DOI 10.1515/gps-2013-0076 — Green Process Synth 2013; 2: 603–609

Review

Yibo Huang and Wei Zhang*

Magnetic nanoparticle-supported organocatalysis

Abstract: Magnetic nanoparticle (MNP)-supported catalysis is a new method to facilitate catalyst separation and reuse. This technique has recently been introduced for organocatalysis. MNP-supported organocatalysts have been evaluated for their activity, selectivity, and recyclability in a range of chemical transformations, especially for asymmetric synthesis. The synthesis and application of Fe_3O_4 MNP-supported organocatalysis are highlighted in this short review article.

Keywords: asymmetric synthesis; catalyst recovery; Fe_3O_4 magnetic nanoparticles; green chemistry; supported organocatalysis.

***Corresponding author: Wei Zhang,** Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, USA, e-mail: wei2.zhang@umb.edu
Yibo Huang: Changzhou Institute of Engineering and Technology, Department of Pharmaceutical and Biological Engineering, Changzhou, Jiangsu, 213164 China

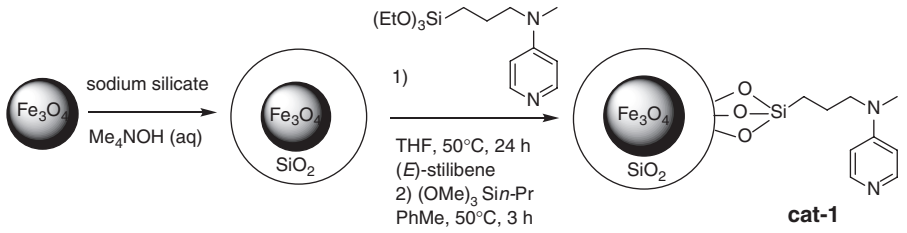
1 Introduction

Catalysis is an important green chemistry tool to increase reaction efficiency, save energy, and reduce chemical waste. Compared to transition metal catalysis and biocatalysis, organocatalysis has unique features such as being toxic heavy metal-free, with novel activation mechanism, relatively low cost, reduced sensitivity to moisture and oxygen, good structural amenability, and good availability from nature sources [1–3]. However, high catalyst loading (up to 20%) is commonly requires for organocatalysis, which makes the catalyst recovery highly desirable. In addition to solids (polymers or silica gel) [4], ionic liquids [5], and fluorous tags [6], magnetic nanoparticles (MNPs) have recently emerged as a new supporting material for catalyst recovery [7, 8]. MNPs have been successfully used to immobilize transition metals, organic ligands, organocatalysts, and biocatalysts through absorption or formation of covalent bonds [9–19]. As a consequence of small size, big surface area and great pore volume, MNP-supported catalysis is quasi-homogeneous and has favorable reaction kinetics. The catalyst can be easily separated by applying an external magnetic field. The liquid phase containing the product is decanted for purification. The magnetic-field-held catalyst is washed with an appropriate solvent and then dried for reuse. Catalyst leaching is usually lower than in other material-supported catalysis. There are several excellent review articles [8–11] with detailed information on the preparation, characterization, tuning, and attachment of MNPs. Discussions on the chemical and physical properties of MNPs are beyond the scope of this short review. This article only focuses on the preparation of Fe_3O_4 MNP-supported organocatalyts and their synthetic applications.

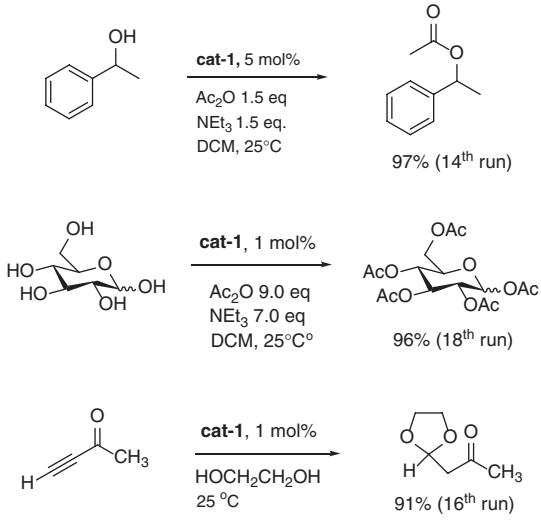
2 Synthesis and application of Fe_3O_4 nanoparticle-immobilized organocatalysts

In contrast to transition metals, which could be non-covalently grated on the MNPs, organocatalysts are attached to Fe_3O_4 by covalent bonds such as –SiOR, –OR, and –SR. The typical loading of organocatalyst on MNP-support is around 0.1–1.0 mmol/g [8–11]. In 2007, the Connon group reported the first example of MNP-supported organocatalysis by the treatment of Fe_3O_4 particles with sodium silicate to form SiO_2-coated Fe_3O_4 particles. The coated-MNP catalyst was then used for the synthesis of 4-*N*,*N*-dialkylaminopyridine (DMAP)-type organocatalyst **cat-1** (Scheme 1) [19]. This catalyst was used for acetylation of 1-phenylethanol, peracetylation of D-glucose, and formal oxidation of alkyne (Scheme 2). The results showed that **cat-1** has good activity and recyclability. At 5 mol% catalyst loading, 1-phenylethanol can be acylated in 94–98% yields. No physical or chemical degradation of the catalyst was observed after 14 consecutive catalyst cycles. It is noteworthy that SiO_2-coated MNPs could reduce catalyst aggregation and facilitate surface functionalization.

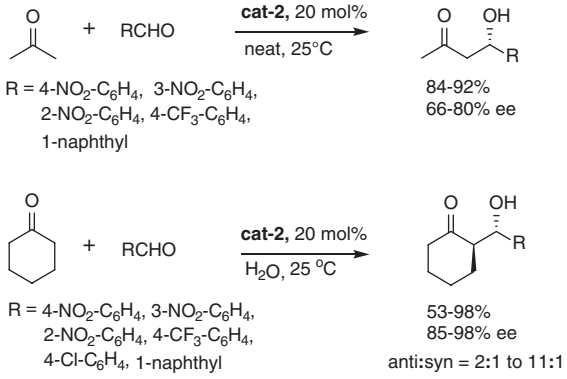
Silylation reaction is a good way to anchor organocatalysts. Cheng and coworkers used this method to synthesize supported bifunctional amino catalyst **cat-2**



Scheme 1 Preparation of DMAP catalyst **cat-1**.



Scheme 2 Acetylation and related reactions promoted by **cat-1**.



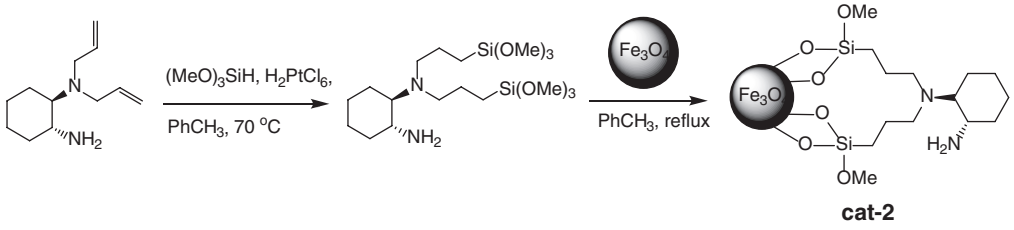
Scheme 4 The aldol reaction promoted by **cat-2**.

(Scheme 3) [20]. It could be used to catalyze aldol reaction of aldehydes with acetone or cyclohexanone (Scheme 4). Acidic additives such as TFA or TfOH were used to improve the yield. Stronger acid TfOH gave slightly better enantioselectivity than TFA for the aldol reaction of acetone. But for the reaction of cyclohexanone, the TFA was more effective to afford the product in high yield and stereoselectivity.

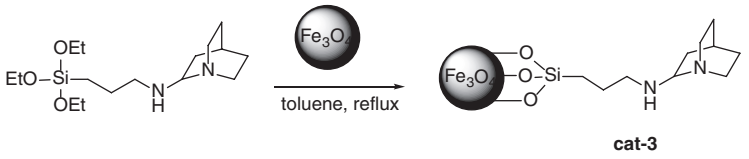
The Cheng group also prepared MNP-immobilized quinucidine catalyst **cat-3** by direct silylation (Scheme 5) [21]. This catalyst was used to promote the Morita-Baylis-Hillman reactions of a wide range of Michael donors with aldehydes (Scheme 6). The yields are 80–99% under the neat condition. The **cat-4** could be reused seven times without significant loss of activity.

The Connon group also reported the preparation of **cat-4** via the reaction of Fe_3O_4-supported *N*-methyl dopamine hydrochloride with (*S*)-α,α-diphenylprolinolcatalyst (Scheme 7) [22]. This catalyst promoted acylative kinetic resolution of racemic mono-protected *cis*-diol (Scheme 8). It was found that 5 mol% catalyst loading could resolve *cis*-diol with a selectivity factor of 10.1 and allowed the generation of resolved alcohol with 99% ee (72% conversion), which is comparable to that obtained with the corresponding homogeneous catalyst of 97% ee (69% conversion) [23].

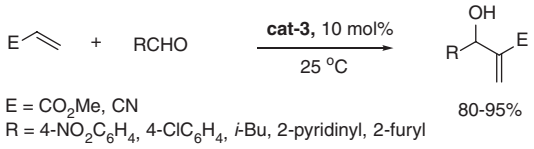
The Pericas group synthesized MNP-attached prolinol catalyst **cat-5** via click chemistry through an azide linker (Scheme 9) [24]. It has been utilized for highly selective



Scheme 3 Preparation of chiral amine catalyst **cat-2**.



Scheme 5 Synthesis of quinuclidine **cat-3**.

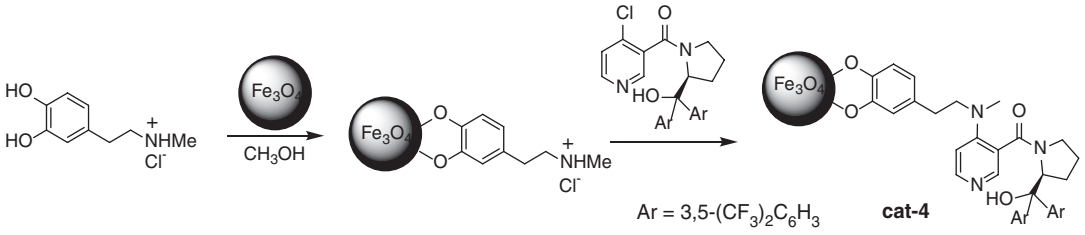


Scheme 6 MBH reaction promoted by **cat-3.**

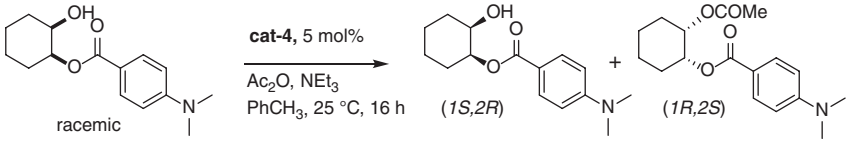
asymmetric Michael reactions of propanal with nitroolefins (Scheme 10). After the third run, a significant decrease in catalytic activity was observed although the enantioselectivity was maintained. This is probably caused by catalyst leaching or decomposition.

Well-known bifunctional organocatalysts such as the cinchona alkaloid/thiourea system have been developed for a broad range of asymmetric reactions [25–28]. The Connon group reported the synthesis of Fe_3O_4-supported bifunctional catalyst **cat-6** through a thiol linker (Scheme 11) [29]. The asymmetric Michael addition of dimethyl malonate with (*E*)-*β*-nitrostyrene could be promoted with **cat-6** (Scheme 12). It was found that **cat-6** is less enantioselective than unsupported bifunctional catalyst probably caused by the "ageing effect", which was previously observed by the Takemoto group in the study of a homogeneous PEG-immobilized thiourea catalyst [30].

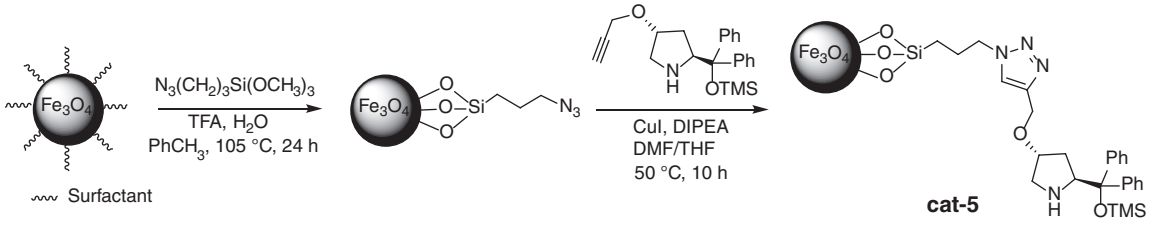
Since **cat-6** was found lacking of recyclability, the synthesis of sulfonamide derivative **cat-7** was conducted by following a literature procedure reported for making polystyrene-supported sulfonamide catalyst [31]. The sulfonamide group is less basic and more stable than the urea group, so Fe_3O_4-supported bifunctional sulfonamide **cat-7** has a better recyclability than **cat-6** (Scheme 13) [29]. In addition, since the C_6F_5 substituent has suitable acidity and is less hindered, it is good for the improvement of catalyst reactivity. Modified bifunctional catalyst **cat-7** was used by the Connon group to promote the asymmetric ring-opening reaction of *meso* succinic-anhydrides



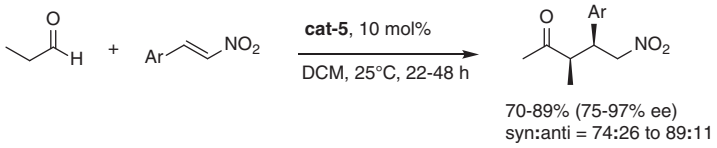
Scheme 7 Preparation of dopamine-L-prolinol catalyst **cat-4.**



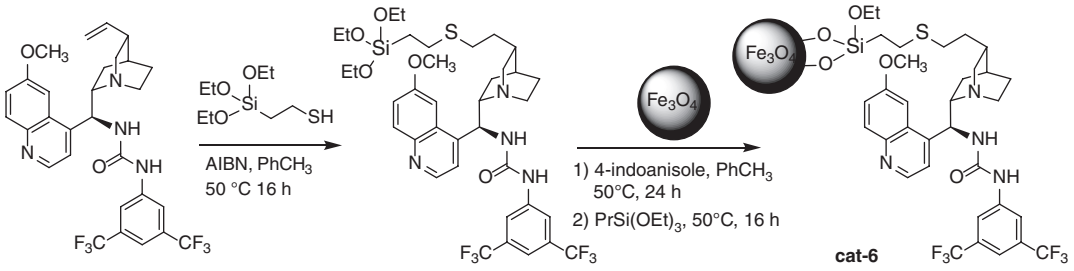
Scheme 8 Kinetic resolution of mono-protected *cis*-diol catalyzed by **cat-4.**



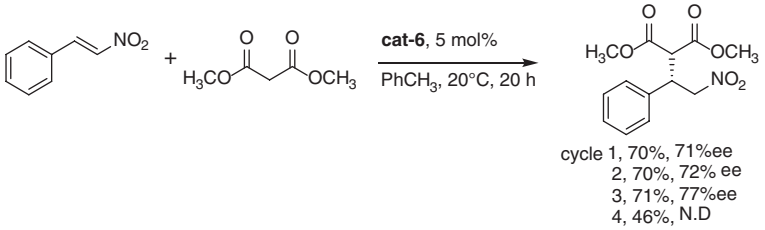
Scheme 9 Preparation of (*S*)-α,α-diphenylprolinol catalyst **cat-5.**



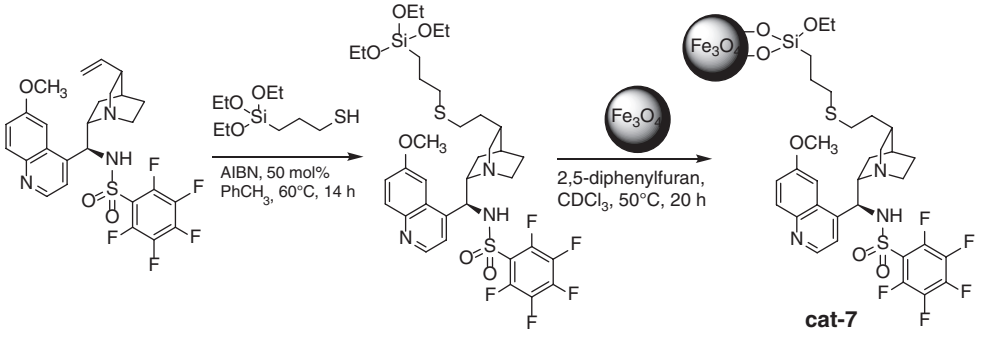
Scheme 10 Michael addition catalyzed by **cat-5.**



Scheme 11 Preparation of bifunctional urea catalyst **cat-6.**



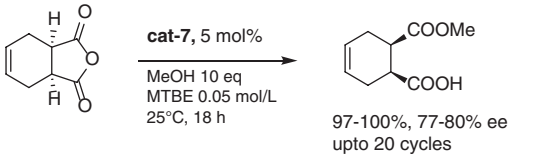
Scheme 12 Asymmetric Michael addition catalyzed by **cat-6.**



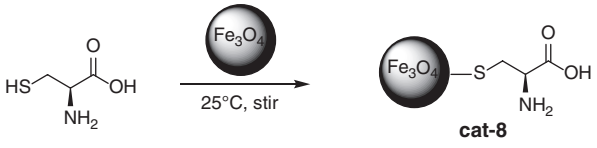
Scheme 13 Synthesis of bifunctional sulfonamide catalyst **cat-7.**

(Scheme 14). This catalyst has a high recyclability and was used for twenty consecutive cycles without significant decrease in catalyst activity and enantioselectivity.

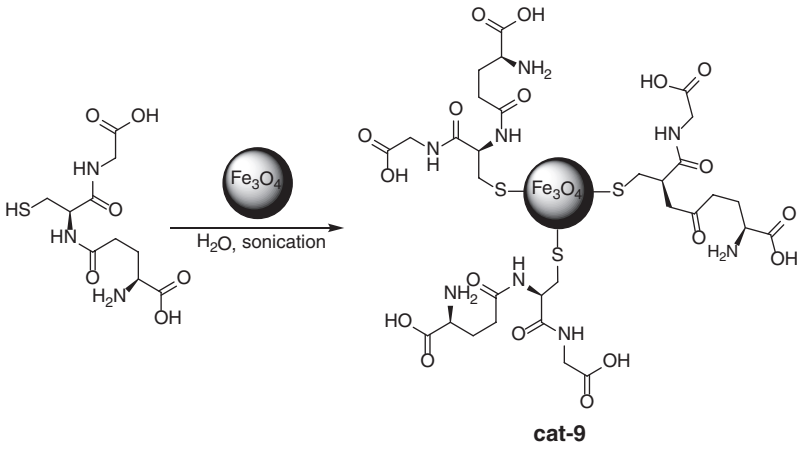
The Gawande and Branco groups recently immobilized amino acids and peptides such as L-cysteine and glutathione on Fe_3O_4 MNPs through the reaction of the



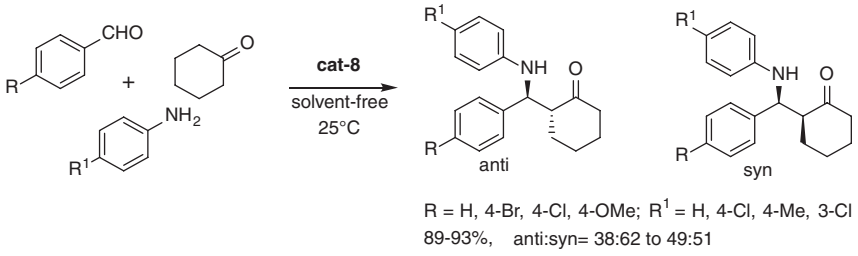
Scheme 14 Asymmetric ring-opening promoted by **cat-7.**



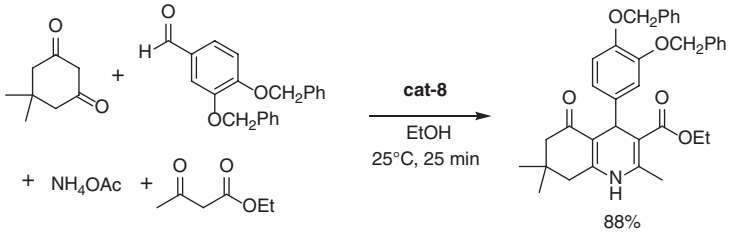
Scheme 15 Synthesis of L-cysteine catalyst **cat-8.**



Scheme 16 Synthesis of glutathione catalyst **cat-9.**



Scheme 17 Synthesis of β-amino carbonyl compounds promoted by **cat-8.**

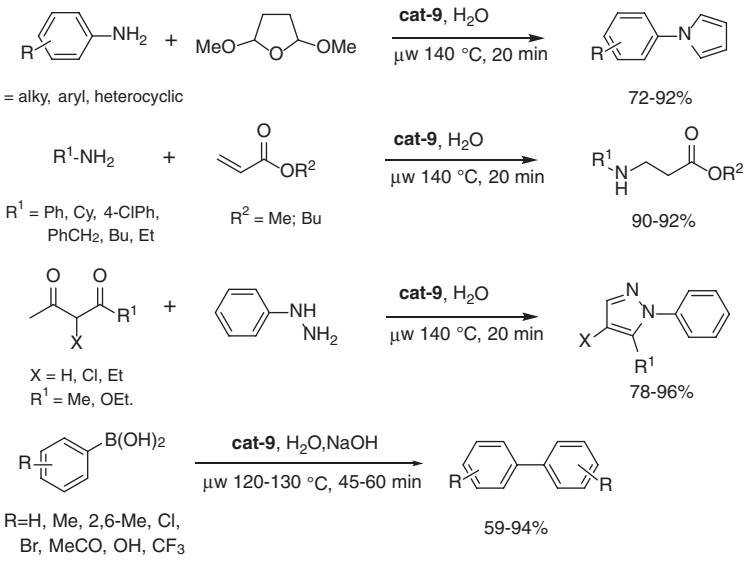


Scheme 18 The Hantzsch reaction promoted by **cat-8.**

thiol group to form **cat-8** and **cat-9** (Schemes 15 and 16) [32, 33]. The Fe_3O_4-supported glutathione **cat-9** could be further treated with $CuCl_2$ solution under a basic condition to generate Cu-coordinated particles [34]. Copper (II) ion is coordinated with the free primary amine and carbonyl groups of the glutathione scaffold in 3:1 ratio.

Catalyst **cat-8** was utilized for the asymmetric Mannich reaction in the synthesis of β-amino carbonyl compounds (Scheme 17) [32]. The reaction of aniline, benzaldehyde, and cyclohexanone was carried out with or without a solvent. Highly reactive **cat-8** was also used to promote the Hantzsch reaction for the preparation of hydroquinolines, a scaffold that has significant interest in medicinal chemistry due to its biological and pharmacological properties (Scheme 18). The reaction yield was good, but the syn:anti selectivity was poor. The magnetic catalyst could be easily recovered via simple magnetic decantation. When R=R¹=H of the substrates, the yield can also be 90% after nine consecutive instances of catalyst recovery. The multicomponent reaction between 3,4-diphenoxy benzaldehyde, ammonium acetate, ethyl acetoacetate, and 5,5-dimethyl cyclohexane-1,3-dione under mild conditions provided hydroquinolines with a yield of 88%. No enantioselectivity information was reported in the paper.

The Varma group employed **cat-9** for the Paal-Knorr [33], aza-Michael [35] and Suzuki coupling reactions [36] (Scheme 19). The Paal-Knorr reaction of amines with tetrahydro-2,5-dimethoxyfuran was performed under



Scheme 19 Reactions catalyzed by **cat-9.**

microwave heating [33, 35]. The traditional Paal–Knorr reactions involve prolonged heating with strong acids in toxic solvents for dehydration. This work uses microwave heating to reduce the reaction time and water as a solvent. For the reaction of benzylamine, the catalyst could be directly recovered more than five times without significant loss of activity. This catalyst was also used for the aza-Michael reaction in the synthesis of pyrazoles [35] and Suzuki coupling reactions [36]. These reactions were conducted in an aqueous phase to eliminate the use of organic solvents.

3 Summary

The synthesis of Fe_3O_4 MNP-supported organocatalysts and their applications for the Paal-Knorr, aza-Michael, Mannich, Hantzsch, aldol, Suzuki coupling, and other reactions are highlighted in this article. MNP-supported organocatalysts is a relatively new field with very limited numbers of publications. It has shown promising results on catalysts reactivity, selectivity, and recyclability. There is no doubt that it will be quickly developed to become a powerful green catalysis technology for enantioselective synthesis. We also expect that some potential challenges related to catalyst functional group compatibility, catalyst stability, and commercialization will be explored and addressed.

Acknowledgements: YH is thankful for the funding support of "Jiangsu Overseas Research & Training Program for University Prominent Young & Middle-aged Teachers" and "Qing-Lang Project of Jiangsu Provincial Department of Education".

Received August 25, 2013; accepted October 28, 2013

References

[1] Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*, Oxford University Press: London, 1998.
[2] Anastas PT, Zimmerman JB. *Environ. Sci. Technol*. 2003, 37, 94A–101A.
[3] Anastas PT, Beach ES. *Green Chem. Lett. Rev*. 2007, 1, 9–24.
[4] Sherrington DC, Kybett AP, Eds., *Supported Catalysts and Their Applications,* Royal Society of Chemistry (Great Britain), London, 2001.
[5] Miao W, Chan TH. *Acc. Chem. Res.* 2006, 39, 897–908.
[6] Gladysz JA, Curran DP, Horvath IT. Eds. *Handbook of Fluorous Chemistry*, Wiley-VCH: Weinheim, 2004.
[7] Arai T, Sato T, Kanoh H, Kaneko K, Oguma K, Yanagisawa A. *Chem. Eur. J.* 2008, 14, 882–885.
[8] Nasir Baig RB, Varma RS, *Green Chem*. 2013, 15, 398–417.
[9] Polshettiwar V, Luque R, Fihri A, Zhu H, Bouhrara M, Basset JM. *Chem. Rev.* 2011, 111, 3036–3075.
[10] Gawande MB, Branco PS, Varma RS. *Chem. Soc. Rev*. 2013, 42, 3371–3393.

[11] Nasir Baig RB, Varma RS. *Chem. Commun*. 2013, 49, 752–770.
[12] Shi F, Tse MK, Zhou S, Pohl M-M, Radnik J, Hubner S, Jahnisch K, Bruckner A, Beller M. *J. Am. Chem. Soc.* 2009, 131, 1775–1779.
[13] Liu S, Wu J, Jiang H, Jin Z, Jiang X. *Chin. J. Org. Chem*. 2009, 29, 1587–1592.
[14] HuA-G, Yee GT, Lin W. *J. Am. Chem. Soc*. 2005, 127, 12486–12487.
[15] Rivera FG, Angurell I, Rossell MD, Emi R, Llorca J, Divins NJ, Muller G, Seco M, Rossell O. *Chem. Eur. J*. 2013, 36, 11805–11815.
[16] Kaboudin B, Mostafalu R, Yokomatsu T. *Green Chem*. 2013, 15, 2266–2274.
[17] Wang D, Salmon L, Ruiz J, Astruc D. *Chem. Commun*. 2013, 49, 6956–6958.
[18] Zhang Q, Su Hong, Luo J, Wei Y. *Catal. Sci. Technol*. 2013, 3, 235–243.
[19] Dálaigh CÓ, Corr SA, GunkoY, Connon SJ. *Angew. Chem. Int. Ed.* 2007, 46, 4329–4332.
[20] Luo S, Zheng X, Cheng JP. *Chem. Commun*. 2008, 5719–5721.
[21] Luo S, Zheng X, Xu H, Mi X, Zhang L, Cheng JP. *Adv. Synth. Catal*. 2007, 349, 2431–2434.
[22] Gleeson O, Tekoriute R, Gun'ko YK, Connon SJ. *Chem. Eur. J*. 2009, 15, 5669–5673.
[23] Dalaigh CO, Hynes SJ, O'Brien JE, McCabe T, Maher DJ, Watson GW, Connon SJ. *Org. Biomol. Chem*. 2006, 4, 2785–2793.
[24] Riente P, Mendoza C, Pericas MA. *J. Mater. Chem*. 2011, 21, 7350–7355.
[25] McCooey S, Connon SJ. *Angew. Chem. Int. Ed.* 2005, 44, 6367–6370.
[26] Tillman AL, Ye J-X, Dixon DJ. *Chem. Commun*. 2006, 1191–1193.
[27] Jiang X-X, Shi X-M, Wang S-L, Sun T, Cao Y-M, Wang R. *Angew. Chem. Int. Ed*. 2012, 51, 2084–2087.
[28] Curti C, Rassu G, Zambrano V, Pinna L, Pelosi G, Sartori A, Battistini L, Zanardi F, Casiraghi G. *Angew. Chem. Int. Ed*. 2012, 51, 6200–6204.
[29] Gleeson O, Davies GL, Peschiulli A, Tekoriute R, Gun'ko YK, Connon SJ. *Org. Biomol. Chem*. 2011, 9, 7929–7940.
[30] Miyabe H, Tuchida S, Yamauchi M, Takemoto Y. *Synthesis* 2006, 38, 3295–3300.
[31] Youk SH, Oh SH, Rho HS, Lee JE, Lee JW, Song CE. *Chem. Commun*. 2009, 45, 2220–2222.
[32] Gawande MB, Velhinho A, Nogueira ID, Ghumman CAA, Teodoro OMND, Branco PS. *RSC Adv.* 2012, 2, 6144–6149.
[33] Polshettiwar V, Baruwati B, Varma RS. *Chem. Commun*. 2009, 45, 1837–1839.
[34] Nasir Baig RB, Varma RS. *Green Chem*. 2012, 14, 625–632.
[35] Polshettiwar V, Varma RS. *Tetrahedron* 2010, 66, 1091–1097.
[36] Luque R, Baruwati B, Varma RS. *Green Chem*. 2010, 12, 1540–1543.

Yibo Huang is an Associate Professor at Changzhou Institute of Engineering & Technology in China. He was a visiting scholar at Dr. Zhang's lab at University of Massachusetts Boston from 2012–2013. His current research interest is focused on immobilization of organocatalysts.

Wei Zhang is a Professor and the Director of the Center for Green Chemistry in the Department of Chemistry, University of Massachusetts Boston. He was a Senior Chemist at DuPont Agricultural Products and Director of Discovery Chemistry at Fluorous Technologies, Inc. He has published over 150 papers on free-radical chemistry, fluorous chemistry, and green chemistry.