Journal of
Nanoscience and Nanotechnology
Vol. 13, 3136–3141, 2013

Aminoclay-Supported Copper Nanoparticles for 1,3-Dipolar Cycloaddition of Azides with Alkynes via Click Chemistry

A. Sravanth Kumar[1], K. K. R. Datta[2, †], T. Srinivasa Rao[1], K. V. Raghavan[3], M. Eswaramoorthy[2], and B. V. Subba Reddy[1, *]

[1] *Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India*
[2] *Nanomaterials and Catalysis Laboratory, Chemistry and Physics of Materials Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur P. O., Bengaluru 560064, India*
[3] *Reaction Engineering Laboratory, Indian Institute of Chemical Technology, Hyderabad 500007, India*

Aminoclay supported copper nanoparticles are effective in promoting [3+2] cycloaddition of azides with terminal alkynes to produce the corresponding 1,2,3-triazoles in excellent yields. The copper nanoparticles are highly reactive in water and can be recycled for four cycles with consistent activity.

Keywords: Click Reaction, Azide, Alkyne, Cu-Aminoclay, Triazoles.

COMMUNICATION

1. INTRODUCTION

In recent years, nanotechnology has received as one of the most active research areas in the field of medicine and biology.[1] The preparation of various nanomaterials is the foundation for development of nanoscience and nanotechnology.[2–3] The key novel materials are metal nanoparticles, porous materials, smart hybrids, etc. which are important functional nanomaterials used extensively in the areas of catalysis, sensors, optics and environment.[4–11] Of various nanomaterials, the metal nanoparticles are important in the field of catalysis for a wide variety of organic and inorganic transformations because of their high surface reactivity.[7–9]

1,2,3-Triazoles are important class of heterocycles because of their wide range of biological properties such as antibacterial, antiviral, antiepileptic and antiallergic behavior.[12–16] They are also used as optical brighteners, light stabilizers, fluorescent whiteners and corrosion retarding agents.[12–14] The 'Click reaction,' is one of the most widely used methods for the synthesis of 1,2,3-triazoles by means of 1,3-dipolar cycloaddition between azides and alkynes.[15–22] However, uncatalyzed or thermal cycloaddition often suffers from poor regioselectivity and low yields. Subsequently, Cu(I) triggered azide-alkyne cycloaddition has been developed for the synthesis of 1,4-disubstituted-1,2,3-triazoles.[15–23] Recently, metal nanoparticles have received importance as active catalysts for various organic transformations.[7–9, 24] In particular, copper nanoparticles, due to its cost effectiveness have gained tremendous impact mainly in the areas of catalysis and biology.[5, 23] Generally, copper nanoparticles are dispersed in various supports to prevent the agglomeration. Indeed, there are few reports on the usage of copper nanoparticles for the synthesis of triazoles.[25–30] However, most of the reactions catalyzed by copper nanoparticles typically require high temperatures and long reaction times (3–12 h) and also suffer from the leaching of nanoparticles from the support. Thus it is highly necessary to develop new alternatives and simpler ways to disperse copper nanoparticles. Datta et al. have reported a simple and versatile method for stabilizing copper and other metal nanoparticles over aminoclay matrix.[31–32] Aminoclay forms a clear solution in water (exfoliation) due to the protonation of amino groups by water which is a key factor for the extended stability of copper nanoparticles and for easy entry of negatively charged species (permselectivity).[32] We herein, report for the first time the catalytic activity of water dispersible Cu-aminoclay nanocomposite for the Click reaction of azides with alkynes to the synthesis of triazoles. Furthermore, the catalyst can be recycled for four times with minimal loss of activity.

*Author to whom correspondence should be addressed.
†Present address: Regional Centre of Advanced Technologies and Materials, Faculty of Science, Department of Physical Chemistry, Palacky University, tr. 17. listopadu 12, 771 46, Olomouc, Czech Republic.

 1533-4880/2013/13/3136/006 doi:10.1166/jnn.2013.7343

2. MATERIALS

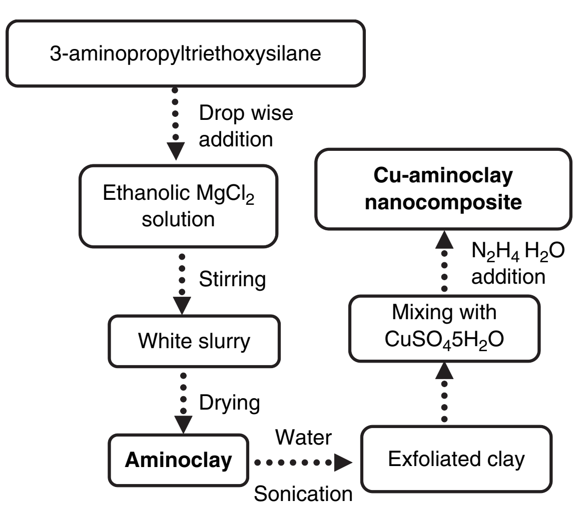
All the reagents and solvents are commercially available and are used as such without any further purification. Compounds were purified on axially compressed columns, packed with silica gel and eluted with *n*-hexane/AcOEt mixtures. Transmission electron microscope (TEM) images were recorded on JEOL JEM 3010 instrument (Japan) operated at an accelerating voltage of 300 kV. For TEM analysis, the aqueous clay-copper nanoparticles composite was first precipitated by addition of excess of ethanol and then redispersed it in ethanol by sonication before drop casting on a carbon-coated copper grid.

2.1. Preparation of the Aminoclay

Aminoclay was prepared by drop wise addition of 3-aminopropyltriethoxysilane (1.3 mL, 5.85 mmol) to an ethanolic solution of magnesium chloride (0.84 g, 3.62 mmol) at room temperature. The white slurry formed after 5 min was stirred overnight and the resulting precipitate was isolated by centrifugation and then washed with ethanol (50 mL) and dried at 50 °C.

2.2. Synthesis of Cu-Aminoclay Nanocomposite

For the synthesis of Cu nanoparticles, $CuSO_45H_2O$ was used as a metal precursor. The aminoclay-Cu nanoparticle composite was prepared as follows.[32] The aminoclay was first exfoliated by dispersing 1 g of clay in 100 mL millipore water by sonication. To this transparent clay suspension, 0.49 g of copper sulfate was added followed by drop wise addition of 2 mL of hydrazine hydrate solution. Thus formed copper-aminoclay nanocomposite was precipitated by addition of ethanol followed by drying at 60 °C. A flowchart depicting the synthesis of aminoclay and aminoclay stabilized Cu nanoparticles are given in Scheme 1.



Scheme 1. Flowchart showing the synthesis of Cu-aminoclay nanocomposite.

2.3. General Procedure for Heterogeneous Click Reaction

A mixture of azide (1 mmol), acetylene (1.2 mmol) and Cu-aminoclay composite (5 mg) in 4 mL water was stirred at 60 °C. The progress of the reaction was monitored by TLC. After completion, the product was extracted with ethyl acetate, washed with water and dried over $MgSO_4$. Removal of the solvent followed by purification on silica gel using a mixture of ethyl acetate and hexane afforded the pure 1,2,3-triazole derivative. The identity and purity of the products were confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

A freshly prepared Cu-aminoclay solution shows wine red color. Upon ageing the solution in air followed by addition of excess of ethanol and then centrifugation gave the brick red precipitate.[32] The brick red precipitate forms a stable and transparent dispersion in water by means of sonication. The transmission electron microscope image of brick red precipitate (in ethanol) shows uniform dispersion of less than 5 nm sized Cu nanoparticles (black spherical dots) on the backdrop of the clay sheets (Fig. 1).

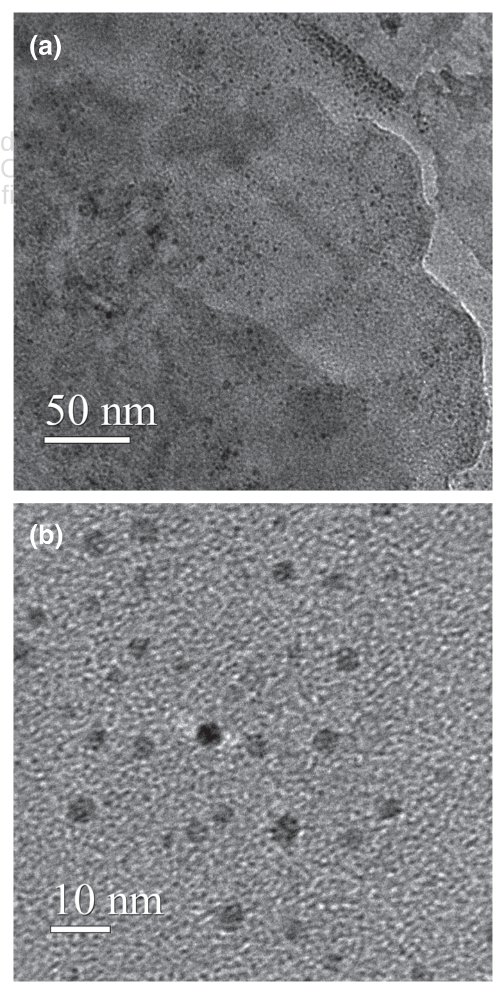
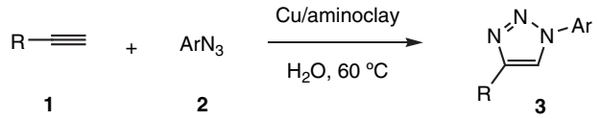


Fig. 1. TEM images (a) low magnification and (b) high magnification of Cu-aminoclay nanocomposite.



Scheme 2. Preparation of triazole **3** *via* 1,3-dipolar cycloaddition.

The brick red colored Cu-aminoclay nanocomposite (5 mg) was used for the catalytic reactions. The reactions of various aromatic azides with different terminal alkynes were successful in water affording the corresponding triazoles in good to excellent yields with high regioselectivity (Scheme 2).

Accordingly, we first evaluated the catalytic activity of Cu-aminoclay nanocomposite in the coupling of benzyl azide with phenyl acetylene using water as a reaction medium at room temperature. After 1 h, the desired product was isolated only in 60%. Next, we attempted the above reaction at 60 °C. Interestingly, the corresponding 1,2,3-triazole was obtained in 91% yield (entry a, Table I). Similarly, ethyl propiolate also underwent smooth coupling with benzyl azide under identical conditions to furnish the *N*-benzyl-1,2,3-triazole in 86% yield (entry b, Table I). Under optimized conditions, the reaction requires 60 °C temperature and 5 mg of Cu-aminoclay nanocomposite to achieve high conversions. Encouraged by the above results, we turned our attention to extend this method for various alkynes and azides. Interestingly, *o*-benzyl protected propargyl and homopropargyl alcohols also participated well in this reaction to provide the corresponding 1,2,3-triazoles in excellent yields (entries c and d, Table I).

The scope and generality of this method was illustrated with respect to various azides and alkynes and the results are summarized in Table I. As shown in Table I, the reaction works well not only with benzyl azide but also with aryl azides such as 1-azido-2-methylbenzene, 2-azido-1,3,5-trimethylbenzene and 2-azido-1,4-dimethoxybenzene (entries e–k, Table I). Remarkably, a sterically hindered 2-azido-1,3,5-trimethylbenzene also gave the corresponding 1,2,3-triazoles in excellent yields (entries g and h, Table I). Both electron-rich and electron-deficient alkynes participated well under similar conditions. The cycloaddition was successful even with aliphatic alkynes such as 1-hexyne (entry k, Table I). No substantial difference in yields was observed with various azides. We further examined the cycloaddition of 2-azido-1-phenylethanol with phenyl acetylene under optimized conditions. The corresponding β-hydroxy-1,2,3-triazole was obtained in 87% yield (entry l, Table I). A variety of functionalities such as ester, ether and hydroxyl groups are compatible under the reaction conditions. The reaction proceeds well in water without the need of additives or activators. In all cases, the products were obtained in excellent yields with high regioselectivity. Mechanistically, the reaction was assumed to be proceeded *via* the activation of alkyne by Cu nanoparticles, although the exact mechanism is unclear. Thus formed Cu-acetylide may undergo 1,3-dipolar cycloaddition with azide to furnish the desired 1,2,3-triazole.

Furthermore, the recycling (Table II) of the Cu-aminoclay nanocomposite was evaluated in the cycloaddition of benzyl azide with ethyl propiolate under optimized conditions (entry b, Table I). The product was easily separated by simple extraction with solvent. The remaining aqueous solution containing the catalyst was used in subsequent runs. The desired triazole **3b** was isolated in 86, 85, 82 and 80% yields over four cycles. It is noteworthy to mention that no distinct difference in yield and reaction time was observed when the recovered catalyst was used. Longer lifetime of the catalyst (Cu-aminoclay nanocomposite) in the triazole synthesis can be explained by efficient binding of Cu nanoparticles over aminoclay support, thus preventing the agglomeration of Cu nanoparticles.

In conclusion, we have demonstrated the Cu-aminoclay nanocomposite catalyzed Click reaction of azides with alkynes. The catalyst can be recycled with minimal loss of activity. No precautions needed to be taken to exclude air and the reactions proceed well under aerobic conditions. This reaction does not require either external base or ligands thus simplifying the reaction protocol. The reaction proceeds well in aqueous media at low catalyst loading (5 mg of Cu-aminoclay nanocomposite) with complete conversion and high regioselectivity which illustrate the exceptional reactivity and stability of the catalyst.

2.4. Spectral Data of 1,2,3-Triazoles

2.4.1. 1-Benzyl-4-Phenyl-1 H-1,2,3-Triazole (3a, Table I)

White solid, m.p. 126–128 °C. IR (KBr): υ_{max} 3140, 3028, 2923, 1607, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80–7.88 (*m*, 2 H), 7.65 (*s*, 1 H), 7.40–7.36 (*m*, 5 H), 7.32–7.28 (*m*, 3 H), 5.55 (*s*, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 134.7, 130.5, 129.1, 128.7, 128.1, 128.0, 125.6, 119.4, 54.1. ESI-MS: m/z=236 $(M+H)^+$.

2.4.2. Ethyl 1-Benzyl -1 H-1,2,3 Triazole-5-Carboxylate(3b, Table I)

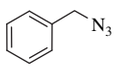
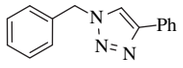
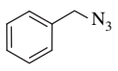
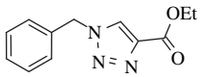
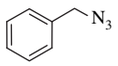
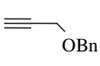
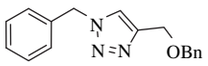
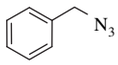
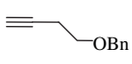
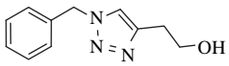
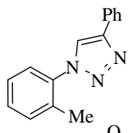
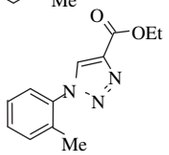
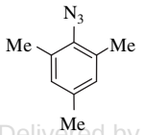
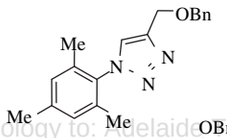
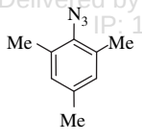
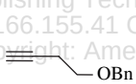
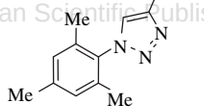
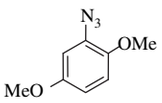
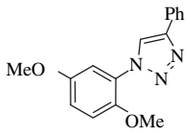
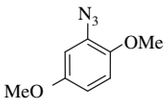
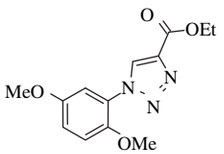
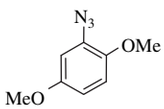
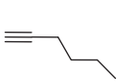
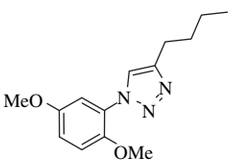
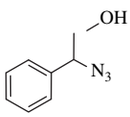
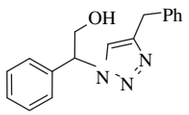
Colorless oil, IR (KBr): υ_{max} 3117, 3036, 2982, 1728, 1528, 1460, 1222, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.39 (*t*, *J*= 7.3 Hz, 3 H), 4.37 (*q*, *J*= 7.3 Hz, 2 H), 5.56 (*s*, 2 H), 7.27–7.38 (*m*, 5 H), 7.95 (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 54.2, 60.9, 127.2, 127.9, 128.7, 128.9, 133.7, 140.1, 160.4. ESI-MS: m/z= 232 $(M+H)^+$.

2.4.3. 2-(1-Benzyl-1 H-1,2,3-triazol-4-yl)Ethanol (3d, Table I)

White solid, m.p. 90-91°C; IR (KBr): υ_{max} 3424, 3136, 3060, 2925, 2859, 1959, 1716, 1550, 1492, 1450 cm^{-1};

COMMUNICATION

Table I. Prepation of trizoles via click reaction using Cu-aminoclay nanocomposite.

Entry	Azide	Alkyne	Triazole[a]	Time (h)	Yield (%)[b]
a				1.0	91
b				1.0	86
c				1.5	82
d				1.5	85
e				1.0	92
f				1.0	87
g				2.0	84
h				2.0	86
i				1.5	88
j				1.5	86
k				1.5	80
l				2.0	87

[a]All products were characterised by NMR, IR and mass spectrometry.

[b]Yield refers to pure products after chromatography.

Table II. Reusability of catalyst[a] for triazole synthesis of 3b.

Cycle	1	2	3	4
Yield[b] (%)	86	85	82	80

Notes: [a]The reaction was performed on 1 mmol of substrate dissolved in 4 mL of water with 5 mg of Cu-aminoclay at 60 °C; [b]Isolated yield.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.78$, (t, 2 H, $J = 6$ Hz), 3.65 (t, 2 H, $J = 6$ Hz), 5.47 (s, 2 H), 7.26-7.35 (m, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 54.04, 61.29, 120.01, 122.27, 126.90, 128.07, 129.67, 130.2, 134.65, 139.46, 148.02; ESI–MS m/z: 203.

2.4.4. Ethyl 1-o-Tolyl-1 H-1,2,3-Triazole-4-Carboxylate (3f, Table I)

Brown color liquid; IR (KBr): υ_{max} 3134, 2983, 2931, 1736, 1543, 1503, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (t, J= 6.8 Hz, 3 H), 2.26 (s, 3 H), 4.45 (q, $J = 6.8$ Hz, 2 H), 7.33–7.35 (m, 2 H), 7.37–7.39 (m, 1 H), 7.41–7.44 (m, 1 H), 8.22 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 17.7, 61.3, 125.9, 126.9, 128.8, 130.4, 131.5, 133.5, 135.6, 140.1, 160.6 ppm. ESI-MS: $m/z = 232$ $(M+H)^+$.

2.4.5. 4-(Benzyloxymethyl)-1-Mesityl-1 H-1,2,3-Triazole (3g, Table I)

Colourless viscous liquid; IR (KBr): υ_{max} 3110, 3071, 2862, 2808, 1494, 1453, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.95 (s, 3 H), 2.35 (s, 3 H), 4.62 (s, 3 H),4.75 (s, 2 H), 6.95 (s, 2 H), 7.25–7.34 (m, 5 H), 7.53 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 21.1, 63.6, 72.4, 124.3, 127.7, 127.8, 128.3, 128.9, 133,4, 134.9, 137.7, 39.9, 145. MS (ESI): $m/z = 308$ $(M+H)^+$.

2.4.6. 1-(2,5-Dimethoxyphenyl)-4-Phenyl-1 H-1,2,3-Triazole (3i, Table I)

Colourless viscous liquid; IR (KBr): υ_{max} 3137, 3012, 2929,2839, 1603, 1512, 1475, 1388, 1309, 1227, 1159 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3 H), 3.79 (s, 3 H), 6.81–6.92 (m, 2 H), 7.21–7.40 (m, 4 H), 7.8 (d, $J = 8.3$, 2 H), 8.28 (s, 1 H);^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.6, 110.3, 113.7, 115.6, 121.7, 125.7, 126.6, 128.0, 128.8, 130.6, 144, 8, 147.3, 153.9. MS (ESI): $m/z = 282$ $(M+H)^+$.

2.4.7. 1-(2,5-dimethoxyphenyl)-1 H-1,2,3-Triazole-4-Carboxylate (3j, Table I)

Solid, m.p. 73–74 °C; IR (KBr): υ_{max} 3164, 2996, 2924, 1739, 1625, 1519, 1476, 1217, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1 H), 7.49–6.92 (m, 3 H),4.46 (q, $J = 7.8$ Hz, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 1.34 (t, $J = 7.8$ Hz, 3 H);^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5, 55.8, 56.2, 61.0, 110.1, 113.4, 115.9, 125.4, 129.4, 139.6, 144.5, 153.6, 160.7.

2.4.8. 2-(4-Benzyl-1 H-1,2,3-Triazol-1-yl)-2-Phenylethanol (3l, Table I):

Solid, m.p. 110–112 °C; IR (KBr): υ_{max} 3384, 3064, 3032, 2926, 2855, 2361, 1605, 1547, 1492, 1453, 1358, 1224, 1053, 728, 699, 535 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12–7.34 (m, 11 H), 5.47 (dd, $J = 8.3$, 3.0 Hz, 1 H), 4.48 (dd, $J = 12.0$, 9.0 Hz, 1 H), 3.93–4.08 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 147.5, 130.2, 129.9, 128.8, 128.1, 125.6, 121.3, 114.4, 69.1, 68.9, 53.1, 20.4. MS (ESI): m/z = 280 $(M+H)^+$.

Acknowledgments: A. Sravanth Kumar and T. Srinivasa Rao thank CSIR, New Delhi for the award of fellowships.

References and Notes

1. P. K. Jain, X. Huang, I. H. E-Sayed, and M. A. E-Sayed, *Acc. Chem. Res*. 41, 1578 (**2008**).
2. G. A. Somorjai, H. Frei, and J. Y. Park, *J. Am. Chem. Soc*. 131, 16589 (**2009**).
3. K. Ariga, A. Vinu, Y. Yamauchi, Q. Ji, and J. P. Hill, *Bull. Chem. Soc. Jpn.* 85, 1 (**2012**).
4. K. Ariga, Q. Ji, M. J. McShane, Y. M. Lvov, A. Vinu, and J. P. Hill, *Chem. Mater.* 24, 728 (**2012**).
5. K. K. R. Datta, B. Srinivasan, H. Balaram, and M. Eswaramoorthy, *J. Chem. Sci.* 120, 579 (**2008**).
6. K. K. R. Datta, D. Jagadeesan, C. Kulkarni, A. Kamath, R. Datta, and M. Eswaramoorthy, *Angew. Chem. Int. Ed*. 50, 3929 (**2011**).
7. L. D. Rogatis, M. Cargnello, V. Gombac, B. Lorenzut, T. Montini, and P. Fornasiero, *Chem. Sus. Chem.* 3, 24 (**2010**).
8. W. Schmidt, *Chem. Cat. Chem*. 1, 53 (**2009**).
9. C.-J. Jia and F. Schüth, *Phys. Chem. Chem. Phys*. 13, 2457 (**2011**).
10. Y. Malam, E. J. Lim, and A. M. Seifalian, *Current Medicinal Chemistry.* 18, 1067 (**2011**).
11. K. Ariga, S. Ishihara, H. Abe, M. Li, and J. P. Hill, *J. Mater. Chem.* 22, 2369 (**2012**).
12. H. Wamhoff, Comprehensive Heterocyclic Chemistry, edited by A. R. Katritzky, C. W. Rees, Pergamon, Oxford (**1984**), Vol. 5, p. 669.
13. W. Q. Fan and A. R. Katritzky, Comprehensive Heterocyclic Chemistry II, edited by A. R. Katritzky, C. W. Rees, E. F. V Scriven, Elsevier Science, Oxford (**1996**), Vol. 4, p. 1–126.
14. V. A. Leoneti, V. L. Campo, A. S. Gomes, R. A. Field, and I. Carvalho, *Tetrahedron* 66, 9475 (**2010**).
15. A. Padwa, Comprehensive Organic Synthesis, B. M. Trost, Pergamon, Oxford (**1991**), Vol. 4, p 1069.
16. H. C. Kolb and K. B. Sharpless, *Drug Discovery Today.* 8, 1128, (**2003**).
17. R. Huisgen, *Angew. Chem.Int. Ed. Engl*. 2, 565 (**1963**).
18. C. W. Tornoe, C. Christensen, and M. Meldal, *J. Org. Chem.* 67, 3057 (**2002**).
19. V. D. Bock, H. Hiemstra, and J. H. V. Maarseveen, *Eur. J. Org. Chem*. 51 (**2006**), doi: 10.1002/ejoc.200500483.
20. H. C. Kolb, M. G. Finn, and K. B. Sharpless, *Angew. Chem. Int. Ed*. 40, 2004 (**2001**).
21. V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem. Int. Ed.* 41, 2596 (**2002**).
22. B. Dervaux and F. E. D. Prez, *Chem. Sci.* 3, 959 (**2012**).
23. D. Astruc, L. Liang, A. Rapakousiou, and J. Ruiz, *Acc. Chem. Res.* 45, 630 (**2012**).
24. M. Zahmakıran and S. Özkar, *Nanoscale*. 3, 3462 (**2011**).

COMMUNICATION

25. A. Kim, B. Sharma, B.-S. Kim, and K. H. Park, *J. Nanosci. Nanotechnol.* 11, 6162 **(2011)**.
26. P. Veerakumar, M. Velayudham, K.-L. Lu, and S. Rajagopal, *Catal. Sci. Technol*. 1, 1512 **(2011)**.
27. F. Alonso, Y. Moglie, G. Radivoy, and M. Yus, *J. Org. Chem*. 76, 8394 **(2011)**.
28. M. L. Kantam, V. S. Jaya, M. M. Rao, B. Sreedhar, and B. M. Choudary, *J. Mol. Catal. A: Chem.* 256, 273 **(2006)**.
29. A. Sarkar, T. Mukherjee, and S. Kapoor, *J. Phys. Chem. C* 112, 3334 **(2008)**.
30. B. J. Borah, D. Dutta, P. P. Saikia, N. C. Barua, and D. K. Dutta, *Green Chem*. 13, 3453 **(2011)**.
31. K. K. R. Datta, M. Eswaramoorthy, and C. N. R. Rao, *J. Mater. Chem*. 17, 613 **(2007)**.
32. K. K. R. Datta, C. Kulkarni, and M. Eswaramoorthy, *Chem. Commun.* 46, 616 **(2010)**.

Received: 11 August 2012. Accepted: 17 September 2012.