View Article Online
View Journal

Green Chemistry

Accepted Manuscript

Green Chemistry

Cutting-edge research for a greener sustainable future

www.rsc.org/greenchem

Volume 12 | Number 9 | September 2010 | Pages 1481–1676

ISSN 1463-9262

RSC Publishing

COMMUNICATION
Luque, Varma and Baruwati
Magnetically seperable organocatalyst for homocoupling of arylboronic acids

CRITICAL REVIEW
Dumesic et al.
Catalytic conversion of biomass to biofuels

1463-9262(2010)12:9;1-U

This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

RSC Publishing

www.rsc.org/greenchem

Registered Charity Number 207890

Copper on Chitosan: recyclable heterogeneous catalyst for azide-alkyne cycloaddition reactions in water

R. B. Nasir Baig and Rajender S. Varma*

Abstract

Copper sulfate has been immobilized over chitosan by simply stirring an aqueous suspension of chitosan in water with copper sulfate; the ensuing catalyst has been utilized for the azide-alkyne cycloaddition in aqueous media and it can be recycled and reused many time without loosing its activity.

Introduction

Enhanced environmental consciousness has promoted the efficiency of chemical reactions under benign conditions with recycling and reuse of the catalysts, a trait that has become an integral part of chemical research today.[1-5] Immobilization of catalysts on solid supports is one of the best methods to improve the efficiency and recycling catalysts;[6-9] many solid supported catalysts have been successfully utilized for catalytic applications.[9, 10] Most commonly used solid supports involve silica,[11] zeolites,[12-18] magnetic-materials,[19-24] and soluble and insoluble polymers.[8, 25, 26] In addition to these, some of the heterogeneous polymers are used for the removal of trace metals.[27-34] During the course of studies in our laboratories, the efficiency of chitosan as a support and its ability to remove the copper from the aqueous medium is found to be very impressive.

In modern drug research, a plethora of active organic molecules was required to be evaluated in a short period of time. That is why simple methods that can easily generate large libraries of compounds are emerging. Click chemistry is one of these methods based on reactions, which are of wider scope, gives high yields, and forms irreversible carbon-heteroatom and carbon-carbon bonds; the Huisgen 1,3-dipolar cycloaddition has become one of the most important reactions in history.[35-44] It involves the ligation of azides and terminal alkynes to generate triazoles and usually entails the use of a copper salt in conjunction with a base. The catalyst could be Cu(I) salt or Cu(I) generated *in situ* by the reduction of Cu(II) salts, usually in organo-aqueous media. Engaged in the development of sustainable benign pathways for organic transformations, nanomaterials, and nano-catalysis,[45, 46] we decided to explore the use of copper deposited over chitosan for such catalytic application. Chitosan is better known for metal extraction,[47-52] their applications as a catalytic support are rather sparse.[53-55] Xia et al. have used chitosan-Schiff base copper(II) complex as a catalyst for the cyclopropanation of styrene with ethyl diazoacetate.[56] Taran and coworkers have synthesized a variety of chitosan schiff base-copper(I) triflate complexes and demonstrated their application for Huisgen cycloaddition.[57] Herein, we report a simple and efficient synthesis of a chitosan-supported, recyclable, and inexpensive copper catalyst and its application in Huisgen 1, 3-dipolar cycloaddition reactions; 1,2,3-triazoles are obtained in aqueous media at room temperature.

Sustainable Technology Division, National Risk Management Research Laboratory, U. S. Environmental Protection Agency, MS 443, Cincinnati, Ohio 45268, USA. Fax: 513- 569-7677; Tel: 513-487-2701. E-mail: varma.rajender@.epa.gov

Results and Discussion

The first step in the accomplishment of this goal was the immobilization of copper over chitosan. The catalyst was prepared by suspending chitosan in an aqueous solution of copper sulfate ($CuSO_4$) for 3 h under neutral conditions. Material with $CuSO_4$ on chitosan was separated using centrifuge and dried under vacuum at 50 ^{o}C for 8 hours. Catalyst characterization was accomplished by X-ray diffraction (XRD) (Fig. 1b) and SEM (Fig.1 a). The signals pertaining to copper metal were not detected in XRD, presumably due to its complexation with chitosan or its low percentage amount. The weight percentage of copper was found to be 5.1 wt % by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis.

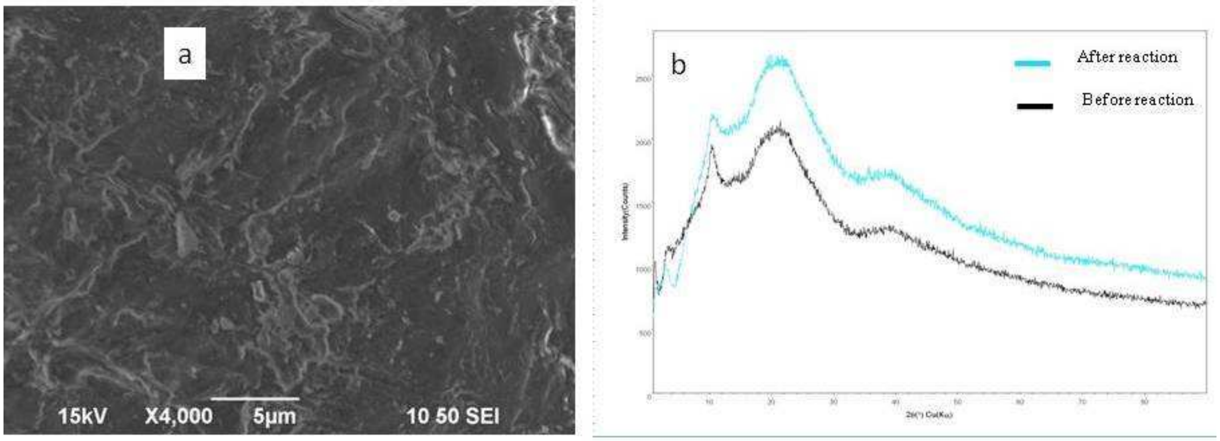
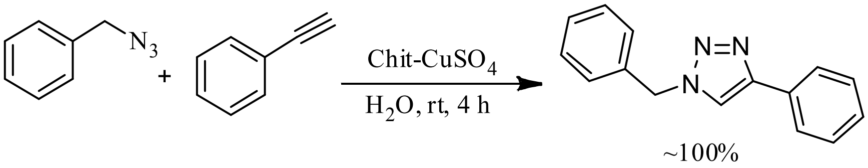


Figure 1 a) SEM image of Chit-$CuSO_4$ Catalyst ; b) X-ray diffraction (XRD) of Chit-$CuSO_4$

The experiments began with the intention of optimizing the reaction conditions for dipolar cycloaddition of benzyl azide and phenylacetylene. Greener conditions were selected to study the reaction; benign water was used as the solvent at room temperature (Scheme 1). The results were very encouraging as the reaction was completed in 4 h and provided quantitative yield of the desired product. Progress of the reaction could be monitored visually as the product crystallized out from the aqueous reaction media (Figure 2). In order to optimize the reaction conditions, we have performed the reaction using varied quantities of the catalyst. There was no difference in yield and reaction time when catalyst loading was reduced to 15 mg, 10 mg and 5 mg. However, it took longer time for completion of the reaction (12 h) when 2 mg of the catalyst was used. Consequently, we decided to use 5 mg of the catalyst for further studies.



Scheme 1 Chit-$CuSO_4$, catalysed dipolar cycloaddtion of benzyl azide and phenyl acetylene

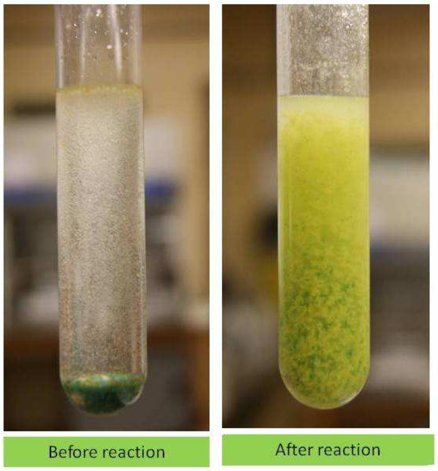
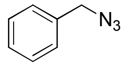
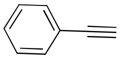
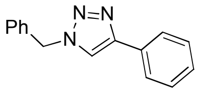
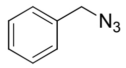
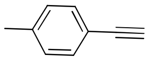
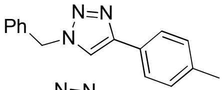
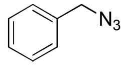
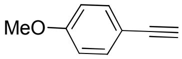
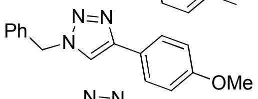
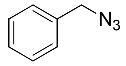
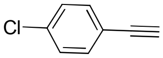
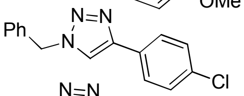
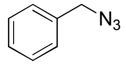
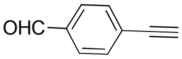
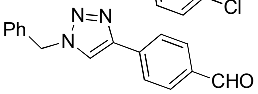
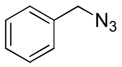
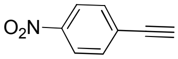
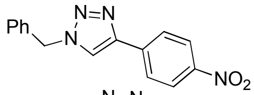
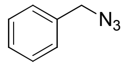
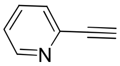
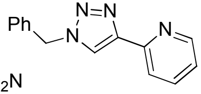
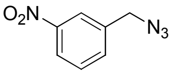
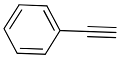
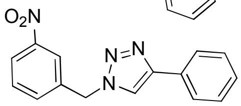
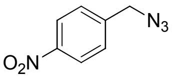
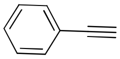
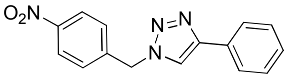
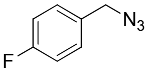
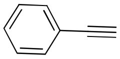
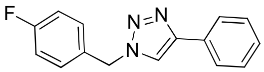
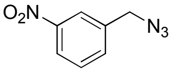
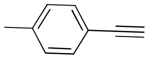
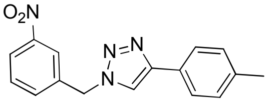
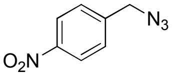
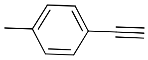
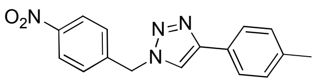
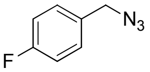
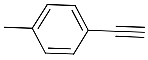
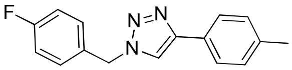
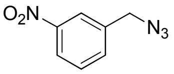
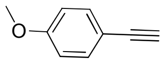
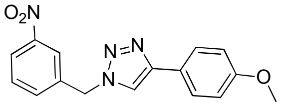
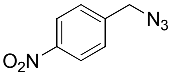
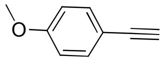
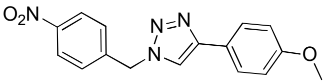
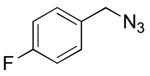
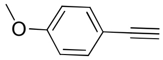
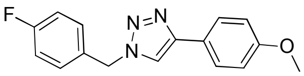
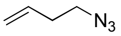
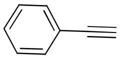
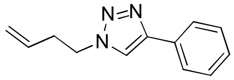
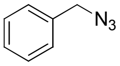
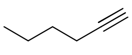
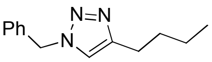


Figure 2 Reaction mixture before and after completion of the reaction

After establishment of the optimum conditions for the cycloaddition of benzyl azide and phenyl acetylene, its scope as a catalyst for the Huisgen [3 + 2]-cycloaddition reactions was explored. A variety of benzyl azides were treated with acetylenes using Chit-$CuSO_4$ catalyst in water at ambient condition (Table 1); most of the reactions were completed within 4-6 hours to give high yields of the corresponding 1,4 triazoles. The substituent's (electron withdrawing, electron rich, and heterocycle) do not have any peculiar effect, as most of the reactions were completed within 4-6 h. However, an aliphatic azide took 12 h for the formation of triazole (entry 17, Table 1). The catalyst was not much effective for aliphatic alkynes (Table 1, entry 18); reaction was very slow and we could isolate less than 12 % of product after overnight (12 h) stirring.

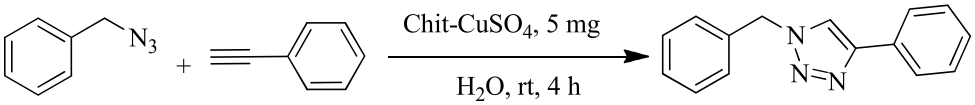
Table 1. Click chemistry using Chit-$CuSO_4$ catalyst

Entry	Alkyl halide	Alkyne	Times	Product[a]	Yield[b]
1			4h		99%
2			4h		99%
3			4h		99%
4			6h		98%
5			6h		97%
6			6h		95%
7			6h		96%
8			6h		94%
9			6h		96%
10			6h		97%
11			6h		94%
12			6h		96%
13			6h		98%
14			6h		96%
15			6h		96%
16			6h		98%
17			12h		93%
18			12h		12%

a) Reaction conditions: 1.2 mmol of alkyl azide, 1.0 mmol of alkyne, 5 mg of Chit-Copper catalyst, H_2O, rt; b) Isolated yield; c) Product were charectorized using NMR and compared with the reported data.

For the practical applications of such heterogeneous systems, the lifetime of the catalyst and its level of reusability are very significant factors. To clarify this issue, a set of experiments were performed for the cycloaddition of benzyl azide and phenylacetylene using the recycled Chit-$CuSO_4$ catalyst. After the completion of the first reaction, the product was extracted using ethyl acetate and the catalyst was recovered by simple decantation and dried at 50 °C. A fresh reaction was then performed with new reactants, under the same conditions. We have also performed recycling experiments using 5 mmol of reagents (Table 2, entry 6-10). After 1h, the reaction was stopped, the catalyst recovered and reused for the next cycle thus making it is clear that the Chit-$CuSO_4$ catalyst could be reused at least 5 times without any change in its activity.

Table 2 Recycling of Chit-$CuSO_4$ catalyst



No of cycles	Yield
1	>99%
2	>99%
3	>95%
4	>97%
5	>97%
6	>28%[a]
7	>29%[a]
8	>29%[a]
9	>28%[a]
10	>28%[a]

a) Recycling experiments were performed using 5 mmol of reagents for 1 h

Metal leaching was studied by ICP-AES analysis of the catalyst before and after the 5th reaction cycle. The Cu concentration was found to be 5.1 % before reaction and 5.02 % after the reaction. The SEM image of the catalyst taken after the 5th cycle of the reaction did not show significant change in the morphology (Fig. 3), which indicates the retention of the catalytic activity after recycling. No Cu metal was detected in the reaction solvent (water) after completion of the reaction. This confirms the fact that chitosan provides enough binding sites on the surface to minimize deterioration and metal leaching and facilitates efficient catalyst recycling.

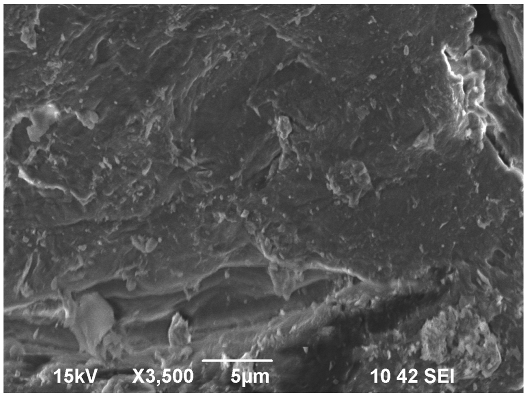


Figure 3 SEM image of the Chit-$CuSO_4$ catalyst after the reaction.

Conclusions

Copper sulfate immobilized on chitosan, Chit-Cu catalyst, has been utilized for the azide-alkyne cycloaddition reactions in aqueous media at ambient temperature. In general, the reaction can be monitored visually as the desired product crystallizes out from the aqueous reaction media. Most of the reactions proceed faster with the exception of the aliphatic azide and alkyne substrates. The catalyst can be recycled and reused many times without losing its activity. Further investigations using this catalyst system are under investigation.

Experimental procedure:

Experimental procedure for synthesis of Chitosan copper catalyst (Chit-$CuSO_4$):

Chitosan (5 g, medium molecular weight, Aldrich, CSA # 9012-76-4) was suspended in 100 mL of water. To this suspension, 1 g of $CuSO_4.5H_2O$ was added and stirring was continued for 2h. The catalyst was separated using centrifuge (5000 rpm 5 min), dried under vacuum at 50 ^oC. The catalyst was characterized by X-ray diffraction (XRD) (Fig 1b, MS) and using SEM (Fig.1 a, MS). The signals pertaining to copper metal were not detected in XRD; it may be due to complexation with chitosan or low percentage. The weight percentage of copper was found to be 5.1 % by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis.

Synthesis of triazole from alkyl azide and alkyne

1.2 mmol of alkyl azide, 1.0 mmol of alkyne and 5 mg of Chit-$CuSO_4$ catalyst were placed in a reaction tube. To this 5 mL of water and a stirring bar was added. The reaction tube was placed on a magnetic stirrer and stirs the reaction mixture for 4-12 h at room temperature. After the completion of the reaction, product was separated using ethyl acetate extraction and catalyst by centrifuge (5000 rpm, 5 min). The products were purified by re-crystallization or column chromatography. The recovered catalyst was dried and reused at least five times without losing its activity.

Acknowledgements

Nasir Baig was supported by the Postgraduate Research Program at the National Risk Management Research Laboratory administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Environmental Protection Agency. We thank Dr. Jiahui Kou for recording SEM image and .

References:

1. V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara and J.-M. Basset, *Chem. Rev.*, 2011, **111**, 3036-3075.
2. R. B. Nasir Baig and R. S. Varma, *Green Chemistry*, 2013, **15**, 398-417.
3. R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2013, **49**, 752-770.
4. V. Polshettiwar, C. Len and A. Fihri, *Coord. Chem. Rev.*, 2009, **253**, 2599-2626.
5. R. B. N. Baig and R. S. Varma, *Chem. Soc. Rev.*, 2012, **41**, 1559-1584.
6. S. E. García-Garrido, J. Francos, V. Cadierno, J.-M. Basset and V. Polshettiwar, *ChemSusChem.*, 2011, **4**, 104-111.
7. A. Fihri, D. Cha, M. Bouhrara, N. Almana and V. Polshettiwar, *ChemSusChem.*, 2012, **5**, 85-89.
8. N. Madhavan, C. W. Jones and M. Weck, *Acc. Chem. Res.*, 2008, **41**, 1153-1165.
9. A. Schätz, R. N. Grass, W. J. Stark and O. Reiser, *Chemistry – A European Journal*, 2008, **14**, 8262-8266.
10. S. Bhadra, B. Sreedhar and B. C. Ranu, *Adv. Synth. Catal.*, 2009, **351**, 2369-2378.
11. R. Dey, B. Sreedhar and B. C. Ranu, *Tetrahedron*, 2010, **66**, 2301-2305.
12. P. H. Espeel, M. C. Tielen and P. A. Jacobs, *J. Chem. Soc. Chem. Commun.*, 1991, **0**, 669-671.
13. J. M. Fraile, J. I. Garcia and J. A. Mayoral, *Chem. Commun.*, 1996, **0**, 1319-1320.
14. R. Neumann and A. M. Khenkin, *Chem. Commun.*, 1996, **0**, 2643-2644.
15. Q. Zhu, J. N. Kondo, T. Setoyama, M. Yamaguchi, K. Domen and T. Tatsumi, *Chem. Commun.*, 2008, **0**, 5164-5166.

16. L. Gu, D. Ma, S. Yao, C. Wang, W. Shen and X. Bao, *Chem. Commun.*, 2010, **46**, 1733-1735.

17. M. Iwasaki and H. Shinjoh, *Chem. Commun.*, 2011, **47**, 3966-3968.

18. Y. Zhu, Z. Hua, X. Zhou, Y. Song, Y. Gong, J. Zhou, J. Zhao and J. Shi, *RSC Adv.*, 2013.

19. R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2012, **48**, 2582-2584.

20. Q. M. Kainz, A. Späth, S. Weiss, T. D. Michl, A. Schätz, W. J. Stark, B. König and O. Reiser, *ChemistryOpen.*, 2012, **1**, 125-129.

21. A. Schätz, R. N. Grass, Q. Kainz, W. J. Stark and O. Reiser, *Chem. Mat.*, 2009, **22**, 305-310.

22. A. Schätz, M. Hager and O. Reiser, *Adv. Funct. Mat.*, 2009, **19**, 2109-2115.

23. A. Schätz, T. R. Long, R. N. Grass, W. J. Stark, P. R. Hanson and O. Reiser, *Adv. Funct. Mat.*, 2010, **20**, 4323-4328.

24. A. Schätz, O. Reiser and W. J. Stark, *Chemistry – A European Journal.*, 2010, **16**, 8950-8967.

25. R. N. Dhital, C. Kamonsatikul, E. Somsook, K. Bobuatong, M. Ehara, S. Karanjit and H. Sakurai, *J. Am. Chem. Soc.*, 2012, **134**, 20250-20253.

26. J. Zhang, D. Han, H. Zhang, M. Chaker, Y. Zhao and D. Ma, *Chem. Commun.*, 2012, **48**, 11510-11512.

27. J. Sun, S. Rao, Y. Su, R. Xu and Y. Yang, *Coll. Surf., A*, 2011, **389**, 97-103.

28. S. Kadouche, H. Lounici, K. Benaoumeur, N. Drouiche, M. Hadioui and P. Sharrock, *J. Polym. Environ.*, 2012, **20**, 848-857.

29. K. Kondo, Y. Ohigashi and M. Matsumoto, *J. Mater. Sci. Eng. A.*, 2012, **2**, 584-592.

30. A. Moyna, D. Connolly, E. Nesterenko, P. N. Nesterenko and B. Paull, *J. Chromatogr., A*, 2012, **1249**, 155-163.

31. V. S. Nagpurkar, L. Deshmukh and L. J. Paliwal, *Chem. Sin..*, 2012, **3**, 824-829.

32. B. Zornoza, C. Tellez, J. Coronas, J. Gascon and F. Kapteijn, *Microporous Mesoporous Mater.*, 2013, **166**, 67-78.

33. R. Ramya and P. N. Sudha, *Polymer Composites.*, 2013, **34**, 233-240.

34. S.-J. Wu, T.-H. Liou, C.-H. Yeh, F.-L. Mi and T.-K. Lin, *J. App. Poly. Sci.*, 2013, **127**, 4573-4580.

35. V. Sai Sudhir, R. B. Nasir Baig and S. Chandrasekaran, *E. J. Org .Chem.*, 2008, **2008**, 2423-2429.

36. V. Sai Sudhir, N. Y. Phani Kumar, R. B. Nasir Baig and S. Chandrasekaran, *J. Org. Chem.*, 2009, **74**, 7588-7591.

37. F. Amblard, J. H. Cho and R. F. Schinazi, *Chem. Rev.*, 2009, **109**, 4207-4220.

38. S. Dedola, S. A. Nepogodiev and R. A. Field, *Org. Bio. Chem.*, 2007, **5**, 1006-1017.

39. E. M. Sletten and C. R. Bertozzi, *Acc. Chem. Res.*, 2011, **44**, 666-676.

40. D. Kumar and V. B. Reddy, *Synthesis.*, 2010, **2010**, 1687-1691.

41. R. B. N. Baig and R. S. Varma, *Chem. Commu.*, 2012, **48**, 5853-5855.

42. V. Ganesh, V. S. Sudhir, T. Kundu and S. Chandrasekaran, *Chemistry – An Asian Journal.*, 2011, **6**, 2670-2694.

43. D. Kumar, G. Patel and V. B. Reddy, *Synlett.*, 2009, **2009**, 399-402.

44. D. Kumar, V. B. Reddy, A. Kumar, D. Mandal, R. Tiwari and K. Parang, *Bioorg. Med. Chem Lett.*, 2011, **21**, 449-452.

45. R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2012, **48**, 6220-6222.

46. R. B. Nasir Baig and R. S. Varma, *Green Chemistry*, 2012, **14**, 625-632.

47. B. Guan, W. Ni, Z. Wu and Y. Lai, *Sep. Purif. Technol.*, 2009, **65**, 269-274.

48. A. Jideowno, J. M. Okuo and P. O. Okolo, *Pak. J. Sci. Ind. Res.*, 2006, **49**, 443-447.

49. K. Inoue and Y. Baba, *Ion Exch. Solvent Extr.*, 2007, **18**, 339-374.

50. A. Jideowno, J. M. Okuo and P. O. Okolo, *Trends Appl. Sci. Res.*, 2007, **2**, 211-217.

51. K. Inoue and K. Ohto, *Kidorui*, 2009, **54**, 44-45.

52. M. S. Rana, M. A. Halim, S. Safiullah, M. M. Mollah, M. S. Azam, M. A. Goni, M. K. Hossain and M. M. Rana, *J. Appl. Sci.*, 2009, **9**, 2762-2769.

53. K. Martina, S. E. S. Leonhardt, B. Ondruschka, M. Curini, A. Binello and G. Cravotto, *J.Mol. Catal A: Chem.*, 2011, **334**, 60-64.

54. S. R. Hall, A. M. Collins, N. J. Wood, W. Ogasawara, M. Morad, P. J. Miedziak, M. Sankar, D. W. Knight and G. J. Hutchings, *RSC Adv.*, 2012, **2**, 2217-2220.

55. D. M. Alonso, S. G. Wettstein and J. A. Dumesic, *Green Chemistry*, 2013, **15**, 584-595.

56. W. Sun, C.-G. Xia and H.-W. Wang, *New J. Chem.*, 2002, **26**, 755-758.

57. M. Chtchigrovsky, A. Primo, P. Gonzalez, K. Molvinger, M. Robitzer, F. Quignard and F. Taran, *Angew. Chem. Int. Ed.,* 2009, **48**, 5916-5920.