DOI 10.1002/aoc.3695

#### COMMUNICATION

#### WILEY Applied Organometallic Chemistry

# Copper oxide supported on magnetic nanoparticles (CuO@ $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>): An efficient and magnetically separable nanocatalyst for addition of amines to carbodiimides towards synthesis of substituted guanidines<sup>†</sup>

### Sepideh Abbasi<sup>1</sup> | Dariush Saberi<sup>2</sup> | Akbar Heydari<sup>1</sup>

<sup>1</sup>Chemistry Department, Tarbiat Modares University, PO Box 14155-4838 Tehran, Iran

<sup>2</sup> Fisheries and Aquaculture Department, College of Agriculture and Natural Resources, Persian Gulf University, Bushehr 75169, Iran

#### Correspondence

Akbar Heydari, Chemistry Department, Tarbiat Modares University, PO Box 14155-4838, Tehran, Iran.

Email: heydar\_a@modares.ac.ir <sup>†</sup>This article is dedicated to memory of Mohammad Jahanara Copper oxide supported on magnetic nanoparticles was used as a green magnetic nanocatalyst for hydroamination of carbodiimides towards the synthesis of guanidines. Easy preparation and separation, low cost, non-sensitivity to moisture and reusability of the catalyst along with diversity and high yield of products are significant features of this method.

#### KEYWORDS

carbodiimide, copper oxide, guanidine, heterogeneous catalysis, magnetic nanoparticles

#### **1** | **INTRODUCTION**

Catalysis is a prominent feature in most chemical reactions so that one of the twelve principles of green chemistry revolves around this matter. Features such as high activity and stability, great selectivity, efficient recovery, good recyclability and low preparation cost restrict the choice of catalyst.

Catalysts are conventionally divided into two categories, homogeneous and heterogeneous, each with its own advantages and disadvantages: that is, high activity and selectivity of homogeneous catalysts against easy isolation and separation of heterogeneous ones.<sup>[1]</sup> Efforts to achieve a catalyst system including most of the features mentioned above have involved the use of magnetic nanoparticles. Due to their magnetic properties and large surface-to-volume ratio, magnetic nanoparticles are easily separable from a reaction mixture, using an external magnet, along with having good activity and selectivity. These salient properties lead magnetic nanoparticles to play an important role in catalytic systems used in chemical reactions, either directly as catalysts or as supports.<sup>[2]</sup> Among magnetic nanoparticles, magnetite (Fe<sub>3</sub>O<sub>4</sub>) and maghemite ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) are magnetic iron oxides that are extensively used as supports for magnetic heterogeneous catalysts.<sup>[3]</sup> Easy production, low cost and non-toxicity make them ideal for this purpose.

Because of their presence as building blocks in natural products and biologically active compounds, guanidines are an important class of organic compounds.<sup>[4]</sup> Moreover, they are used as base catalysts as well as ancillary ligands for metal complexes.<sup>[5]</sup> Hence, the development of green synthetic methods for their preparation is of high importance.

Common methods developed for the synthesis of guanidine scaffolds include treatment of an amine with various activated guanidinylating reagents,<sup>[6]</sup> transamination of guanidines,<sup>[7]</sup> and hydroamination of carbodiimides.<sup>[8]</sup> It seems that the latter one is a more popular method, in view of product diversity and atom efficiency, although a catalyst is needed for convenience of this transformation. In recent years, various catalytic systems such as metal salts, aluminium alkyl complexes, transition metal imido complexes and rare earth metal organic complexes have been employed to promote this reaction and satisfactory results have been obtained in terms of reaction efficiency, conditions and catalyst recyclability, although the problems of isolation and recycling of the catalyst as well as strict conditions for their preparation accompany these methods.

Recently, we have reported the preparation, characterization and catalytic evaluation of maghemite-supported copper oxide nanocatalyst for the N—H insertion reaction with ethyl diazoacetate.<sup>[9]</sup> Continuing our work of designing and using 2 of 5 WILEY-Organometallic-Chemistry

magnetic heterogeneous catalysts,<sup>[10]</sup> in the work reported herein we used this magnetic nanocatalyst for the addition of amines to carbodiimides towards the synthesis of substituted guanidines. Facile preparation of the catalytic system from low-cost starting materials, easy separation from reaction mixture using an external magnet, with the ability to re-use and recycle, as well as the synthesis of various guanidines under mild reaction conditions are significant features of this procedure.

#### 2 | EXPERIMENTAL

#### 2.1 | Chemicals, instrumentation and analysis

All reagents were purchased from commercial suppliers and used without further purification. All experiments were carried out under air. Inductively coupled plasma (ICP) analysis was accomplished using a VISTA-PRO, CCD simultaneous ICP analyser. Fourier transform infrared (FT-IR) spectra were obtained in the region 400–4000 cm<sup>-1</sup> with a Nicolet IR100 FT-IR spectrometer with spectroscopic grade KBr. <sup>1</sup>H NMR spectra were recorded with a Bruker Avance (DRX 500 MHz) in pure deuterated CDCl<sub>3</sub> solvent with tetramethylsilane as internal standard.

## 2.2 | Preparation of nanostructured cuO@γ-Fe<sub>2</sub>O<sub>3</sub> catalyst

 $CuO@\gamma$ -Fe<sub>2</sub>O<sub>3</sub> as a magnetically separable nanostructured catalyst was synthesized by hydrolysing cupric chloride in a suspension of freshly prepared maghemite nanoparticles. Maghemite nanoparticles were first synthesized according to a previously reported procedure,<sup>[11]</sup> starting from FeCl<sub>2</sub>·4H<sub>2</sub>O and FeCl<sub>3</sub>·6H<sub>2</sub>O in 1:2 ratio as iron sources and using ammonia for precipitation. The pH of the mixed iron solution was adjusted to 11 by adding concentrated ammonia and the resulting mixture was refluxed for about 1 h without using inert atmosphere. After multiple times washing with distilled water, a 0.01 M solution of CuCl<sub>2</sub>·2H<sub>2</sub>O was added to the precipitates and then the pH of the solution was adjusted to 13 with 1 M NaOH. The amount of copper was adjusted to yield ca 30% w/w CuO@y-Fe<sub>2</sub>O<sub>3</sub> (Cu/Fe atomic ratio of 0.29). After 24 h stirring at room temperature, particles were precipitated by a magnet, washed several times with distilled water to neutralization and were dried at 110 °C for 24 h.

#### 2.3 | General procedure for synthesis of products 3a-x

Carbodiimide (1 mmol) and CuO@ $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (40 mg, 19.2 mol% of CuO, calculated by ICP analysis) were placed in a 10 ml round-bottomed flask and the mixture heated for 10 min at 80 °C. Then, amine (1.2 mmol) was added to it and allowed to stir for 6 h. Progress of the reaction was followed by TLC. After completion, the reaction

vessel was cooled to room temperature. EtOAc (10 ml) was added to it and placed in an ultrasonic bath for 2 min. Magnetic nanocatalyst was then adsorbed onto the surface of the stir bar and was separated from the solution using an external magnet. The product was obtained by evaporation of the volatiles under reduced pressure and the residue was purified by column chromatography, if necessary. In the case of secondary amines, a slightly modified procedure was employed, which utilized  $Et_3N$  as the base. All compounds were identified from melting point and FT-IR and <sup>1</sup>H NMR spectra. The spectral data of known compounds were compared with those reported in the literature.

#### **3** | RESULTS AND DISCUSSION

N.N-То determine the optimum conditions, dicyclohexylcarbodiimide and aniline were chosen as model substrates. Solvent, temperature and amount of catalyst were the parameters studied. The results are listed in Table 1. Firstly, N,N-dicyclohexylcarbodiimide (1 mmol) and aniline (1.2 mmol) reacted in water (2 ml) as solvent in the presence of CuO@y-Fe<sub>2</sub>O<sub>3</sub> (20 mg, 19.2 mol% of CuO) at 60 °C. After 6 h of reaction time, the corresponding guanidine was obtained in only 20% yield (Table 1, entry 1). The effect of some organic solvents, tetrahydrofuran (THF), n-hexane, CH<sub>2</sub>Cl<sub>2</sub> and toluene, was investigated on the reaction efficiency but none of them were promising (Table 1, entries 2-5). When the model reaction was conducted under

TABLE 1 Optimization of reaction conditions<sup>a</sup>

$\bigcirc$	-N=C=N-	$ \frac{MH_2}{Cut}$	Divent, Temp. $C$	Cy-NH C=N-
Entry	Solvent	Catalyst (mg	g) Temp. (°C)	Yield (%) <sup>b</sup>
1	ЧО	20	60	20

1	H <sub>2</sub> O	20	60	20
2	THF	20	60	10
3	<i>n</i> -Hexane	20	60	20
4	CH <sub>2</sub> Cl <sub>2</sub>	20	60	50
5	Toluene	20	60	20
6	Solvent-free	20	60	70
7	Solvent-free	20	80	94
8	Solvent-free	20	100	94
9	Solvent-free	20	r.t	10
10	Solvent-free	10	80	50
11	Solvent-free	30	80	90
12	Solvent-free	_	80	_
13	Solvent-free	20 <sup>c</sup>	80	_

<sup>a</sup>Reaction conditions: *N,N*-dicyclohexylcarbodiimide (1 mmol), aniline (1.2 mmol), solvent (2 ml).

<sup>b</sup>Isolated yield.

<sup>c</sup>γ-Fe<sub>2</sub>O<sub>3</sub> was used as catalyst.

solvent-free conditions, efficiency was increased, with a yield of up to 70% (Table 1, entry 6). Fortunately, it was observed that increasing the temperature to 80 °C enhanced the yield



**FIGURE 1** Scope of starting materials. Reaction conditions: carbodiimide (1 mmol), aniline (1.2 mmol), 80 °C, 6 h. The yields refer to the isolated pure products. In the case of secondary amines,  $Et_3N$  (1.5 equiv.) as base was added to the reaction mixture

TABLE 2 Catalyst recyclability in model reaction<sup>a</sup>

Run	Yield of product 3a (%)
1	94
2	94
3	93
4	92

<sup>a</sup>Reaction conditions were similar to those shown in Figure 1.



up to 94%, whereas reducing it to room temperature led to a significant reduction in the efficiency of the reaction. Moreover, increasing the temperature to 100 °C did not enhance the yield (Table 1, entries 7–9).

By reducing the amount of catalyst, the yield was decreased; on increasing the amount, the yield did not change (Table 1, entries 10 and 11). In the absence of catalyst or in the presence of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles, no product was formed, indicating that CuO plays an important role in this transformation (Table 1, entries 12 and 13).

After establishment of the optimized reaction conditions, the scope of starting materials was investigated. As shown in Figure 1, various derivatives of aniline bearing electrondonating and electron-withdrawing substituents at ortho, positions reacted with N.Nmeta and para dicyclohexylcarbodiimide, and the corresponding guanidines were obtained in high yields. The results show that the reaction was not sensitive to the electronic nature and ring position of the substrates. Also, 1-naphthylamine, a polycyclic amine, was well coupled with N,N-dicyclohexylcarbodiimide and the corresponding guanidine was formed in good yield (product 3p). When secondary amines such as morpholine and pyrrolidine, aliphatic cyclic amines, were subjected to the reaction conditions with N,N-dicyclohexylcarbodiimide, Et<sub>3</sub>N (1.5 equiv.) as base was added to the reaction mixture to afford the corresponding guanidines (products 3g and **3r**). Also, *N*,*N*-diisopropylcarbodiimide was a good reaction partner, and the corresponding products were obtained in good yields, when reacted with some aniline derivatives (products 3r-3x).

The ability of the catalyst to be re-used and recycled was evaluated in the model reaction. For this purpose, after completion of the first run of the reaction, the catalyst was removed from the reaction mixture by simple decantation using an external magnet, washed with methanol, dried at ambient temperature and reused for the next run. The catalyst was recycled up to four times without any significant loss of its catalytic activity (Table 2).

A hot filtration test was performed to prove the heterogeneous nature of the catalyst. For this purpose, the catalyst was allowed to stir under the reaction conditions. After 6 h, EtOAc (10 ml) was added and the catalyst was

TABLE 3 Comparison of performance of our catalyst with that of some previously reported catalysts

Entry	Catalyst	Conditions (temp./ solvent/ time)	Yield (%)	Ref.
1	Yttrium complex	80 °C, C <sub>6</sub> D <sub>6</sub> , 1 h	99	[8p]
2	Samarium amido complex	60 °C, THF, 12 h	91	[12]
3	Neodymium complex	60 °C, solvent-free, 24 h	93	[13]
4	$[Ca{N(SiMe_3)_2}_2(THF)_2]$	80 °C, hexane, 1 h	74	[14]
5	AlClMe <sub>2</sub>	r.t., toluene, 18 h	93	[8q]
6	$[(Me_3Si)_2N]_3Yb(\emph{i-Cl})Li(THF)_3$	60 °C, THF, 4 h	95	[8h]
7	$Cy[NC=CH_2)-2-(C_5H_4N)AlMe_2]_2$	r.t., toluene, 1 h	96	[15]
8	Nano ZnO	80 °C, toluene, 8 h	97	[8s]
9	CuO@y-Fe <sub>2</sub> O <sub>3</sub>	80 °C, solvent-free, 6 h	96	This work



SCHEME 1 Plausible mechanism for  $CuO@\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-catalysed hydroamination of carbodiimides

removed from the reaction vessel using an external magnet. ICP analysis of the decantation revealed no decrease in the copper content.

The efficiency of our catalytic system was compared with that of some previously reported procedures in the synthesis of product **3 s** via hydroamination pathway (Table 3). As is evident from Table 3, our catalytic system is comparable with others in terms of reaction conditions and yields. Nevertheless, low cost, non-sensitivity to moisture, easy separation and reusability are advantages of CuO@ $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> over the other catalysts.

Although there was no attempt to understand the exact mechanism of this transformation, it seems that the interaction between CuO nanoparticles and C=N double bond paves the way for the nucleophilic attack of amine to carbon atom of carbodiimide followed by hydroamination reaction on C=N double bond. A plausible mechanism is depicted in Scheme 1.

#### 4 | CONCLUSIONS

We have developed the use of magnetic nanoparticles as support in the catalytic synthesis of guanidines via hydroamination reaction of carbodiimides. CuO stabilized on maghemite nanoparticles was used as an efficient and magnetically separable as well as reusable catalyst for this goal. Various derivatives of guanidines were synthesized under mild and clean reaction conditions in high yields.

#### ACKNOWLEDGMENTS

We acknowledge Tarbiat Modares University for partial support of this work.

#### REFERENCES

- a) N. Mizuno, M. Misono, Chem. Rev. 1998, 98, 199; b) B. Cornils, W. A. Herrmann, Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook, VCH, Weinheim 1996; c) P. Barbaro, F. Liguori, Heterogenized Homogeneous Catalysts for Fine Chemicals Production: Catalysis by Metal Complexes, Vol. 33, Springer, Dordrecht 2010.
- [2] a) S. Laurent, D. Forge, M. Port, A. Roch, C. Robic, L. V. Elst, R. N. Muller, *Chem. Rev.* 2008, 108, 2064; b) B. Karimi, F. Mansouri, H. M. Mirzaei, *Chem. Cat. Chem.* 2015, 7, 1736; c) A. H. Lu, E. L. Salabas, F. Schüth, *Angew. Chem. Int. Ed.* 2007, 46, 1222. d) *Angew. Chem.* 2007, 119, 1242.
- [3] R. Cano, D. J. Ramón, M. Yus, J. Org. Chem. 2011, 76, 5547.
- [4] a) A. Mori, B. D. Cohen, A. Lowenthal (Eds), Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds, Plenum Press, New York 1985; b) Y. Robin, B. Marescau, in Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds, (Eds: A. Mori, B. D. Cohen, A. Lowenthal), Plenum Press, New York 1985 383; c) A. Mori, B. D. Cohen, H. Coide (Eds), Guanidines 2: Further Exploration of the Biological and Clinical Significance of Guanidino Compounds, Plenum Press, New York 1987.
- [5] a) C. Pi, Z. Zhu, L. Weng, Z. Chen, X. Zhou, *Chem. Commun.* 2007, 2190;
  b) A. Otero, J. Fernandez-Baeza, A. Antinolo, J. Tejeda, A. Lara-Sanchez, L. F. Sanchez-Barba, I. Lopez-Solera, A. M. Rodriguez, *Inorg. Chem.* 2007, 46, 1760;
  c) P. J. Bailey, S. Pace, *Coord. Chem. Rev.* 2003, 240, 157;
  d) M. P. Coles, *Dalton Trans.* 2006, 985.
- [6] a) K. S. Kim, L. Qian, *Tetrahedron Lett.* 1993, *34*, 7677; b) C. Levallet, J. Lerpiniere, S. Y. Ko, *Tetrahedron Lett.* 1997, *53*, 5251; c) K. Feichtinger, C. Zapf, H. L. Sings, M. Goodman, *J. Org. Chem.* 1998, *63*, 3804; d) M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *Tetrahedron Lett.* 1993, *34*, 3389; e) Y. Q. Wu, S. K. Hamilton, D. E. Wilkinson, G. S. Hamilton, *J. Org. Chem.* 2002, *67*, 7553; f) P. Molina, M. Alajarin, J. Saez, *Synth. Commun.* 1983, *13*, 6; g) Y. F. Yong, J. A. Kowalski, M. A. Lipton, *J. Org. Chem.* 1997, *62*, 1540; h) M. A. Poss, E. Iwanowicz, J. A. Reid, J. Lin, Z. Gu, *Tetrahedron Lett.* 1992, *33*, 5933; i) D. H. R. Barton, J. D. Elliott, S. D. Gero, *J. Chem. Soc. Perkin Trans.* 2085, *1*, 1982; j) C. A. Maryanoff, R. C. Stanzione, J. N. Plampin, J. E. Mills, *J. Org. Chem.* 1986, *51*, 1882; k) D. R. Kent, W. L. Cody, A. M. Doherty, *Tetrahedron Lett.* 1996, *37*, 8711; l) Z. X. Guo, A. N. Cammidge, D. C. Horwell, *Synth. Commun.* 2000, *30*, 2933.
- [7] a) T.-G. Ong, G. P. A. Yap, D. S. Richeson, J. Am. Chem. Soc. 2003, 125, 8100; b) H. Shen, Z. Xie, Organometilics 2008, 27, 2685.
- [8] a) S. Zhou, S. Wang, G. Yang, Q. Li, L. Zhang, Z. Yao, Z. Zhou, H.-B. Song, Organometallics 2007, 26, 3755; b) H. Shen, Z. Xie, J. Organometal. Chem. 2009, 694, 1652; c) D. Li, J. Guang, W.-X. Zhang, Y. Wang, Z. Xi, Org. Biomol. Chem. 2010, 8, 1816; d) H. Shen, H.-S. Chan, Z. Xie, Organometallics 2006, 25, 5515; e) L. Xu, Y.-C. Wang, W. Ma, W.-X. Zhang, Z. Xi, J. Org. Chem. 2014, 79, 12004; f) M. R. Crimmin, A. G. M. Barrett, M. S. Hill, P. B. Hitchcock, P. A. Procopiou, Organometallics 2008, 27, 497; g) D. Li, J. Guang, W.-X. Zhang, Y. Wang, Z. Xi, Org. Biomol. Chem. 2012, 10, 6266; h) Q. Li, S. Wang, S. Zhou, G. Yang, X. Zhu, Y. Liu, J. Org. Chem. 2007, 72, 6763; i) Z. Du, W. Li, X. Zhu, F. Xu, Q. Shen, J. Org. Chem. 2008, 73, 8966; j) H. Shen, Y. Wang, Z. Xie, Org. Lett. 2011, 13, 4562; k) W.-X. Zhang, D. Li, Z. Wang, Z. Xi, Organometallics 2009, 28, 882; 1) X. Zhu, Z. Du, F. Xu, Q. Shen, J. Org. Chem. 2009, 74, 6347; m) W.-X. Zhang, M. Nishiura, Z. Hou, Synlett 2006, 1213. n) F. Montilla, A. Pastor, A. Galindo, J. Organometal. Chem. 2004, 689, 993; o) Y. Wu, S. Wang, L. Zhang, G. Yang, X. Zhu, C. Liu, C. Yin, J. Rong, Inorg. Chim. Acta 2009, 362, 2814; p) W.-X. Zhang, M. Nishiura, Z. Hou, Chem. -Eur. J. 2007, 13, 4037; q) C. N. Rowley, T.-G. Ong, J. Priem, T. K. Woo, D. S. Richeson, Inorg. Chem. 2008, 47, 9660; r) P.-H. Wei, L. Xu, L.-C. Song, W.-X. Zhang, Z. Xi, Organometallics 2014, 33, 2784; s) M. L. Kantam, S. Priyadarshini, P. J. A. Joseph, P. Srinivas, A. Vinu K. J. Klabunde, Y. Nishina, Tetrahedron 2012, 68, 5730.
- [9] A. Ebrahimi, A. Heydari, A. Esrafili, Catal. Lett. 2014, 144, 2204.
- [10] a) M. Arefi, D. Saberi, M. Karimi, A. Heydari, ACS Comb. Sci. 2015, 17, 341; b) D. Saberi, A. Heydari, Appl. Organometal. Chem. 2014, 28, 101; c) D. Saberi, M. Sheykhan, K. Niknam, A. Heydari, Catal. Sci. Technol. 2013, 3, 2025; d) K. Azizi, M. Karimi, F. Nikbakht, A. Heydari, Appl. Catal. A 2014, 482, 336; e) K. Azizi, A. Heydari, RSC Adv. 2014, 4, 6508.

[11] L. M'amani, A. Heydari, M. Sheykhan, Appl. Catal. A 2010, 384, 122.

- [12] C. Liu, S. Zhou, S. Wang, L. Zhang, G. Yang, Dalton Trans. 2010, 39, 8994.
- [13] B. Zhao, Y. Xiao, D. Yuan, C. Lu, Y. Yao, Dalton Trans. 2016, 45, 3880.
- [14] J. R. Lachs, A. G. M. Barret, M. R. Crimmin, G. Kociok-kohn, M. S. Hill, M. F. Mahon, P. A. Procopiou, *Eur. J. Inorg. Chem.* 2008, 4173.
- [15] Y. Wei, S. Wang, S. Zhou, Z. Feng, L. Guo, X. Zho, X. Mu, F. Yao, Organometallics 2015, 34, 1882.

#### SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Abbasi S, Saberi D, Heydari, A. Copper oxide supported on magnetic nanoparticles (CuO@ $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>): An efficient and magnetically separable nanocatalyst for addition of amines to carbodiimides towards synthesis of substituted guanidines. *Appl Organometal Chem.* 2017;e3695. doi: 10.1002/aoc.3695