, 50.47, 70.86, 109.20, 112.07, 114.24, 121.07, 123.49, 124.41, 126.63, 152.44, 154.39 ppm.

4-Bromo-2-[(4-methoxyphenyl)(dibenzylamino)methyl]phenol, 6q. Solid; mp 147–149 °C; IR (KBr): 3417, 2852, 1606, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.39 (d, 2H, J = 7.8 Hz, $ArCH_2$), 3.90 (s, 3H), 3.95 (d, 2H, J = 13.2 Hz, $ArCH_2$), 5.11 (s, 1H), 6.86 (d, 1H, J = 8.7 Hz, ArH), 6.95 (d, 1H, J = 2.1 Hz, ArH), 7.03 (d, 2H, J = 8.7 Hz, ArHs), 7.29 (m, 1H, ArH), 7.29 (m, 1H, ArH), 7.30 (m, 2H, ArHs), 7.31–7.33 (m, 6H, ArHs), 7.36 (s, 2H, ArHs), 7.39–7.41 (m, 2H, ArHs), 12.45 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.87, 55.36, 67.08, 110.81, 114.10, 126.31, 126.97, 127.76, 128.74, 129.77, 131.64, 131.88, 132.15, 136.78, 156.89, 159.68 ppm.

4,6-Dichloro-2-[(phenyl)(dibenzylamino)methyl]phenol, 6r. Yellow solid; mp 122–125 °C; IR (KBr): 3322, 3018, 2862, 1602, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.40 (d, 2H, J = 13.2 Hz, $ArCH_2$), 3.93–3.97 (d, 2H, J = 13.2 Hz, $ArCH_2$), 5.12 (s, 1H), 6.80 (d, 1H, J = 2.4 Hz, ArH), 6.90 (d, 1H, J = 8.4 Hz, ArH), 7.15 (dd, 1H, J = 8.7 and 2.4 Hz, ArH), 7.29 (s, 2H, ArH), 7.30–7.33 (m, 3H, ArHs), 7.36 (s, 2H, ArHs), 7.38–7.45 (m, 4H, ArHs), 7.47–7.49 (m, 3H, ArHs), 12.24 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.10, 63.14, 113.28, 118.87, 121.37, 123.01, 123.89, 123.98, 125.00, 125.00, 129.95, 131.91, 151.52 ppm.

2-[(3-Nitrophenyl)(piperidin-1-yl)methyl]phenol, 6s. Yellow solid; mp 118–120 °C; IR (KBr): 3322, 3018, 2862, 1602, 1550, 1345 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27–1.30 (m, 2H), 1.51 (s, 2H), 1.68 (s, 4H), 2.42 (s, 2H), 4.59 (s, 1H), 6.75 (t, 1H, $J = 7.5$ Hz, ArH), 6.90 (d, 2H, $J = 7.2$ Hz, ArHs), 7.13–7.18 (m, 1H, ArH), 7.52 (t, 1H, $J = 8.1$ Hz, ArH), 7.85 (s, 1H, ArH), 8.15 (d, 1H, $J = 8.1$ Hz. ArH), 8.26 (s, 1H, ArH), 12.14 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.93, 25.91, 29.71, 52.80, 75.83, 117.33, 119.54, 122.94, 123.58, 124.35, 128.95, 129.01, 130.01, 134.53, 141.91, 148.31, 156.64 ppm.

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