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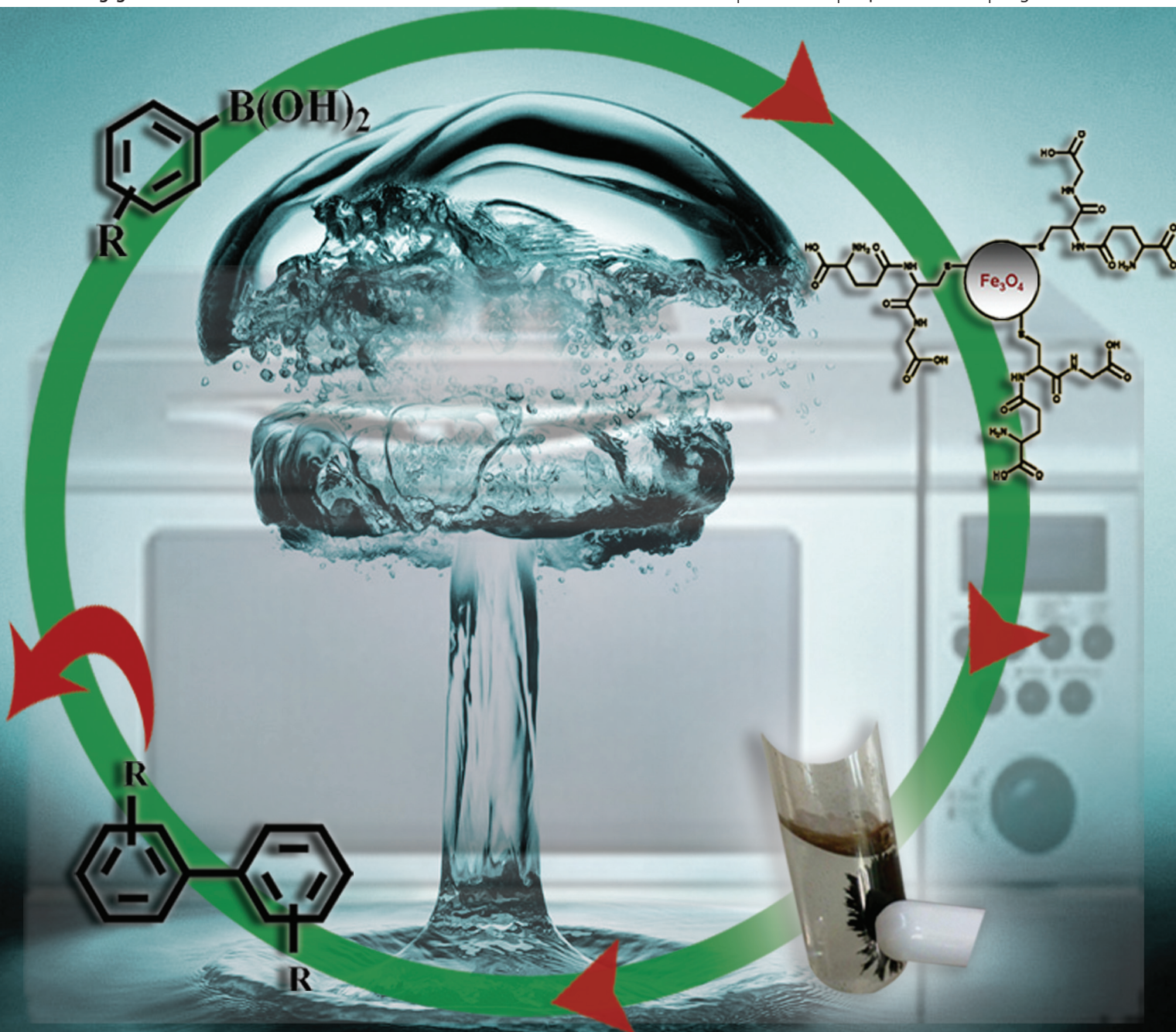
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Magnetically separable nanoferrite-anchored glutathione: aqueous homocoupling of arylboronic acids under microwave irradiation

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**A highly active, stable and magnetically separable glutathione-based organocatalyst provided very good to excellent yields to symmetric biaryls in the homocoupling of arylboronic acids under microwave irradiation.**

Symmetrical biaryl motifs are present in a wide range of natural products which have interesting properties including antivirals,[1] polymers[2] and ligands employed in catalysis.[3] This important family of compounds can be synthesized by a number of organic protocols including the Suzuki and Sonogashira cross coupling reactions[4,5] as well as their homocoupling alternatives.[4–6] Both types of reactions have generally been reported to be catalysed with a variety of supported transition metal and/or transition metal complexes (mostly palladium) and oxidants under base conditions in a range of solvents.[4,6]

More recently, Fe has joined the group of catalysts employed for such purposes and reports of iron-catalysed Suzuki[7] and Sonogashira[8] protocols as well as related C–N[9] and three-component couplings[10] have recently been described. However, the effect of impurities of other metals including palladium in these systems have created the need of further investigations to prevent metal-trace contaminant catalysed processes.[11]

We have recently reported a novel magnetically-separable glutathione-based organocatalyst that can provide high activities and selectivites in a variety of base-catalysed processes including the Knoevenagel and Paal–Knorr reactions.[12] Inspired by a recent report of the Pd-catalysed homocoupling of arylboronic acids in water[6a,13] and our previous results that showed high activities of supported iron oxide nanoparticles in the efficient homocoupling of thiophenols,[14] we envisioned the potential use of the nanoferrite-glutathione material in the microwave (MW)-assisted aqueous homocoupling of aryl boronic acids as alternative to Suzuki catalysed synthesis of symmetric biaryls (Scheme 1).
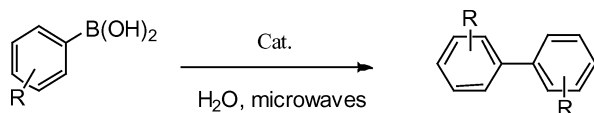
Scheme 1 Microwave-assisted heterogeneously catalysed homocoupling of boronic acids in water.

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Experimental

Materials preparation

Materials were synthesized following the protocol previously described by our group.[12,15] A typical preparation of the glutathione-based organocatalyst was performed as follows: Nano-Fe_3O_4 (0.5 g) was dispersed in 15 mL water and 5 mL of methanol and sonicated for 15 min. Glutathione (reduced form) (0.4 g) dissolved in 5 mL of water was added to this solution and again sonicated for 2 h. The glutathione-functionalized nanomaterial (nano-organocatalyst) was then isolated by centrifugation, washed with water and methanol, and dried under vacuum at 50 to 60 °C.

Materials characterisation

MMS X-ray diffractometer with a Cu-Kα source in the 20 to 80 2θ range. The data were collected with a step of 1° min^{-1}. The phase and crystallinity of the catalyst were determined by powder X-ray diffraction (XRD) (Fig. 1). All diffraction planes could be well assigned to the magnetite (JCPDS card no. 00-002-1035) phase of iron oxide without the presence of any detectable amount of impurities from other oxide or hydroxide phases. Broadening of the XRD peaks clearly indicate the nanocrystalline nature of the material.
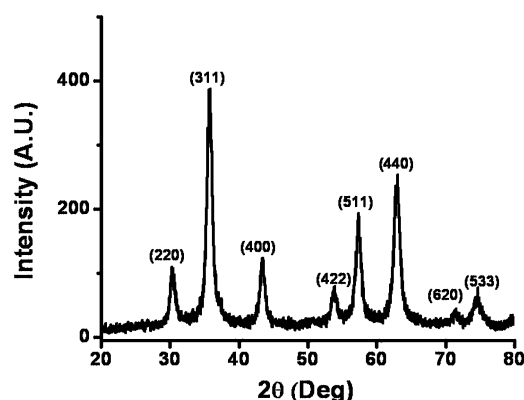
Fig. 1 X-Ray diffraction pattern for the as-synthesized catalyst.

TEM micrographs were recorded on a Phillips CM 20 TEM microscope at an operating voltage of 200 kV. A drop of as-synthesized nanoparticles was loaded on a carbon-coated copper grid and then allowed to dry at room temperature before recording the micrographs. The image depicted in Fig. 2 showed uniform-sized particles with cube like morphology with an average size range of 10–15 nm, in good agreement with
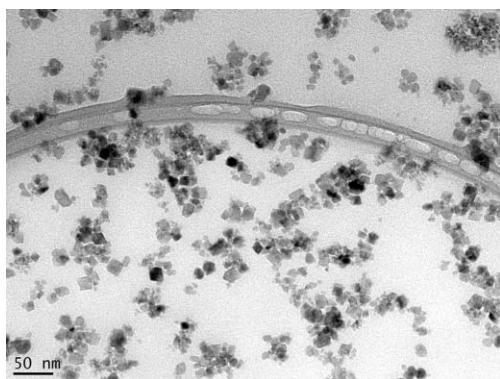
Fig. 2 TEM image of the as-synthesized catalyst.

the crystallite size (10 ± 0.5 nm) calculated using the Scherrer equation from the full width at half-maximum (FWHM) of the major XRD diffraction planes (Fig. 1).

FTIR spectra (not shown) were recorded on a Perkin-Elmer SPETRUM 2000 FTIR instrument in the range 400–3700 cm^{-1}. A band observed at 592 cm^{-1} was due to the vibration of the Fe–O bond of ferrite. This spectrum also provided evidences of the strong linkage of thiol groups from glutathione to the nanoferrite as previously reported[12]

Catalytic experiments

Homocoupling reactions under microwave irradiation conditions were carried out in a Microwave CEM-DISCOVER reactor with PC control and monitored by sampling aliquots of reaction mixture that were subsequently analysed by Gas Chromatography-Mass Spectrometry (GC/GC-MS) using an Agilent 6890 N GC model equipped with a 7683B series autosampler fitted with a DB-5 capillary column and an FID detector. Experiments were conducted on a closed vessel (pressure controlled) under continuous stirring. The microwave method was generally power controlled. The samples were microwave-irradiated (300 W, maximum power output) and

different temperatures ranging from 150 to 170 °C were reached depending on the reaction and/or the catalyst employed. The identity of the ensuing reaction products were also confirmed by ^{1}H NMR using a JEOL 400 spectrometer operating at 400.13 MHz. Chemical shifts were calibrated using the internal SiMe$_4$ resonance.

A typical catalytic test was performed as follows: 1 mmol phenyl boronic acid was dissolved in 2 mL water after addition of a few drops of NaOH 0.1 M solution and then 0.05 g catalyst was added. The resulting mixture was microwaved for 45–60 min at 300 W (maximum power output, 120 °C maximum temperature reached) and the contents were subsequently analysed by GC (confirmed by HPLC). The response factors of the main reaction products were determined with respect to the starting materials from GC analysis using known compounds in calibration mixtures of specified compositions. Reagents were used as purchased from Sigma-Aldrich, Fluka or Avocado.

Isolated yields were obtained from the resulting reaction mixture *via* filtration of the crude product through Celite (solvent removed under reduced pressure) and purification of the residue (if needed) by flash chromatography on silica gel (hexane–ethyl acetate) to afford the corresponding products.

Results and discussion

Initial experiments with phenyl boronic acid showed the homo-coupling reaction proceeded smoothly with almost quantitative conversion of starting material after 45–60 min reaction under the optimised conditions (Table 1).

Interestingly, a glutathione-free ferrite catalyst (Fe$_3$O$_4$) showed significantly reduced activity under identical reaction conditions (Table 1, entry 2). This phenomenon seems to be related to the inherent basicity of the nano-ferrite glutathione system as compared to the parent ferrite, in good agreement with previous reports in which an optimum basicity of the buffer concentration was needed to provide optimised yields of products.[13] However, these authors did not consider any potential effect of the support in the activity of the systems.

Table 1 Optimisation of the activities of nanoferrite materials in the MW-assisted aqueous homocoupling of phenylboronic acid^a

Entry	Catalyst	Time/min	Conversion (mol%)	$S_{homocoupling}$ (mol%)
1	Blank (no catalyst)	120	<5	—
2	Nano-ferrite	60	35	>95
3	Nano-ferrite + 0.5 mL NaOH 0.1 M	60	48	>95
4	Nano-ferrite + 1 mL NaOH 0.1 M	60	60	>90
5	Nano-ferrite + 2 mL NaOH 0.1 M	60	39	>90
6	Nano-ferrite glutathione	45	94	>99
7	Nano-ferrite glutathione + 0.5 mL NaOH 0.1 M	45	95	>95
8	Nano-ferrite glutathione + 1 mL NaOH 0.1 M	45	82	>95
9	Nano-ferrite glutathione + 2 mL NaOH 0.1 M	45	67	>90
10^b	Nano-ferrite glutathione	1440^b (conventional heating)	—	—

^{a} Reaction conditions: 1 mmol phenyl boronic acid, 2 mL water with few drops of NaOH 0.1 M solution (to facilitate dissolution of the boronic acid), 0.05 g catalyst, 300 W, 120 °C (maximum temperature reached). ^{b} Conventionally heated reaction, 120 °C, 24 h, same conditions as for microwave experiments.

A further addition of NaOH solution to the nanoferrite material increased yields to some extend but inferior activities were observed in all cases (Table 1, entries 3–5) compared to those achieved with the ferrite-glutathione catalyst.

Moreover, the addition of increasing quantities of NaOH solution has a detrimental effect on the yield of the products for the nano-ferrite glutathione system, possibly due to the partial cleavage of glutathione moieties from the catalyst under MW irradiation conditions. The combination of the transition metal iron oxide catalyst with the basicity of the amine groups from the gluthatione moiety is therefore the key asset for the successful homocoupling of phenyl boronic acid under the investigated conditions.

MW-assisted reactions were also found to remarkably superior to the activities of the catalyst under a conventionally heated system, in which negligible conversion of starting material was observed after 24 h reaction under identical conditions to those utilised in the MW protocol (1 mmol boronic acid, 2 mL water with NaOH 0.1 M, 120 °C, 0.05 g catalyst). Selectivities, in general, were very good for the homocoupling product, although increasing quantities of deborylated products were obtained at higher quantities of basic solution used (Table 1). This is a side reaction of Suzuki/homocoupling reactions involving boronic acids that corroborates earlier observations.[16]

Upon optimisation of reaction conditions, the scope of the protocol was subsequently extended to a range of substituted arylboronic acids (Table 2). Results summarized here demonstrate the methodology was also amenable to a wide range of substituents regardless of their electron-donating or withdrawing nature, making this environmentally-friendly protocol very useful from the viewpoint of simplicity and versatility (high conversions typically obtained in 45–60 min under microwave irradiation conditions). Of particular interest were the selectivities obtained for pyridyl and pyrazole boronic acids (Table 2, entries 11 and 12). Only small quantities of homocoupling products were obtained in these reactions, confirming the previously reported lability of such substrates to deborylation phenomena.[16]

The catalyst was also found to be highly stable and reusable under the investigated reaction conditions, preserving over 90% of its initial activity after 4 cycles (Fig. 3, left) and easily separable from the final reaction mixture with a simple magnet[17] (Fig. 3,
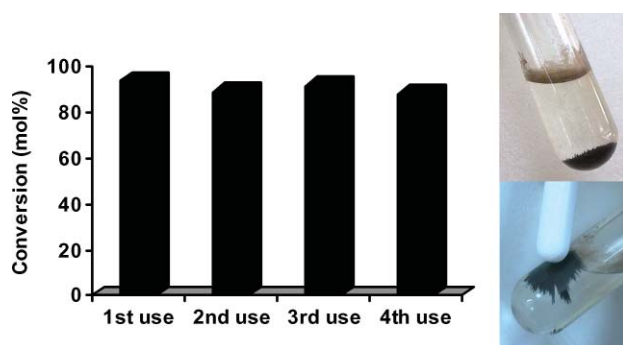
Fig. 3 Reuses of the magnetically separable nanoferrite-glutathione catalyst in the microwave-assisted homocoupling of phenylboronic acid. Reaction conditions: 1 mmol phenyl boronic acid, 2 mL water with few drops of NaOH 0.1 M solution, 0.05 g catalyst, 300 W, 120 °C max. temp. reached (left); catalyst separation using an external magnet (right).

Table 2 MW-assisted aqueous homocoupling of substituted arylboronic acids using nanoferrite glutathione as catalyst[a]

Entry	Substrate	Time/min	Conversion (mol%)	$S_{homocoupling}$ (mol%)
1	$(HO)_2B$— phenyl	45	94	>99
2	$(HO)_2B$— 4-methylphenyl	60	90	>99
3	$(HO)_2B$— 4-OH phenyl	60	87	>95
4	$(HO)_2B$— 4-Cl phenyl	45	91	>99
5	$(HO)_2B$— 4-Br phenyl	45	89	>99
6	$(HO)_2B$— 4-MeCO phenyl	60	80	>99
7	$(HO)_2B$— 4-OMe phenyl	60	84	>99
8	$(HO)_2B$— 4-CF₃ phenyl	45	92	>99
9	$(HO)_2B$— 2,6-dimethylphenyl	60	70	85
10	$B(OH)_2$ naphthyl	60	75	>90
11	$(HO)_2B$— pyridyl	60	59	<40[b]
12	$(HO)_2B$— pyrazole	60	67	65[b]

[a] Reaction conditions: 1 mmol boronic acid, 2 mL water with few drops of NaOH 0.1 M solution (to facilitate dissolution of the boronic acid), 0.05 g nano-ferrite glutathione catalyst, 300 W, 120-130 °C (maximum temperature reached). [b] The difference in selectivity to 100 corresponds to the respective deborylation products.

right). These results were in good agreement with previous reports of the activity of such materials in microwave-assisted catalysed processes.[12,17] The strong anchoring of the glutathione to the ferrite support through the thiol group seem to be related with the observed high reusability of the catalyst.

Further studies related to the observed deborylation side reaction as well as the use of iron oxide nanoparticles in related coupling processes are currently under active investigation in our laboratories.

Conclusions

We have reported the preparation of versatile glutathione-based nano-organocatalysts nanoparticles that are catalytically active in the microwave-assisted homocoupling of aryl boronic acids in water. We envisage these materials to be of utility in other coupling reactions as well as related base-catalysed processes, thus paving the way for the discovery of cheaper, simple and more environmentally compatible catalysts in the general domain of heterogeneously catalysed organic processes.

Acknowledgements

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