Green Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: W. Sun, Y. Wang, X. Wu and X. Yao, *Green Chem.*, 2013, DOI: 10.1039/C3GC40980E.

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

RSCPublishing

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.

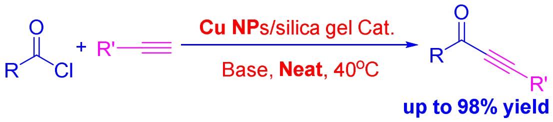
RSCPublishing

www.rsc.org/greenchem

Registered Charity Number 207890

View Article Online
DOI: 10.1039/C3GC40980E

The coupling of acyl chlorides and terminal alkynes was catalyzed by copper nanoparticles under a palladium-, ligand-, and solvent-free condition.



Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

View Article Online
DOI: 10.1039/C3GC40980E

ARTICLE TYPE

Palladium-, ligand-, and solvent-free synthesis of ynones by the coupling of acyl chlorides and terminal alkynes in the presence of a reusable copper nanoparticle catalyst

Weijiang Sun,[#] Yan Wang,[#] Xuan Wu, and Xiaoquan Yao*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Supported copper nanoparticles are utilized for the first time as a highly efficient and reusable catalyst in the coupling reaction of acyl chlorides and terminal alkynes to prepare various ynones. The reaction is carried out under a palladium-, ligand-, and solvent-free condition. The catalyst can be simply recovered and reused for several times without significant loss in catalytic activities.

α,β-Acetylenic carbonyl derivatives (ynones) are of great interest due to their extensive application in natural products and organic synthesis. They are extremely versatile intermediates for the preparation of heterocyclic derivatives.[1] Many synthetic strategies for ynones have been reported. Among them, the cross-coupling reaction of carboxylic acid derivatives and stoichiometric metal acetylides was one of important approaches to synthesize ynones, in which the usage of magnesium[2], silver[3], cadmium[4], silicon[5], copper[6], tin[7], lithium[8], aluminum[9], thallium[10], gallium[11], stibium[12], indium[13], zinc[14] and boron[15] reagents and carboxylic acid derivatives all led to the formation of ynones. However, using a large amount of sensitive metal acetylides made the reaction drastic and uneconomical. As a result, an alternative catalytic coupling of acyl chlorides and terminal alkynes utilizing palladium-copper catalyst, known as a Sonogashir-type reaction, drew more attention.[16] In the past few decades, much progress has been made to improve this methodology, and various palladium species were reported.[17] Cox and his co-workers utilized $Pd(PPh_3)_2Cl_2/CuI$ to proceed the reaction at room temperature and shortened the reaction time significantly.[18] Nájera and co-workers reported an oxime derived palladacycle as catalyst alone instead of Pd/Cu.[19] The reaction proceeded under a phosphine and copper free condition at high temperature. $Pd(OAc)_2$ were also ultilzed independently as catalyst in the reaction at room temperature.[20] A palladium-free catalytic reaction was reported by Chowdhury and Kundu with CuI as catalyst, but only moderate yields were observed and suffered higher catalyst loading and much longer reaction time.[21] Gallagher and Maleczka developed a catalytic system consisting of CuCl, CsF and polymethylhydrosiloxane.[22] The reaction resulted in moderate yields involving a *in situ* generation of a siloxyl intermediate.

In view of green and sustainable chemistry, many recyclable catalytic system were reported for the coupling reaction in recent years. Chen and Li reported the first example in water by using $Pd(PPh_3)_2Cl_2/CuI$ as catalyst with sodium lauryl sulfate as surfactant.[23] Heterogenous palladium also proved to be efficient catalysts in the coupling reaction,[24-27] in which sillica-immobilized palladium(II) catalyst could also be used in water medium.[28] On the other hand, supported zinc bromide was also reported as an efficient recyclable catalyst in the reaction.[29]

In recent years, there has been a great interest in using nanoparticles as catalysts in organic reactions.[30] Because of easy preparation and being relative stable in air, the nanoparticles of coinage metals were widely reported, and there are many excellent examples on their applications as catalysts.[31] Based on our continuous investigation on copper and silver nanoparticles catalyzed reactions,[32] we wish to report herein a palladium-, ligand- and solvent-free, copper nanoparticles (Cu-nps) catalyzed cross-coupling reaction of acyl chlorides and terminal alkynes for the synthesis of ynones. The reaction proceeded smoothly under a mild condition in the absence of ligands and solvents. A variety of acyl chlorides and terminal alkynes were examined, and good to excellent yields were achived with only 1 mol% of catalyst loading. By using solid supporters, the catalysts can be easily separated from the reaction mixture and reused for several cycles without significant decrease in catalytic activities.

The copper nanocatalysts were prepared following the reported procedure by using cupric acetate as raw material, water as solvent, polyvinylpyrrolidone (PVP) as protecting agent and sodium borohydride as reducing agent.[33-34] Considering their convenience in handling and storage, espically in catalyst recovery and product separation, two

---

Department of Applied Chemistry, School of Material Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing 210016, PR China. Fax: 86 25 52112626; Tel: 86 25 52112626; E-mail: yaoxq@nuaa.edu.cn

[#] *These authors contributed equally to this work.*

† Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic and analytical data. See DOI: 10.1039/b000000x/

View Article Online
DOI: 10.1039/C3GC40980E

kinds of supported catalysts, γ-Al_2O_3- and sillica gel-supported copper nanoparticles were also synthesized respectively, and their TEM images were shown in Fig. 1.

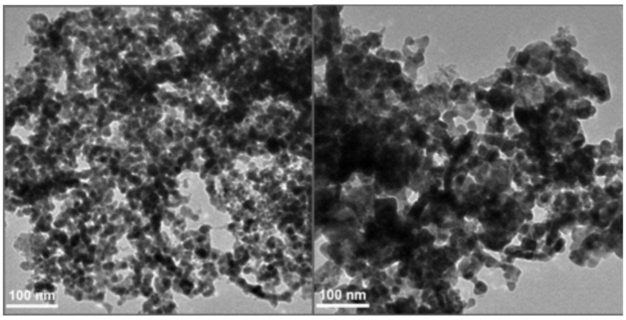


Fig. 1 The TEM image of supported copper nanoparticles: Cu-nps/silica gel (left); Cu-nps/γ-Al_2O_3 (right)

It can be seen from the images that the two catalysts have similar particle size, but sillica gel supported Cu-nps exhibit a smaller size, better morphology and more uniform distribution.

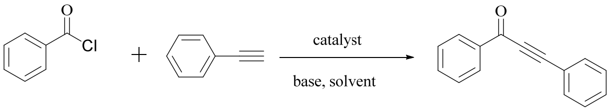
With the prepared Cu-nps catalysts, we then examined them in the reaction of acyl chlorides and terminal alkynes toward ynones. The cross-coupling reaction of benzoyl chloride and phenylacetylene was selected as the prototype, and the results were summirized in Table 1.

Cu-nps was ultilized alone to catalyze the reaction at first with toluene as solvent and Et_3N as base. After overnight reaction at 40°C, 82% of desired product was isolated without the promotion of any ligand (entry 1, Table 1), whereas other organic solvents, such as DCM, MeCN and DMF, resulted in low conversions (entries 2-4). Superisingly, when the catalytic reaction was carried out under a solvent-free & ligand-free condition, Cu-nps catalyst showed the highest activity and up to 98% of yield was achieved (entry 5).

Other bases, such as K_2CO_3, N,N-diisopropylethylamine, trioctylamine and 2,6-lutidine, were also evaluated for the reaction instead of TEA under neat condition. However, all of them lead to very poor results (entries 6-10). Reducing the amount of Et_3N led to the decrease in reactivities significently (entries 11-12), and the reaction did not work at all in the absence of TEA as base (entry 13). The same tend was also obsevrved when reducing the ammount of Cu-nps catalyst (entry 14). On the other hand, Ag-nps was also scaned as catalyst instead of copper, but no reaction occurred(entry 15).

The nature of the supporting materials proved to be an important influential factor to catalytic activities of nanoparticles in our previous report.[32c] To further improvement of the reaction, espically the convenience in recovering and recycling the catalyst, γ-Al_2O_3- and sillica gel- supported copper nanoparticles were employed as catalysts. It is worthy to note that the supported Cu-nps could decrease the catalyst loading significiently. Sillica gel-supported catalyst gave the best result, and even 1 mol% of catalyst is enough to generate an 95% yield of the desired product (entries 17-20).

Table 1 Copper nanoparticles catalyzed cross-coupling reaction of benzoyl chloride and phenylacetylene [a]

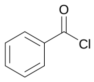
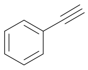
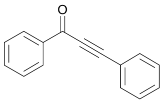
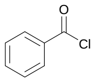
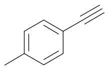
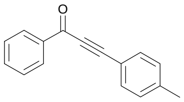
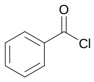
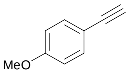
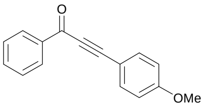
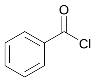
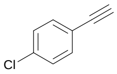
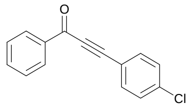
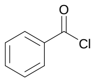
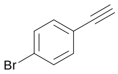
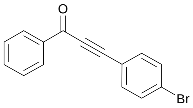
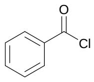
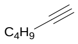
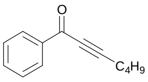
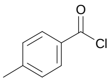
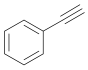
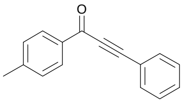
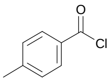
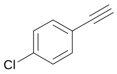
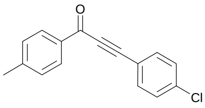
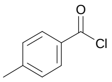
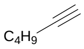
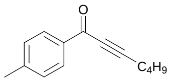
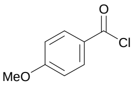
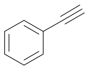
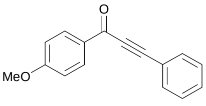
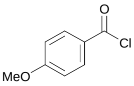
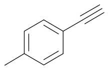
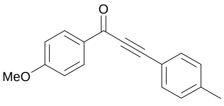
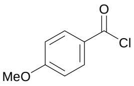
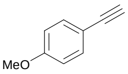
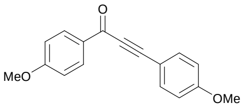
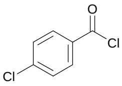
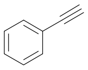
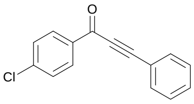
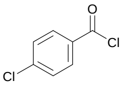
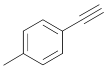
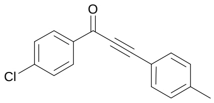
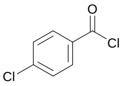
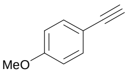
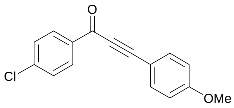
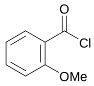
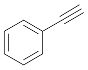
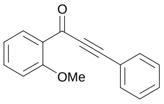
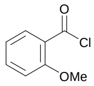
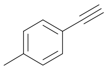
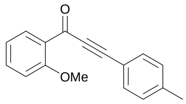
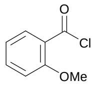
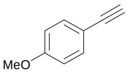
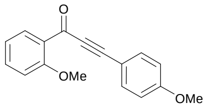
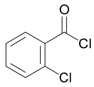
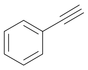
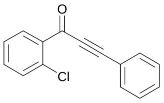
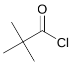
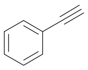
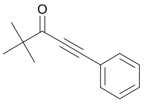
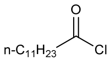
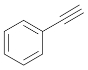
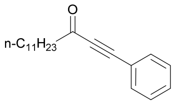
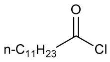
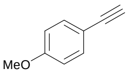
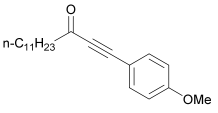


entry	catalyst (mol %)	solvent	base (equiv)	yield (%)[b]
1	Cu-nps (5)	toluene	TEA (3)	82
2	Cu-nps (5)	DCM	TEA (3)	12
3	Cu-nps (5)	MeCN	TEA (3)	49
4	Cu-nps (5)	DMF	TEA (3)	N.D.
5	Cu-nps (5)	free	TEA (3)	98
6	Cu-nps (5)	free	K_2CO_3 (3)	N.D.
7	Cu-nps (5)	free	2,6-lutidine (3)	N.D.
8	Cu-nps (5)	free	i-Pr_2NEt (3)	32
9	Cu-nps (5)	free	$(n\text{-}C_8H_{17})_3N$ (3)	N.D.
10	Cu-nps (5)	free	$PhNMe_2$ (3)	N.D.
11	Cu-nps (5)	free	TEA (2)	87
12	Cu-nps (5)	free	TEA (1)	64
13	Cu-nps (5)	free	free	N.D.
14	Cu-nps (2.5)	free	TEA (3)	87
15	Ag-nps (5)	free	TEA (3)	N.D.
16	free	free	TEA (3)	N.D.
17	Cu-nps/γ-Al_2O_3 (5)	free	TEA (3)	98
18	Cu-nps/γ-Al_2O_3 (1)	free	TEA (3)	89
19	Cu-nps/silica gel (5)	free	TEA (3)	98
20	Cu-nps/silica gel (1)	free	TEA (3)	95

[a] Reaction conditions: phenylacetylene (0.5 mmol), benzoyl chloride (1.5 equiv), solvent (2 mL), 40 °C overnight. [b] The yields were determined by GC with dimethyl phthalate as internal standard.

Cite this: DOI: 10.1039/c0xx00000x
www.rsc.org/xxxxxx
View Article Online
DOI: 10.1039/C3GC40980E

Table 2 Synthesis of ynones by coupling of acyl chlorides with terminal alkynes.[a]

entry	acyl chlorides	alkynes	products	yield (%)[b]
1	 **1a**	 **2a**	 **3a**	92
2	 **1a**	 **2b**	 **3b**	98
3	 **1a**	 **2c**	 **3c**	91
4	 **1a**	 **2d**	 **3d**	96
5	 **1a**	 **2e**	 **3e**	80
6	 **1a**	 **2f**	 **3f**	79
7	 **1b**	 **2a**	 **3g**	88
8	 **1b**	 **2d**	 **3h**	82
9	 **1b**	 **2f**	 **3i**	78
10	 **1c**	 **2a**	 **3j**	81
11	 **1c**	 **2b**	 **3k**	80
12	 **1c**	 **2c**	 **3l**	89
13	 **1d**	 **2a**	 **3m**	94
14	 **1d**	 **2b**	 **3n**	90
15	 **1d**	 **2c**	 **3o**	89
16	 **1e**	 **2a**	 **3p**	87
17	 **1e**	 **2b**	 **3q**	82
18	 **1e**	 **2c**	 **3r**	81
19	 **1f**	 **2a**	 **3s**	84
20	 **1g**	 **2a**	 **3t**	84
21	 **1h**	 **2a**	 **3u**	71
22	 **1h**	 **2c**	 **3v**	35

[a] Reaction conditions: alkyne (0.5 mmol), acyl chloride (1.5 equiv), Et_3N (3 equiv), supported Cu-nps (1 mol %), 40 °C overnight. [b] Isolated yield.

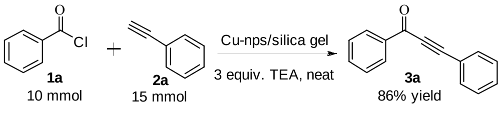
Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

View Article Online
DOI: 10.1039/C3GC40980E

ARTICLE TYPE

Subsequently, the scope of the reaction was investigated with various acyl chlorides and terminal alkynes under the optimized condition (entry 20, Table 1), and good to excellent yields were achieved (Table 2). It can be seen from Table 2 that most of aromatic alkynes with electron-donating or electron-withdrawing substitutents resulted in excellent yields, except the brom-substituted alkyne **2e** (entries 1-4 vs entry 5, Table 2). It is worthynote that aliphatic alkyne **2f,** which was less active substrate in many previous reports, also gave 79% of yield to the desired product (entry 6). On the other hand, aromatic acyl chlorides were suitable substrates. Even with the aromtic acyl chlorides **1e** and **1f** as substrates, which had steric hindrance at the ortho position, 81-87% yields were achieved sucessfully (entries 16-19). Aliphatic acyl chlorides also gave good to moderate results with **2a** as terminal alkyne (entries 20-21). However, a lower yield was observed in the reaction of **1h** and **2c** (entry 22).



Scheme 1. Gram-scale reaction of **1a** and **3a**.

To further investigate the efficiency of the catalytic reaction, a 10 mmol-scale reaction of **1a** and **2a** was carried out, and 86% of isolated yield was achieved.

Table 3 Recycling studies[a].

entry	supporter	first run yield (%)[b]	second run yield (%)[b]	third run yield (%)[b]
1	γ-Al_2O_3	89	83	78
2	silica gel	95	90	84
3[c]	silica gel	92	88	85

[a] Reaction conditions: alkyne (0.5 mmol), acyl chloride (1.5 equiv), Et_3N (3 equiv), 40 °C overnight, supported Cu-nps (1 mol %). [b] Yield determined by GC using dimethyl phthalate as internal standard. [c] Reaction in 2 mmol scale.

One of the advantages of heterogeneous catalysts is their easy separation from the reaction mixture. The supported Cu-nps catalyst could be separated and recovered conveniently by centrifugation from the reaction mixture, and then, new substrate and base were added to set up a new reaction. Following this procedure, the catalyst was recycled effectively, and the results were summarized in Table 3. Obviously, the silica gel-supported catalyst showed much better recycling ability than the Al_2O_3-supported (entries 2-3 vs. entry 1, Table 3). On the other hand, in order to further investigate the reusability of the catalyst, the scale of the reaction was increased from 0.5 mmol to 2 mmol, and there was no obvious decrease in catalytic activities observed after several recycles.

In conclusion, a highly efficient palladium-, ligand-, and solvent-free, copper nanoparticles catalyzed coupling reaction of acyl chlorides with terminal alkyns were developed successfully. A variety of acyl chlorides and terminal alkynes were employed as substrates to synthesis ynones under a mild condition, and good to excellent yields were acheived. Further more, the catalysts could be easily separated and reused for several cycles without significant decrease in catalytic activity. The detailed mechanism, the effect of particle size[35] and particle support as well as the scope of the reaction are currently under further investigations.

This work was financially supported by the National Natural Science Foundation of China (21172107) .

Notes and references

1 Some recent examples: (a) A. V. Kel'in and V. Gevorgyan *J. Org. Chem.* 2002, **67**, 95. (b) B. G. V. Hoven, B. E. Ali and H. Alper, *J. Org. Chem.* 2000, **65**, 4131. (c) D. B. Grotjahn, S. Van, D. Combs, D. A. Lev, C. Schneider, M. Rideout, C. Meyer, G. Hernandez and L. Mejorado, *J. Org. Chem.* 2002, **67**, 9200. (d) A. S. Karpov and T. J. J. Müller, *Org. Lett.* 2003, **5**, 3451. (e) C. G. Savarin, J. A. Murry and P. G. Dormer, *Org. Lett.* 2002, **4**, 2071. (f) Y. Xing and G. A. O'Doherty, *Org. Lett.* 2009, **11,** 1107. (g) N.-J. Kim, H. Moon, T. Park, H. Yun, J.-W. Jung, D.-J. Chang, D.-D. Kim and Y.-G. Suh, *J. Org. Chem.* 2010, **75,** 7458. (h) T. M. Trygstad, Y.;Pang and C. J. Forsyth, *J. Org. Chem.* 2009, **74,** 910. (i) D. A. Rooke and E. M. Ferreira, *J. Am. Chem. Soc.* 2010, **132**, 11926. (j) V. S. Aulakh and M. A. Ciufolini, *J. Am. Chem. Soc.*, 2011, **133**, 5900.

2 J. W. kroeger and J. A. Nieuwland, *J. Am. Chem. Soc.*, 1936, **58**, 1861.

3 R. B. Davis and D. H. Scheiber, *J. Am. Chem. Soc.*, 1956, **78**, 1675.

4 O. G. Yashina, T. V. Zarva, T. D. Kaigorodova and L. I. Vereshchagin, *Zh. Org. Khim.*, 1968, **4**, 2104.

5 D. R. Waiton and F. Waugh, *J. Organometal. Chem.*, 1972, **37**, 45.

6 M. W. Logue and G. L. Moore, *J. Org. Chem.*, 1975, **40**, 131.

7 M. W. Logue and K. Teng, *J. Org. Chem.*, 1982, **47**, 2549

8 H. C. Brown, U. S. Racherla and S. M. Singh, *Tetrahedron Lett.*, 1984, **25**, 2411.

9 T. Wakamatsu, Y. Okuda, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2425.

10 I. E. Markó and J. M. Southern, *J. Org. Chem.*, 1990, **55**, 3368.

11 Y. Han, L. Fang, W.-T. Tao and Y.-Z. Huang, *Tetrahedron Lett.*, 1995, **36**, 1287.

12 N. Kakusawa, K. Yamaguchi, J. Kurita and T. Tsuchiya, *Tetrahedron Lett.*, 2000, **41**, 4143.

13 I. Pérez, J. P. Sestelo, and L. A. Sarandeses, *J. Am. Chem. Soc.*, 2011, **123**, 4155.

14 K. Y. Lee, M. J. Lee and J. N. Kim, *Tetrahedron*, 2005, **61**, 8705.

15 Y. Nishihara, D. Saito, E. Inoue, Y. Okada, M. Miyazaki and Y. Inoue, *Tetrahedron Lett.*, 2010, **51**, 306

16 Y. Tohda, K. Sonogashira and N. Hagihara, *Synthesis*, 1977, 777.

17 A recent review, see: R. Chinchilla, C. Nájera *Chem. Rev.* 2007**, 107**, 874-922

18 R. J. Cox, D. J. Ritson, T. A. Dane, J. Berge, J. P. H. Charmant and A. Kantacha, *Chem. Commun.*, 2005, 1037

19 D. A. Alonso, C. Nájera and M. C. Pacheco, *J. Org. Chem.* 2004, **69**, 1615.

20 S. S. Palimkar, P. H. Kumar, N. R. Jogdand, T. Daniel, R. J. Lahoti and K. V. Srinivasan *Tetrahedron Lett.* 2006, **47**, 5527

21 C. Chowdhury and N. G. Kundu, *Tetrahedron*, 1999, **55**, 7011.

22 W. P. Gallagher and R. E. Maleczka Jr, *J. Org. Chem.* 2003, **68**, 6775.

23 L. Chen and C.-J. Li, *Org. Lett.*, 2004, **6**, 3151.

24 P. R. Likhar, M. S. Subhas, M. Roy, S. Roy, and M. L. Kantam, *Helv. Chim. Acta*, 2008, **91**, 259.

25 J.-Y. Chen, T.-C. Lin, S.-C. Chen, A-J. Chen, C.-Y. M and F.-Y. Tsai, *Tetrahedron*, 2009, **65**, 10134.

26 M. Bakherad, A. Keivanloo, B. Bahramian and M. Rajaie, *Tetrahedron Lett.*, 2010, **51**, 33.

27 A. Keivanloo, M. Bakherad, B. Bahramian, M. Rahmani and S. A. N. Taheri, *Synthesis*, 2011, 325.

28 (a) C. Kang, J. Huang, W. He and F. Zhang, *J. Organometal. Chem.*, 2010, **695**, 120; (b) F. Zhang, C. Kang, Y. Wei and H.Li *Adv. Funct. Mater.* 2011, **21**, 3189.

29 A. Keivanloo, M. Bakherad, B. Bahramian, M. Rahmani, and S. A. N. Taheri *Synthesis* 2011, 0325

30 For recent reviews, see: (a) N. R. Shiju and V. V. Guliants, *Appl. Catal. A: General,* 2009, **356**, 1; (b) G. A. Somorjai and J. Y. Park, *Angew. Chem. Int. Ed.*, 2008, **47**, 9212; (c) Y. Gu and G. Li, *Adv. Synth. Catal*., 2009, **351**, 817; (d) L. L. Chng, N. Erathodiyil and J. Y. Ying, *Acc. Chem. Res.,* 2013, **135**, ASAP.

31 Selected reviews: (a) D. Astruc, F. Lu and J. M. Aranzaes, *Angew. Chem. Int. Ed.*, 2005, **44**, 7852; (b) A. Corma and H. Garcia, *Chem. Soc. Rev.*, 2008, **37**, 2096; (c) Ref. 30(c).

32 (a) M. Yu, M. Lin, C. Han, L. Zhu, C.-J. Li and X. Yao, *Tetrahedron Lett.*, 2010, **51**, 6722; (b) C. Han, M. Yu, W. Sun and X. Yao, *Synlett.* 2011, 2363; (c) M. Yu, Y. Wang, W. Sun and X. Yao, *Adv. Synth. Catal.* 2012, **354**, 71

33 A. Sarkar, T. Mukherjee and S. Kapoor, *J. Phy. Chem. C,* 2008, **112**, 3334.

34 Y. Wang and T. Asefa, *Langmuir,* 2010, **26**, 7469.

35 As a primary result for the effect of particle size, we prepared the copper NPs without surfactant, and the size of the particles was around 50 μm with a wide distribution. Only 76% of **3a** was obtained with 5 mol % catalyst.