

## Greener routes to organics and nanomaterials: Sustainable applications of nanocatalysts\*

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**Abstract:** Sustainable synthetic activity involving alternate energy input and greener reaction medium under aqueous or solvent-free conditions is summarized. This includes the synthesis of heterocyclic compounds, coupling reactions, and a variety of reactions catalyzed by basic water or recyclable and reusable magnetic nanocatalysts in aqueous media using microwave (MW) irradiation. Micropine-structured catalysts and magnetic nanoferrites and their post-synthetic modification with ligands and other nanometals serve as sustainable nanocatalysts in benign media. The strategic approach attempts to fulfill most of the green chemistry principles in a comprehensive manner and aims to create sustainable functional chemicals that may find large-scale use with significant waste minimization.

**Keywords:** chemical synthesis; green chemistry; heterocyclic chemistry; microwaves; nanomaterials; nanostructured materials.

### INTRODUCTION

The concept of “green chemistry” to meet the scientific challenges of protecting human health and the environment is central to the novel design aspects in conducting business in the chemical sciences. Green chemistry is defined as “the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products” and emphasizes minimum hazard as the criteria while designing new chemical processes [1]. The use of bio-renewable raw materials in benign reaction media and recyclable nanocatalysts in atom-economic syntheses are some of the frontier thrust areas [2]. This may include alternative reaction activation methodology, such as photocatalysis, mechanochemical mixing, and microwave (MW) and ultrasonic irradiation [3]. MW heating has emerged as an alternative energy source to accomplish expeditious chemical transformations in organic [3,4] and, more recently, in materials synthesis [5]. Chemical processes in the syntheses of pharmaceuticals, fine chemicals, and polymers that use alternative energy input in combination with nanocatalysts shorten the reaction times, which eliminate or minimize side product formation [6]. Developments in these thematic areas, especially involving benign reaction media, such as polyethylene glycol (PEG) and water, in conjunction with photoactivation, MW and ultrasonic irradiation, and/or ball-milling under solvent-free conditions [7], may help deliver sustainable pathways for chemical synthesis and transformations as exemplified in the sections below. The approach must encompass “benign by design” principles and make an effort to utilize biodegradable and bio-renewable resources.

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\**Pure Appl. Chem.* **85**, 1611–1710 (2013). A collection of invited papers based on presentations at the 4<sup>th</sup> International IUPAC Conference on Green Chemistry (ICGC-4), Foz do Iguaçu, Brazil, 25–29 August 2012.

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In the synthesis of nanocatalysts, the use of MWs is now more often deployed as the material properties are based largely on their size and shape; often, nanoparticles of uniformly small size are obtainable using this approach [5]. This is because the growth of the materials on nanoscale is predominantly dependent on the thermodynamic and kinetic barriers in the reaction as defined by the reaction trajectory. The recyclability and reuse aspects are equally important especially when it comes to using rare and precious nanocatalysts. Several “greener” applications in catalysis have been addressed via magnetically recyclable and recoverable nanocatalysts for oxidation, reduction, and condensation reactions [8], where there has been a significant impact on sustainable synthesis.

## NANOMATERIALS

The production of engineered nanomaterials represents a major breakthrough in materials science and nanobased materials. The conventional bottom-up approach for the production of nanoparticles often requires the use of aggressive reducing agents, namely, hydrazines or sodium borohydride, the use of a capping agent, such as polyvinylpyrrolidone (PVP), and may additionally need the use of a volatile organic solvent including halogenated organics. Consequently, there is a necessity to develop more environmentally benign methods. The choice of an eco-friendly reducing agent, an environmentally compatible solvent system, and a nonhazardous capping agent for stabilizing the ensuing nanoparticles are some of the main criteria for “greener” nanoparticle synthesis [9].

### Greener synthetic strategies

Our unique risk-reduction approach avoids the exposure to or eliminates the use and generation of the hazardous substances normally used in the preparation of these nanomaterials; several pathways have been developed using benign reagents particularly in the matrix in which they are to be used, thus avoiding excessive handling or manipulation of nanoparticles [9]. Eco-friendly synthetic strategies have been developed in recent years to prepare these nanometals via routes that use benign reagents rather than hazardous substances [9]. The sustainable preparation of nanoparticles may involve the use of vitamins B<sub>1</sub>, B<sub>2</sub>, C, and tea and wine polyphenols [9,10], which function both as reducing and capping agents. This circumvents the use of toxic reducing agents, such as borohydrides or hydrazines and capping agents like PVP. These simple and aqueous protocols generate bulk quantities of nanocatalysts [11] without the usage of large amounts of insoluble templates and have been applied in the catalysis arena.

#### *Use of agricultural residues and plant polyphenols*

The synthesis of nanometal/nanometal oxide/nanostructured composites and their stabilization simply involves the use of naturally occurring bio-renewable resources, such as plant extracts and polyphenolic antioxidants from tea and coffee [12], biodegradable polymers, such as carboxymethyl cellulose (CMC) [13], reducing sugars [14] and agricultural materials (beet juice) [15a], and residual waste material (red grape pomace from winery waste) [15b].

#### *Use of vitamins and sugars*

Our sustainable activity for the preparation of nanoparticles involves the use of vitamins B<sub>1</sub>, B<sub>2</sub> [11], and C [16] and tea [12] and wine polyphenols [15b]. These vitamins or phenolic constituents function both as reducing and capping agents, provide simple, greener synthetic methods to bulk quantities of nanospheres, nanorods, nanowires, and nanoballs of aligned nanobelts, and nanoplates of the metals in water, circumventing the need for large amounts of insoluble templates [11]. Bulk and shape-controlled synthesis of noble nanostructures with various shapes, such as cubes, prisms, and hexagons occurs via MW-assisted spontaneous reduction of noble metal salts using an aqueous solution of  $\alpha$ -D-glucose, sucrose, and maltose [14]. The size of the ensuing nanoparticles can be simply controlled by varying the concentration of the sugars; higher concentration provides uniformly smaller size particles, which increase with a decrease in the concentration of the sugars. A general method has been developed for

the cross-linking reaction of poly(vinyl alcohol) (PVA) with metallic systems, such as Pt, Cu, and In; bimetallic systems, such as Pt–In, Ag–Pt, Pt–Fe, Cu–Pd, Pt–Pd, and Pd–Fe [17]; single-wall carbon nanotubes (SWNTs); multiwall carbon nanotubes (MWNTs); and Buckminsterfullerenes (C-60) [18]. The strategy can be extended to the formation of biodegradable carboxymethylcellulose (CMC) composite films with noble nanometals [13]. The metal decoration and alignment of carbon nanotubes in CMC is possible using a MW-assisted approach [19], which enables the shape-controlled bulk synthesis of Ag and Fe nanorods in PEG [20].

## ALTERNATE ENERGY INPUT: MW HEATING

MW heating has become an alternative energy source to accomplish chemical transformations in minutes, instead of hours or even days [3]. Conventional heating techniques essentially drive the reaction via the conduction of blackbody radiation where the reaction vessel acts as an intermediary for energy transfer from the oil bath or heating mantle to the solvent and finally to the reacting molecules. This non-uniform reaction condition has been a challenge in the synthesis of nanomaterials where uniform nucleation and growth rates are critical to material quality. MW heating has addressed these problems of inhomogeneous heating in conventional thermal techniques as its use provides increased reaction kinetics, rapid initial heating, and hence, enhanced reaction rates culminating in clean reaction products with rapid consumption of starting materials and higher yields [5]. The methodology is applicable under a variety of conditions even for enzymatic and biological systems.

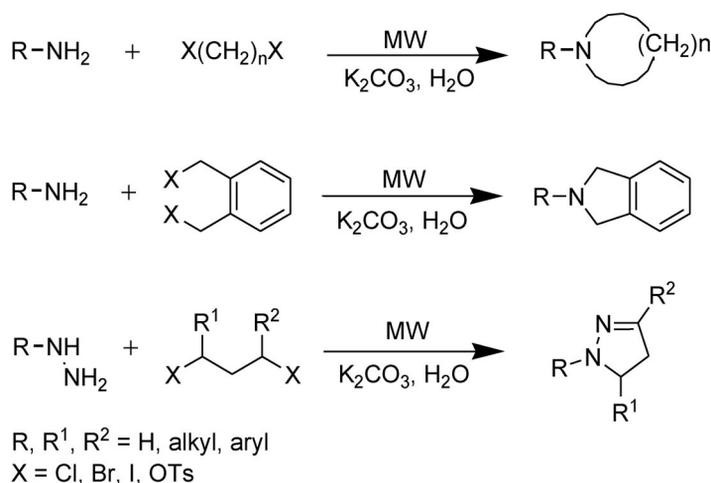
## Solvent-free MW-assisted synthesis

In the early 1990s, our laboratory focused on this MW-expedited approach under solvent-free conditions using an unmodified kitchen MW oven in open reaction vessels [4]. The synthesis of a variety of industrially important compounds and intermediates, namely, imines, enamines, enones, nitroalkenes, oxidized sulfur species, and heterocycles was accomplished and was exemplified by a concise synthesis of flavones, 2-arylbenzofurans, tetrahydroquinolones, and thiazole derivatives, thus demonstrating the use of in situ generated reactive intermediates in a one-pot synthesis of heterocyclic compounds [21]. The strategy was later extended to rapid and parallel synthesis in solvent-free multicomponent reactions as shown in the assembly of imidazo[1,2-*a*]annulated pyridines, pyrazines, pyrimidines (Ugi reaction), and dihydropyrimidine-2(1*H*)-ones (Biginelli reaction) [4].

## MW-assisted synthesis of *N*-heterocycles in water

*N*-heterocycles are of great significance to everyday life because these structural subunits occur in several natural products, such as antibiotics, vitamins, hormones, and alkaloids, as well as pharmaceuticals and dyes. A general synthetic approach to a broad category of nitrogen-containing heterocycles, such as azetidines, pyrrolidines, piperidines, azepanes, *N*-substituted 2,3-dihydro-1*H*-isoindoles, 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines, has been accomplished in a basic aqueous medium using MWs; the reactions proceed via double *N*-alkylation of primary amines and hydrazine derivatives (Scheme 1) with readily available alkyl dihalides (or ditosylates), thus providing facile entry to important classes of building blocks in pharmaceuticals [22–24].

This MW-assisted approach abbreviated the reaction time significantly and utilized readily available amines and hydrazines with alkyl dihalides or ditosylates to assemble two C–N bonds in a simple S<sub>N</sub>2-like sequential heterocyclization experimental protocol, which has not been fully realized under conventional reaction conditions. The strategy avoids multistep reactions and functional group protection/deprotection sequences and eliminates the use of expensive phase-transfer and transition-metal catalysts.



**Scheme 1** Synthesis of nitrogen-heterocycles in aqueous media using MW irradiation.

It is important to note that this reaction is not a homogeneous single-phase system as neither reactant is soluble in aqueous alkaline reaction medium. The selective absorption of MWs by polar molecules and intermediates in a multiphase system could substitute as a phase-transfer catalyst without using any phase-transfer reagent, thereby providing the observed acceleration as has been observed for ultrasonic irradiation [25].

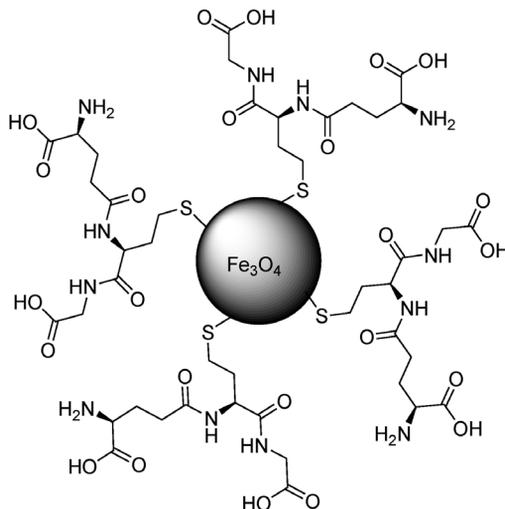
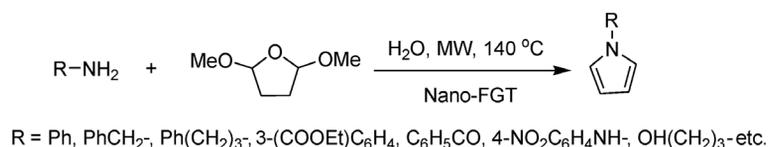
The experimental observation is in accord with the mechanistic postulation wherein the polar transition state of the reaction is favored by MW irradiation with respect to the dielectric polarization nature of MW energy transfer. In large-scale experiments, the phase separation of the desired product in either solid or liquid form from the aqueous media can facilitate product purification by simple filtration or decantation instead of tedious column chromatography, distillation, or extraction processes, which reduces the usage of volatile organic solvents [24].

## CATALYSTS ON MAGNETIC NANOSUPPORTS

The use of magnetic nanoparticles (MNPs) as catalysts in organic synthesis has become a subject of intense investigation as the recovery of expensive catalysts after the reaction and reusing them without losing its activity are important features in the sustainable process development [8]. The greener generation of nanoparticles and their eco-friendly applications in catalysis via magnetically recoverable and recyclable nanocatalysts for a variety of oxidation, reduction, and condensation reactions [26–31], has made a tremendous impact on the development of sustainable pathways. The functionalization of the surfaces of nanosized magnetic materials provides a quasi-homogeneous phase and acts as a bridge between hetero- and homogeneous catalysis, thus retaining the relative advantages of both of the systems. The heterogenization of the catalyst using MNPs allows it to be recovered and reused using an external magnet. Because of the reduced size in nm range, most of the catalyst's surface is accessible for reaction as it provides quasi-homogeneous media for the catalysts, which can be separated using an external magnet.

### Post-synthetic modification of MNPs

Glutathione (GT) molecules have been anchored on magnetic nanoferrites via their thiol groups and the ensuing catalyst (nano-FGT) displayed high activity for the efficient synthesis of a wide variety of alkyl, aryl, and heterocyclic amines (Fig. 1). The functionalized amines could be selectively converted into the



**Fig. 1** Nano-FGT-catalyzed Paal–Knorr reactions.

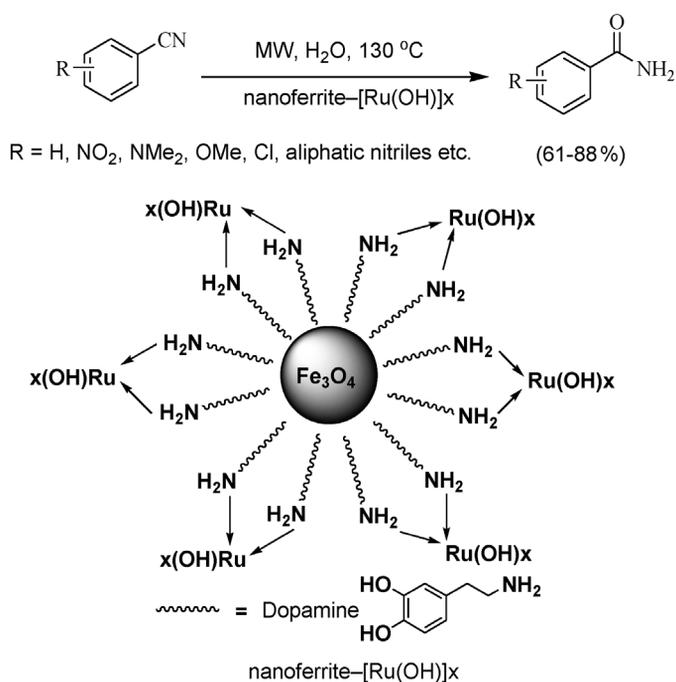
corresponding pyrroles without affecting several sensitive functional groups (such as esters, ketones, alcohols, C=C bonds, etc.).

These novel magnetically recoverable and nanoparticle-supported organocatalysts catalyze the Paal–Knorr and other heterocyclic reactions with high yield exclusively in a pure aqueous medium. This precludes the use of toxic organic solvents, even in the work-up stage [6,26,31].

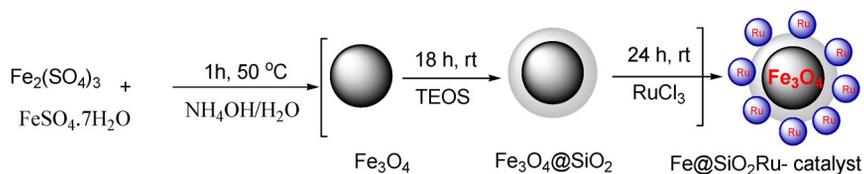
The post-synthetic modification of nanoferrites with dopamine and then anchoring of the metal particles (Fig. 2) provides wide-ranging possibilities to deploy these nanocatalysts effectively. As an example, hydration of benzonitrile with ruthenium hydroxide on magnetic nanoferrites transforms it to benzamide in water. After completion of the reaction, as the stirring stopped, the reaction mixture turned clear and the catalyst was deposited on the magnetic bar because of the paramagnetic nature of the nanoferrite-Ru(OH)<sub>x</sub>. The catalyst can be easily removed using an external magnet, thus avoiding a filtration step. After separation of the catalyst, the clear reaction mixture was cooled slowly and crystals of benzamides with acceptable purity were precipitated. The entire procedure was carried out in a pure aqueous medium using no organic solvents during the reaction nor in the work-up steps [27]. The remarkable feature of these protocols is that the reaction proceeded with high turnover numbers attributed to the use of a nanocatalyst and at high turnover frequencies (because of the use of MWs). The catalyst could be successfully used several times and left no remnants of metal in the end-product.

In order to further simplify this conceptual theme for synthetic chemists who are not so well versed in materials science, we have successfully demonstrated a one-pot synthesis of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>Ru for the hydration of nitriles in aqueous media (Scheme 2) via sequential addition of reagents to generate and coat the magnetic particles [32].

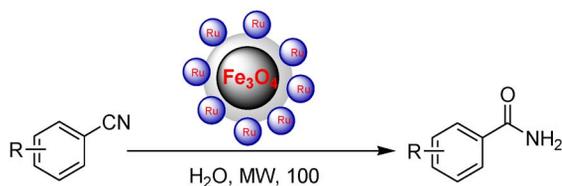
The first example of a magnetically separable nano-FGT-Cu catalyst for azide alkyne cycloaddition (AAC) reaction was developed recently [33] where this general reaction could be performed in one pot via in situ azide generation followed by cycloaddition in aqueous media (Scheme 3); nano-FGT-Cu catalyst could be reused three times without losing its activity.



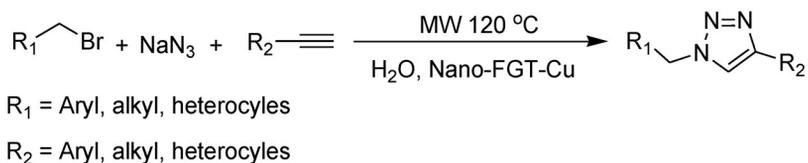
**Fig. 2** Nanoferrite-[Ru(OH)]<sub>x</sub>-catalyzed aqueous hydration of nitriles.



One pot synthesis of nano-Fe@SiO<sub>2</sub>Ru catalyst

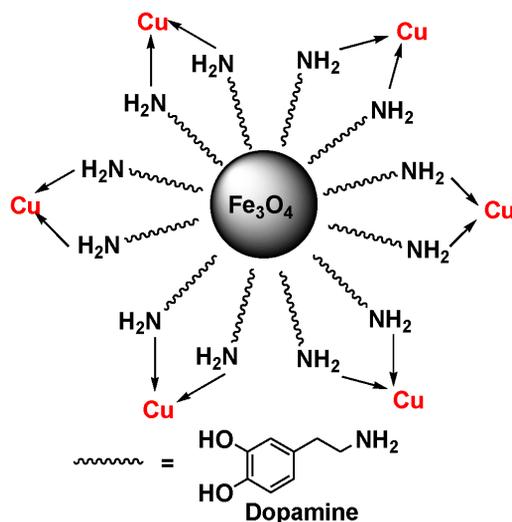


**Scheme 2** Hydration of nitriles catalyzed by nano-Fe@SiO<sub>2</sub>Ru catalyst.

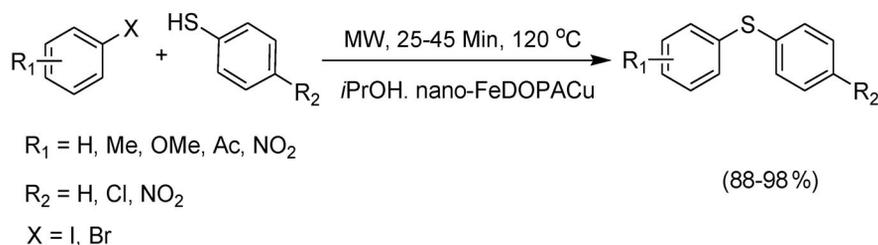


**Scheme 3** Nano-FGT-Cu-catalyzed “click” 1,3-dipolar cycloaddition reactions.

A similar nano-FeDOPACu bimetallic catalyst (Fig. 3) has found useful application in the C-S coupling of aryl halides and thiophenols under MW heating conditions [34]. A wide variety of commercially available iodides and bromides undergo reaction with thiophenols nicely, affording the corresponding diaryl sulfides; aryl chloride, however, did not participate in this coupling reaction (Scheme 4).



**Fig. 3** Nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-Cu catalyst (nano-FeDOPACu) (reproduced by permission from the Royal Society of Chemistry, ref. [8]).



**Scheme 4** Nano-FeDOPACu-catalyzed cross-coupling of aryl halides with thiophenols.

## CONCLUSION

The evolution in the development of “greener processes” continues from solvent-free reactions to the use of alternative energy-input systems, such as MW or mechanochemical mixing in benign reaction media such as PEG and water. The utility of nanoparticles, especially those that can be retrieved magnetically, are garnering special attention as nanocatalysts. The modification of the MNP surface with organic ligands enhances the adsorption of catalytically active metal nanoparticles, which provide identical or better reactivity than the corresponding homogeneous catalysts. The excellent dispersity of the MNPs in various solvents is an additional advantage, since it exposes the surface-bound active reaction sites for the reactants in the best possible manner. In the coming years, the novel design of magnetically recoverable heterogeneous asymmetric catalysts supported on [Fe<sub>3</sub>O<sub>4</sub>] nanoparticle systems will find exciting applications in various asymmetric C–C bond formation reactions, asymmetric hydrogenations, and asymmetric cycloaddition reactions.

## ACKNOWLEDGMENT

I wish to thank my collaborators and colleagues, past and present, whose names appear in the reference section for their immense contribution to our efforts in green and sustainable chemistry.

## REFERENCES

1. P. T. Anastas, J. C. Warner. *Green Chemistry: Theory and Practice*, Oxford University Press, New York (1998).
2. A. M. Balu, B. Baruwati, E. Serrano, J. Cot, J. Garcia-Martinez, R. S. Varma, R. Luque. *Green Chem.* **13**, 2750 (2011).
3. R. B. Nasir Baig, R. S. Varma. *Chem. Soc. Rev.* **41**, 1559 (2012).
4. R. S. Varma. *Green Chem.* **1**, 43 (1999).
5. M. N. Nadagouda, T. Speth, R. S. Varma. *Acc. Chem. Res.* **44**, 469 (2011).
6. V. Polshettiwar, R. S. Varma. *Green Chem.* **12**, 743 (2010).
7. R. S. Varma. *Green Chem.* **10**, 1129 (2008).
8. (a) R. B. Nasir Baig, R. S. Varma. *Chem. Commun.* **49**, 752 (2013); (b) R. B. Nasir Baig, R. S. Varma. *Green Chem.* **15**, 398 (2013); (c) M. B. Gawande, P. S. Branco, R. S. Varma. *Chem. Soc. Rev.* **42**, 3371 (2013).
9. R. S. Varma. *Curr. Opin. Chem. Eng.* **1**, 123 (2012).
10. J. Virkutyte, R. S. Varma. *Chem. Sci.* **2**, 837 (2011).
11. M. N. Nadagouda, R. S. Varma. *Green Chem.* **8**, 516 (2006).
12. M. N. Nadagouda, R. S. Varma. *Green Chem.* **10**, 859 (2008).
13. M. N. Nadagouda, R. S. Varma. *Biomacromolecules* **8**, 2762 (2007).
14. M. N. Nadagouda, R. S. Varma. *Cryst. Growth Des.* **7**, 686 (2007).
15. (a) J. Kou, R. S. Varma. *ChemSusChem* **5**, 2435 (2012); (b) B. Baruwati, R. S. Varma. *ChemSusChem* **2**, 1041 (2009).
16. M. N. Nadagouda, R. S. Varma. *Cryst. Growth Des.* **7**, 2582 (2007).
17. M. N. Nadagouda, R. S. Varma. *Macromol. Rapid Commun.* **28**, 465 (2007).
18. M. N. Nadagouda, R. S. Varma. *Macromol. Rapid Commun.* **28**, 842 (2007).
19. M. N. Nadagouda, R. S. Varma. *Macromol. Rapid Commun.* **29**, 155 (2008).
20. M. N. Nadagouda, R. S. Varma. *Cryst. Growth Des.* **8**, 291 (2008).
21. R. S. Varma, R. B. Nasir Baig. In *Microwaves in Organic Synthesis*, 3<sup>rd</sup> ed., A. de la Hoz, A. Loupy (Eds.), Chap. 10, pp. 431–487, Wiley-VCH, Weinheim (2012).
22. Y. Ju, R. S. Varma. *Tetrahedron Lett.* **46**, 6011 (2005).
23. Y. Ju, R. S. Varma. *Org. Lett.* **7**, 2409 (2005).
24. Y. Ju, R. S. Varma. *J. Org. Chem.* **71**, 135 (2006).
25. R. S. Varma, K. P. Naicker, D. Kumar. *J. Mol. Cat. A: Chemical* **149**, 153 (1999).
26. V. Polshettiwar, B. Baruwati, R. S. Varma. *Chem. Commun.* 1837 (2009).
27. V. Polshettiwar, R. S. Varma. *Chem.—Eur. J.* **15**, 1582 (2009).
28. V. Polshettiwar, B. Baruwati, R. S. Varma. *Green Chem.* **11**, 127 (2009).
29. V. Polshettiwar, B. Baruwati, R. S. Varma. *ACS Nano* **3**, 728 (2009).
30. R. Luque, B. Baruwati, R. S. Varma. *Green Chem.* **12**, 1540 (2010).
31. V. Polshettiwar, R. S. Varma. *Tetrahedron* **66**, 1091 (2010).
32. R. B. Nasir Baig, R. S. Varma. *Chem. Commun.* **48**, 6220 (2012).
33. R. B. Nasir Baig, R. S. Varma. *Green Chem.* **14**, 625 (2012).
34. R. B. Nasir Baig, R. S. Varma. *Chem. Commun.* **48**, 2582 (2012).