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Nanoparticle-Supported and Magnetically Recoverable Ruthenium Hydroxide Catalyst: Efficient Hydration of Nitriles to Amides in Aqueous Medium

Vivek Polshettiwar and Rajender S. Varma*[a]

The hydration of nitriles is one of the most imperative technologies for the large-scale synthesis of amides, which are a very significant group of compounds in the chemical and pharmaceutical industry.[1,2] Conventionally, amides have been synthesized by the hydration of nitriles, catalyzed by strong acids[3] and bases.[4] However, under these conditions, various by-products, such as carboxylic acids, are formed by hydrolysis of the starting nitriles and as well as amides. Also, many sensitive functional groups do not endure such harsh conditions, which consequently decrease the selectivity of reaction protocol. Therefore, the development of efficient procedures for the synthesis of amides that circumvent the extravagant use of stoichiometric reagents and/or acidic and basic media is highly desirable.

Several protocols, which predominantly use homogeneous metal complexes, have been reported for hydration of nitriles.[5] These methods suffer various drawbacks, especially the difficulty in separation of product and catalyst from the reaction mixture, as well as the use of inert atmosphere for handling air-sensitive metal catalysts. Heterogeneous systems have also been reported, such as alumina,[6] potassium fluoride doped Al_2O_3[7] and phosphates,[8] silica supported manganese oxides,[9] modified hydroxyapatite,[10] and ruthenium hydroxide coated on alumina and ferrites.[11] However, turnover numbers of these protocols are still very low and reusability of the catalyst is difficult. Pioneers in this field, Cadierno et al. recently developed excellent hydration protocol in pure water under neutral conditions.[12] Although this work led the way to advance the hydration reaction in aqueous medium, the protocol still needs traditional workup, using organic solvents to isolate the product and uses exotic ruthenium complexes as catalysts. Thus, the mild and efficient hydration of nitriles in eco-friendly conditions, a challenging research area, still far from being achieved by synthetic chemists.

Magnetic nanoparticles have emerged as realistic substitutes for conventional materials such as silica, polymer, etc. and as a robust, high-surface-area heterogeneous catalyst support.[13] Magnetic recoverability, which eliminates the necessity of catalyst filtration after completion of the reaction, is an additional attribute of these materials. In quest to exploit the diverse catalytic applications of magnetic nanomaterials with special emphasis on the development of sustainable organic transformations[14] and nanomaterials,[15] herein, we report a simple and efficient synthesis of nanoferrite-supported, magnetically recyclable ruthenium hydroxide $[Ru(OH)_x]$ catalyst and its application in the hydration of nitriles in a benign aqueous medium, which circumvents the use of organic solvents , even in the reaction workup stage.

The primary step of this objective was achieved by the synthesis and functionalization of magnetic nanoparticles (Scheme 1). The catalyst was prepared by sonicating nanoferrites with dopamine (which acts as a robust anchor and avoid $[Ru(OH)]_x$-leaching) in water for 2 h, followed by addition of ruthenium (Ru) chloride at a basic pH. Material with $[Ru(OH)]_x$ on the amine-functionalized nanoferrites was obtained in excellent yield.

Catalyst characterization by X-ray diffraction (XRD) (Figure 1b,d) and transmission electron microscopy (TEM) (Figure 1a,c) confirm the formation of the single-phase $[Fe_3O_4]$ nanoparticles, with spherical morphology and a size range of 11–16 nm, which is comparable with the crystallite size calculated from X-ray spectrum by using the Scherer formula (11.52 nm). Analysis of the FT-IR spectra confirms the anchoring of dopamine on ferrite surfaces (Figure S3 in the Supporting Information). The signals of Ru and $[Ru(OH)]_x$ were not detected in XRD, owing to the highly dispersed low percentage of Ru in the sample. The weight

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[a] Dr. V. Polshettiwar, Prof. Dr. R. S. Varma
Sustainable Technology Division
National Risk Management Research Laboratory
U. S. Environmental Protection Agency
MS 443, Cincinnati, Ohio 45268 (USA)
Fax: (+1) 513-569-7677
E-mail: varma.rajender@epa.gov
polshettiwar.vivek@epa.gov

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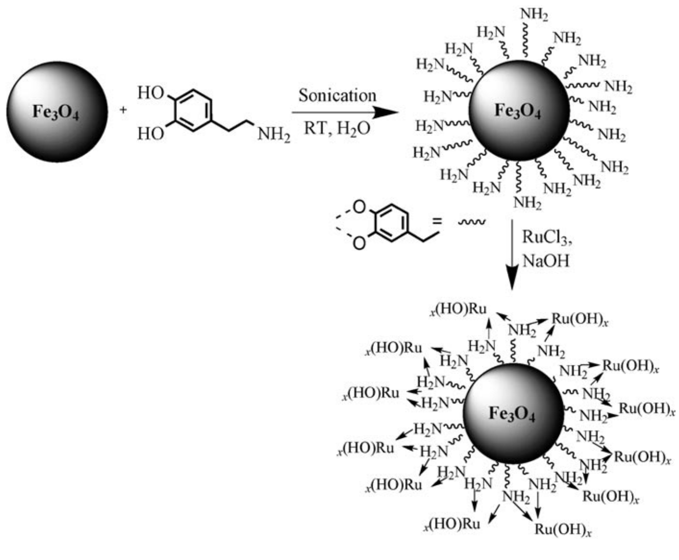


Scheme 1. Synthesis of nanoferrite–$[Ru(OH)]_x$.

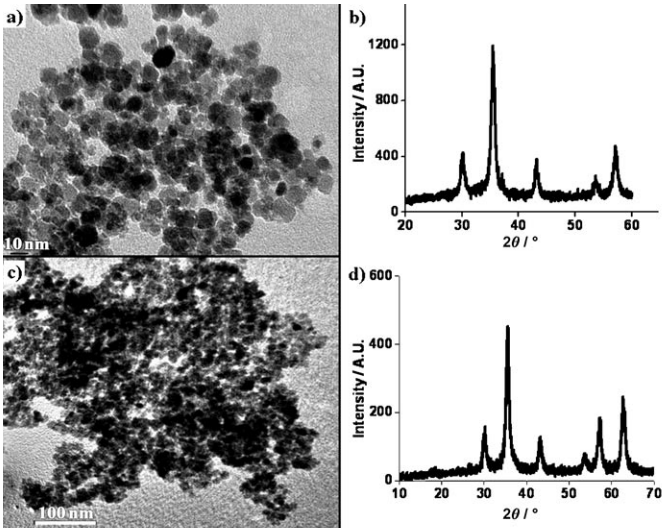
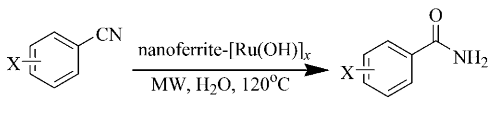


Figure 1. a) TEM of $[Fe_3O_4]$, b) XRD of $[Fe_3O_4]$, c) TEM of $[Fe_3O_4]$–$[Ru(OH)]_x$, and d) XRD of $[Fe_3O_4]$–$[Ru(OH)]_x$.

percentage of Ru was found to be 3.22% by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis.

This ruthenium hydroxide coated nanomaterial was then explored as a heterogeneous catalyst for hydration of nitriles in aqueous medium as a benign solvent,[16] under microwave (MW) irradiation conditions (Scheme 2). Use of MW-assisted chemistry is due to the efficiency of the interaction of polar nanocatalysts as well as water molecules with microwaves[13a,17] and the reaction mixture is rapidly heated to requisite temperatures under MW irradiation with the precise control of the reaction temperature.[18]



Scheme 2. Nanoferrite–$[Ru(OH)]_x$-catalyzed hydration of nitriles. X = Cl, OMe, NO_2, NMe_2, heterocycles.

Initially, experiments were performed to optimize reaction conditions for hydration of benzonitrile as a substrate, in aqueous medium (Table 1). First, the reaction was conducted using nanoferrites with particle sizes from 10–15 nm (Figure 1a,b) and hydration did not proceed at 100 °C as well as at 130 °C even after 30 min of MW exposure (Table 1, entries 1 & 2). We then tested nanoferrite–$[Ru(OH)]_x$ with particle sizes from 11–16 nm (Figure 1c,d) as catalyst at 100 °C for 20 min under MW irradiation and the low conversion of nitrile to amide (30%) was observed (Table 1, entry 3). However, when the reaction temperature was increased to 130 °C, the reaction proceeded expeditiously with 65% conversion within 20 min (Table 1, entry 4), which was further increased to 85% by extending the reaction time by another 10 min (Table 1, entry 5).

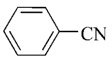
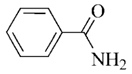
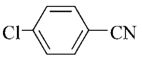
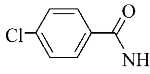
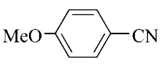
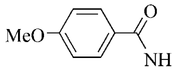
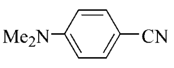
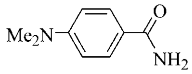
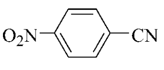
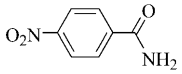
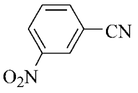
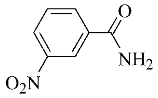
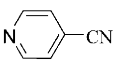
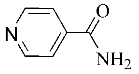
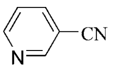
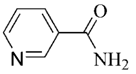
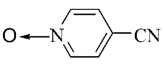
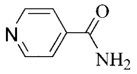
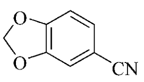
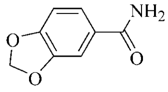
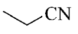
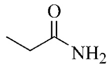
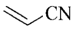
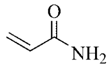
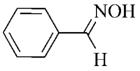
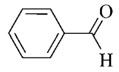
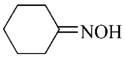
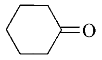
Table 1. Optimization of reaction conditions.[a]

Entry	Catalyst	T [°C][b]	t [min][c]	Conversion [%]
1	nano$[Fe_3O_4]$	100	30	0
2	nano$[Fe_3O_4]$	130	30	0
3	nano$[Fe_3O_4]$–$[Ru(OH)]_x$	100	20	30
4	nano$[Fe_3O_4]$–$[Ru(OH)]_x$	130	20	65
5	nano$[Fe_3O_4]$–$[Ru(OH)]_x$	130	30	85

[a] Reactions were carried out with 1 mmol of benzonitrile, 100 mg nanocatalyst, in water under MW irradiation. [b] Reaction temperature. [c] Reaction time.

Using the above optimized conditions, the scope of the present nanoferrite–$[Ru(OH)]_x$ catalyst was then explored for hydration of a variety of nitriles (Table 2). Nanoferrite–$[Ru(OH)]_x$ has shown high catalytic activity for hydration of activated, inactivated, and heterocyclic nitriles in pure water. A variety of benzonitriles derivatives (Table 1, entries 1 & 10) as well as aliphatic nitriles (Table 1, entries 11 & 12) were smoothly hydrated to corresponding amides in excellent yield. The rates were barely influenced by the electronic effects of the substituent's on the aromatic ring of benzonitriles. Interestingly, the hydration of *m*- and *p*-nitro benzonitriles (Table 2, entries 5 & 6) as well as 3- and 4-cyano pyridine (Table 2, entries 7 & 8) proceeded with similar rate, without any difference in reactivity, which shows negligible influence of substituent's position on reaction rate. Heterocyclic nitriles (Table 2, entries 7 to 10), extensively used building-blocks in drug discovery underwent hydration reaction with high yield, proving the suitability of this protocol for assembly of bio-molecules. However, hydration of isonicotinonitrile *N*-oxide does not yield corresponding isonicotinoamide *N*-oxide, instead isonicotinoamide was obtained (Table 2, entry 9). Hydration of the benzo[1,3-*d*]dioxole-5-carbonitrile proceeded only at cyano group to afford the corresponding amide, while keeping the dioxole ring intact (Table 2, entry 10) This chemoselective

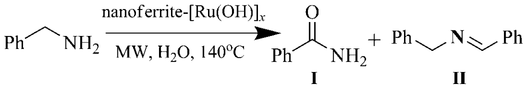
Table 2. Hydration of nitriles using nanoferrite–$[Ru(OH)]_x$.[a]

Entry	Substrate	Product	Yield [%][b]
1			85
2			88
3			84
4			61[c]
5			88
6			85
7			88
8			85
9			75
10			80
11			86
12			76
13			82
14			85

[a] Reactions were carried out with 1 mmol of nitrile, 100 mg nanocatalyst at 130 °C for 30 min, in water under MW irradiation. [b] Isolated yield. [c] Reaction time 45 min.

aspect of the protocol bodes well for total synthesis of drug molecules, for which it is required that a nitrile group be selectively hydrated to its amide counterpart without affecting other functional groups. We evaluated this catalyst for hydration of *syn*-benzaldoxime (Table 2, entry 13) and cyclohexanone oxime (Table 2, entry 14); which produced the corresponding benzaldehyde and cyclohexanone in good yield.

The scope of this catalyst was also examined for the oxidation of amines to amides (Scheme 3). First the reaction was conducted using 1 mmol of benzyl amine and 100 mg of catalyst at 140 °C under MW irradiation for 30 min and formation of corresponding amide (**I**) and by-product benzylidenebenzylamine (**II**) were observed, with poor conversions and as the reaction time increased up to 45 min, **II** was obtained with moderate (32 %) conversion. However, when



Reaction time	Yield [%]
30 min	**I** = 10, **II** = 12
45 min	**I** = 13, **II** = 32
60 min	**I** = 15, **II** = 78

Scheme 3. Nanoferrite–$[Ru(OH)]_x$-catalyzed oxygenation of benzylamine.

the reaction time was further increased to 60 min, the reaction proceeded expeditiously with 71 % benzylidenebenzylamine (**II**). These results open up a benign route for the conversion of benzylamine to benzylidenebenzylamine and prove the versatility of this catalyst system.

Separation and recovery of the catalyst is an important aspect for the synthesis of fine chemicals; which is generally performed by filtration with reduced efficiency. In our catalytic system, because of the super-paramagnetic nature of the nano$[Fe_3O_4]$–$[Ru(OH)]_x$, it can be recovered by simply using external magnets, with high efficiency and up to 95 % recovery of catalyst (Figure 2). After completion of the reaction, the reaction mixture turned clear and the catalyst was deposited on the magnetic bar within 30–45 sec (Figure 2b), which was easily removed from reaction mixture using an external magnet (Figure 2c). After separation of catalyst, the clear liquid was cooled slowly and analytically pure crystals of benzamides appeared (Figure 2d), which can be isolated from water medium by simple decantation. Thus, whole process was carried out in benign aqueous medium and no organic solvents were used, even in the workup steps of the reaction.

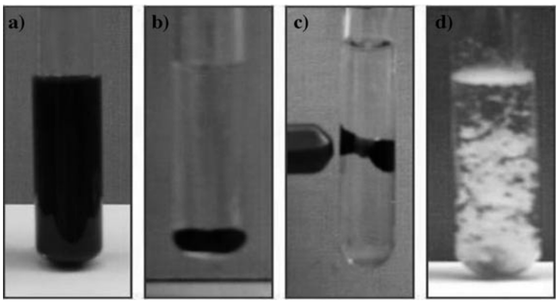


Figure 2. Hydration of benzonitrile to benzamide using nanoferrite–$[Ru(OH)]_x$ catalyst. a) During reaction under stirring, b) after completion of reaction without stirring, c) catalyst removal by external magnet, and d) product crystals appeared after cooling the aqueous solution.

For practical applications of heterogeneous systems, the lifetime of the catalyst and its level of reusability are very important factors. To clarify this issue, we established a set of experiments for the hydration of benzonitrile using the nanoferrite–$[Ru(OH)]_x$ catalyst. After the completion of the first reaction to afford the corresponding benzamide, the catalyst was recovered magnetically, washed with methanol, and finally dried at 50 °C. A new reaction was then performed with fresh benzonitrile under the same conditions. The nanoferrite-supported ruthenium hydroxide catalyst could be used at least 3 times without any change in the activity.

Heterogeneity and metal leaching of this catalyst for the hydration of benzonitrile was examined by the modified 'hot filtration' test. The reaction was stopped at 25 % conversion (10 min reaction time) and after 30 sec, the reaction mixture turned clear liquid and solid catalyst was deposited on the magnetic bar. Half portion of the liquid reaction mixture was taken into another reaction tube under hot conditions. After an additional 20 min MW exposure at 130 °C, the portion containing the nanocatalyst had proceeded to 85 % conversion, while the catalyst-free portion reacted only upto 32 %, evidently proving the heterogeneity of catalyst. Metal leaching was studied by ICP-AES analysis of the catalyst before and after the three reaction cycles. The Ru concentration of the catalyst was found to be 3.22 % before the reaction and 3.16 % after the reaction and there was no Ru detected in the final hydration product, which confirmed negligible Ru leaching. This is owed to a well defined amine-binding site located on the surface of nanoferrite (Scheme 1), which acts as a pseudo-ligand by non-covalent binding with $[Ru(OH)]_x$ through metal-ligand interaction. This non-covalent anchoring minimizes deterioration and metal leaching and allows efficient catalyst recycling. The most important criterion in choosing a catalyst is the metal recovery. It would be preferable to use a magnetically recoverable nanoferrite–$[Ru(OH)]_x$ catalyst, provided that the reaction proceeds at high turnover number (TON) and turnover frequencies (TOF) (Figure S4 in the Supporting Information) and that the catalyst leaves no remnants of metal in the end product, since metal contamination is highly regulated by the chemical industries. All above conditions were well satisfied by our recyclable nanoferrite-supported $[Ru(OH)]_x$ catalyst.

In summary, we have developed a convenient synthesis of nanoferrite-supported ruthenium hydroxide catalyst, which can be readily prepared from inexpensive starting materials in water. This nanomaterial then catalyzed the hydration of nitriles with high yield and excellent selectivity, which proceed exclusively in aqueous medium without using any organic solvents even in the workup stage. Also, being magnetically separable eliminated the requirement of catalyst filtration after completion of the reaction, which is an additional sustainable attribute of this oxidation protocol.

Experimental Section

Synthesis of magnetic nanoferrites: $FeSO_4{\cdot}7H_2O$ (13.9 g) and $Fe_2(SO_4)_3$ (20 g) were dissolved in 500 mL water in a 1000 mL beaker. Ammonium hydroxide (25 %) was added slowly to adjust the pH of the solution to 10. The reaction mixture was then continually stirred for 1 h at 50 °C. The precipitated nanoparticles were separated magnetically, washed with water until the pH reached 7, and then dried under a vacuum at 60 °C for 2 h.

Surface modification of nanoferrites: Nano$[Fe_3O_4]$ (2 g) was dispersed in 25 mL water by sonication for 30 min. Dopamine hydrochloride (2 g) dissolved in 5 mL of water was added to this solution and again sonicated for 2 h. The amine-functionalized nanomaterial was then precipitated using acetone, isolated by using an external magnet, and dried under vacuum at 50 °C for 2 h. Analysis of the FT-IR spectra confirms the anchoring of dopamine on ferrite surfaces (Figure S3 in the Supporting Information).

Synthesis of nanoferrite–$[Ru(OH)]_x$ catalyst: Amine-functionalized nano-$[Fe_3O_4]$ (2 g) was dispersed in water and $RuCl_3$ solution in water (60 mL, 8.3×10^{-3} M) was added to it and stirred for 20 min. Aqueous solution of sodium hydroxide (1 M) was added dropwise to bring the pH of this mixture to 13, and the resulting slurry was stirred for 36 h at room temperature. The product was separated magnetically, washed several times with water and methanol, and dried under vacuum at 50 °C for 2 h. The weight percentage of Ru in the catalyst was found to be 3.22 % by ICP-AES analysis.

Hydration of nitriles using nanoferrite–$[Ru(OH)]_x$ catalyst: 1 mmol of nitrile and 100 mg of nanoferrite–$[Ru(OH)]_x$ (0.003 mole % of Ru) catalyst were placed in a crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer and 5 mL of water was then added to the reaction mixture. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 130 ± 5 °C (temperature monitored by a built-in infrared sensor), power 50 to 140 Watt and pressure 10–60 psi for 30 min (Table 2). After completion of the reaction, the reaction mixture turned clear and catalyst was deposited on the magnetic bar within 30–45 sec (Figure 2b), which was easily removed from reaction mixture using an external magnet (Figure 2c). After separation of catalyst, the clear liquid was cooled slowly and analytically pure crystals of benzamides were obtained (Figure 2 d), which can be isolated from water medium by simple decantation/filtration.

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Keywords: amides · green chemistry · nanotechnology · ruthenium · supported catalysts

[1] a) C. E. Mabermann *in Encyclopedia of Chemical Technology*, Vol. 1 (Ed.: J. I. Kroschwitz,), Wiley, New York, **1991**, p. 251–266; b) *The Chemistry of Amides* (Ed.: J. Zabicky), Wiley-Interscience, New York, **1970**.

[2] a) P. K. Mascharak, *Coord. Chem. Rev.* **2002**, *225*, 201–214; b) R. Opsahl, *in Encyclopedia of Chemical Technology*, Vol. 2 (Ed.: Kroschwitz, J. I.), Wiley, New York, **1991**, p. 346–356.

[3] J. N. Moorthy, N. Singhal, *J. Org. Chem.* **2005**, *70*, 1926–1929.

[4] a) N. Kornblum, S. Singaram, *J. Org. Chem.* **1979**, *44*, 4727–4729; b) A. R. Katritzky, B. Pilarski, L. Urogdi, *Synthesis* **1989**, 949–950.

[5] a) A. Goto, K. Endo, S. Saito, *Angew. Chem.* **2008**, *120*, 3663–3665; *Angew. Chem. Int. Ed.* **2008**, *47*, 3607–3609; b) T. Oshiki, H. Yamashita, K. Sawada, M. Utsunomiya, K. Takahashi, K. Takai, *Organometallics* **2005**, *24* , 6287 –6290; c) K. L. Breno, M. D. Pluth, D. R. Tyler, *Organometallics* **2003**, *22*, 1203–1211; d) M. C. K. B. Dojoman, A. N. Ajjou, *Tetrahedron Lett.* **2000**, *41*, 4845–4850; e) N. V. Kaminskaia, N. M. Kostic, *J. Chem. Soc. Dalton Trans.* **1996**, 3677–3686; f) J. H. Kim, J. Britten, J. Chin, *J. Am. Chem. Soc.* **1993**, *115*, 3618–3622; g) S. I. Murahashi, S. Sasao, E. Saito, T. Naota, *J. Org. Chem.* **1992**, *57*, 2521–2523.

[6] C. P. Wilgus, S. Downing, E. Molitor, S. Bains, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett.* **1995**, *36*, 3469–3472.

[7] C. G. Rao, *Synth. Commun.* **1982**, *12*, 177–181.

[8] S. Sebti, A. Rhiil, A. Saber, N. Hanafi, *Tetrahedron Lett.* **1996**, *37*, 6555–6558.

[9] K. T. Li, M. H. Shih, H. W. Huang, C. J. Hu, *Synthesis* **1988**, 715–717.

[10] a) F. Bazi, H. El Badaoui, S. Tamani, S. Sokori, A. Solhy, D. J. Macquarrie, S. Sebti, *App. Cat. A* **2006**, *311*, 211–214; b) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, *Chem. Commun.* **2001**, 461–462.

[11] a) K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem.* **2004**, *116*, 1602–1606; *Angew. Chem. Int. Ed.* **2004**, *43*, 1576–1580; b) M. Kotani, T. Koike, K. Yamaguchi, N. Mizuno, *Green Chem.* **2006**, *8*, 735–741.

[12] V. Cadierno, J. Francos, J. Gimeno, *Chem. Eur. J.* **2008**, *14*, 6601–6605.

[13] a) A. Hu, G. T. Yee, W. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 12486–12487; b) N. T. S. Phan, C. S. Gill, J. V. Nguyen, Z. J. Zhang, C. W. Jones, *Angew. Chem.* **2006**, *118*, 2267–2270; *Angew. Chem. Int. Ed.* **2006**, *45*, 2209–2212; c) R. Abu-Reziq, H. Alper, D. Wang, M. L. Post, *J. Am. Chem. Soc.* **2006**, *128*, 5279–5282; d) C. O. Dalaigh, S. A. Corr, Y. Gunko, S. J. Connon, *Angew. Chem.* **2007**, *119*, 4407–4410; *Angew. Chem. Int. Ed.* **2007**, *46*, 4329–4332; e) D. Guin, B. Baruwati, S. V. Manorama, *Org. Lett.* **2007**, *9*, 1419–1421; f) T. Hara, T. Kaneta, K. Mori, T. Mitsudome, T. Mizugaki, K. Ebitanic, K. Kaneda, *Green Chem.* **2007**, *9*, 1246–1251; g) B. Baruwati, D. Guin, S. V. Manorama, *Org. Lett.* **2007**, *9*, 5377–5380; h) A.-H. Lu, E. L. Salabas, F. Schuth, *Angew. Chem.* **2007**, *119*, 1242–1266; *Angew. Chem. Int. Ed.* **2007**, *46*, 1222–1244; i) A. H. Latham, M. E. Williams, *Acc. Chem. Res.* **2008**, *41*, 411–420; j) C. Gonzalez-Arellano, J. M. Campelo, D. J. Macquarrie, J. M. Marinas, A. A. Romero, R. Luque, *ChemSusChem.* **2008**, *1*, 746–750.

[14] a) V. Polshettiwar, R. S. Varma, *Chem. Soc. Rev.* **2008**, *37*, 1546–1557; b) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629–639; c) V. Polshettiwar, R. S. Varma, *Curr. Opin. Drug Discov. Devel.* **2007**, *10*, 723–737; d) V. Polshettiwar, R. S. Varma, *J. Org. Chem.* **2008**, *73*, 7417–7419; e) V. Polshettiwar, R. S. Varma, *J. Org. Chem.* **2007**, *72*, 7420–7422; f) Y. Ju, D. Kumar, R. S. Varma, *J. Org. Chem.* **2006**, *71*, 6697–6700; g) Y. Ju, R. S. Varma, *J. Org. Chem.* **2006**, *71*, 135–141; h) Y. Ju, R. S. Varma, *Org. Lett.* **2005**, *7*, 2409–2411.

[15] a) V. Polshettiwar, M. N. Nadagouda, R. S. Varma, *Chem. Commun.* 2008, 6318–6320; b) V. Polshettiwar, B. Baruwati, and R. S. Varma, *Green. Chem.* **2009**, DOI: 10.1039/b815058c; c) V. Polshettiwar, R. S. Varma, *Org. Bio. Chem.* **2008**, *7*, 37–40; d) M. N. Nadagouda, R. S. Varma, *Cryst. Growth Des.* **2008**, *8*, 291–295; e) M. N. Nadagouda, R. S. Varma, *Cryst. Growth Des.* **2007**, *7*, 686–690; f) M. N. Nadagouda, R. S. Varma, *Cryst. Growth Des.* **2007**, *7*, 2582–2587; g) H. Choi, Y. J. Kim, R. S. Varma, D. D. Dionysiou, *Chem. Mater.* **2006**, *18*, 5377–5384.

[16] J. H. Clark, S. J. Tavener, *Org. Process Res. Dev.* **2007**, *11*, 149–155.

[17] D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563–2591.

[18] C. J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82.

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