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Graphical Abstract

Supported nano gold catalyzed three -component coupling reactions of amines, dichloromethane and terminal alkynes (AHA) Amina Berrichi, Redouane Bachir, Mohamed Benabdallah,	Leave this area blank for abstract info.
Noureddine Choukchou-Braham $Ph \longrightarrow + CH_2Cl_2 + Et_2NH \longrightarrow \frac{2\% \text{ Au/C}}{\text{base, solv}}$	$\frac{\text{CeO}_2}{\text{vent}} \xrightarrow{\text{Ph}} _{\text{NEt}_2}$
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Supported nano gold catalyzed three-component coupling reactions of amines, dichloromethane and terminal alkynes (AHA)

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ABSTRACT

Article history: Received Received in revised form Accepted Available online A simple and efficient method for the synthesis of pharmaceutically relevant propargylamines through one-pot three-component coupling reactions of amines, CH_2Cl_2 and terminal alkynes (AHA) using nano Au/CeO₂ as a heterogeneous catalyst is reported. The catalyst is characterized by DRX, DR-UV visible spectroscopy and TEM. Gold particles are regularly distributed on ceria and range in size from 2-4 nm. 2014 Elsevier Ltd. All rights reserved

Keywords: Propargylamine coupling reaction AHA Heterogeneous catalysis nano gold

Multicomponent reactions (MCRs) involve the construction and cleavage of carbon–carbon and carbon–heteroatom bonds. These reactions are simple, fast and efficient for chemical synthesis. They have considerable economic and ecological benefits.¹ Pharmaceutically relevant propargylamines² can be produced by MCRs. Propargylamines are key intermediates for the preparation of many biologically active nitrogen compounds such as β -lactams³ and therapeutic drugs.^{4,5}

Three-component coupling reactions of amines, aldehydes, and alkynes (A3) are used to synthesize propargylamines via C–H activation.⁶ Different catalysts have been used for these reactions such as copper-based catalysts, ⁷⁻¹⁷ Ag,¹⁸⁻²³ Zn,²⁴⁻²⁸ NiCl₂,²⁹ Fe nanoparticles,^{30,31} FeCl₃,³² BiCl₃³³ and gold salts. ³⁴⁻³⁷ Syntheses of propargylamines under heterogeneous catalysis are particularly attractive as they allow the production and ready separation of large quantities of products using small amounts of catalysts. Supported nano gold particles, Au/CeO₂,³⁸ Au/Al₂O₃, ³⁹ NAP-Mg-Au,⁴⁰ Au/PMO-IL,⁴¹ Au/IRMOF-3⁴² and Au/ZnO⁴³ have been used as catalysts for A3 coupling reactions of benzaldehyde, alkynes, and piperidine.

Dichloromethane is a major industrial solvent⁴⁴ and is commonly used as a medium for MCRs. It can also be used as a source of carbon and replace aldehydes in three-component coupling reactions. Alkynes, halomethane and amine coupling reactions can be achieved and are commonly known as AHA processes (Scheme 1). Significant progress has been made by using homogeneous catalysts. Copper salts,^{45, 46} nano-In₂O₃,⁴⁷ Fe salts,⁴⁸ AgOAc⁴⁹ and gold salts⁵⁰ are the most important. However, compared to various transition-metal-catalyzed A3 coupling reactions, the catalysts employed for AHA couplings are limited.

The activation of the C-Cl bond has been studied using homogeneous catalysis, but there are no reports on the coupling of CH_2Cl_2 , alkynes and amines employing heterogeneous supported gold catalysts. In this work, a supported nano gold catalyst, Au/CeO₂, is used in AHA coupling reactions.



Scheme 1. The AHA coupling reaction

Preparation of catalyst by deposition precipitation with urea

The catalyst, 2% Au/CeO₂, was prepared by deposition precipitation with urea (DPU) as previously described.^{51,52} Commercial nano CeO₂ (1.97 g) was dispersed in 200 mL of distilled water under stirring until the temperature reached 80 °C, then 8 mL (2% Au) of HAuCl₄.3H₂O (10g/L) and 1.2 g of urea were added, and the mixture was stirred for 16 hours. The resulting solid was dried at 80 °C overnight, then charcterized by DR-UV visible spectroscopy, XRD and TEM.

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The AHA coupling procedure:

A terminal alkyne (2 mmol), an amine (2.2 mmol), CH_2Cl_2 (1.5 mmol), a base (2 mmol), and Au/CeO_2 (80 mg) were mixed with 3 ml of solvent. After 24 hours, the reaction mixture was diluted with CH_2Cl_2 and the catalyst was recovered by centrifugation. The mixture was extracted with water/ CH_2Cl_2 and dried over Na_2SO_4 . Evaporation of the solvent furnished the crude product which was subjected to column chromatography. The products were characterized by NMR and FTIR spectroscopy.

Catalyst Characterization



Figure 1: XRD spectra of (a) CeO₂ and (b) Au/CeO₂

First the CeO₂ support and the Au/CeO₂ catalyst were characterized by XRD. The XRD patterns are shown in Figure 1. In Figure 1a, all the peaks match well with the typical spectrum of ceria.⁵³ The Au/CeO₂ spectrum (Figure 1b) reveals no





Figure 2: DR-UV Visible spectra of CeO₂ (__) and Au/CeO₂ (__)

The catalyst was next characterized by DR-UV Visible spectroscopy. Figure 2 shows a band at 570 nm in the spectrum of Au/CeO₂. This band is characteristic of small gold nanoparticles on the surface of ceria. It is related to the plasmon effects of gold nanoparticles.⁵⁴ Finally, we characterized the catalyst by TEM. A typical image (Figure 3a) shows gold nano particles distributed on ceria. Moreover, the histogram of the particle size distribution (Figure 3b) has a Gaussian shape indicating that the majority of the gold particles have sizes between 2 nm and 4 nm and a mean size of 4.8 nm.



Figure 3: TEM image of 2% Au/CeO₂ and the particle size distributions determined by statistical analysis of different TEM images

Table 1: Optimization of the reaction conditions for the synthesis of propargylamine derivatives catalyzed by 2% Au/CeO2

Ph-== +	CH_2Cl_2 + Et_2NH	2% Au/ base, so	CeO ₂ Ph	NE
Entry	Solvent	Base	Temp (°C)	Yield (%) ^f
1	DMSO	DABCO ^a	65	trace
2	DMSO	DABCO ^b	65	trace
3	no solvent	DABCO	65	24
4	DMSO	DABCO	65	30
5	H ₂ O	DABCO	65	44
6	CH ₃ CN	DABCO	65	53
7	CH ₃ CN	DABCO ^c	65	53
8	CH ₃ CN	DABCO	25	trace
9	CH ₃ CN	DABCO ^d	25	trace
10	CH ₃ CN	DABCO	40	trace
11	CH ₃ CN	DABCO	120	50
12	DMF	DABCO	65	39
13	1,4-dioxane	DABCO	65	trace
14	CH_2Cl_2	DABCO	65	41
15	CH ₃ CN	DBU	65	40
16	CH ₃ CN	K ₂ CO ₃	65	24
17	CH ₃ CN	NH ₄ OAc	65	30
18	CH ₃ CN	no base ^e	65	20

 $\begin{array}{c} \text{Reaction conditions: phenylacetylene (2.0 mmol), Et_2NH (2.2 mmol), CH_2Cl_2(23.5 mmol), base (2.0 mmol), solvent (3 ml), Au/CeO_2(80 mg), \\ 65 \ ^\circ\text{C}, 24 \ h \end{array}$

^a No catalyst. ^b The reaction was catalyzed by CeO₂ before gold deposition. ^c After 48-72 h. ^d After 72 h. ^e After 36 h. ^f Isolated yields after column chromatography.

Synthesis of propargylamines by AHA coupling reactions

Initially, to optimize the reaction conditions, diethylamine, phenylacetylene and dichloromethane were used as model substrates, and the influence of various reaction variables such as the base, solvent and temperature on the reaction was investigated (Table 1).

The results show that polar solvents (H_2O , CH_3CN) gave good yields (entries 5 and 6) compared to DMF, 1,4-dioxane and CH_2Cl_2 (entries 12, 13 and 14). Without a solvent the yield of the propargylamine decreased (entry 3).

Moreover, the reaction proceeded more efficiently in the presence of organic bases such as DABCO (1,4-diazabicyclo[2.2.2]octane) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (Table 1, entries 6, 7, 11, 12, 14 and 15), probably due to their high solubility in organic systems. The inorganic bases K_2CO_3 and NH_4OAc were found to be less reactive (Table 1, entries 16 and 17). It should be noted that the yield decreased in the absence of a base (entry 18).

We also examined the temperature effect at room temperature, 40 $^{\circ}$ C, 65 $^{\circ}$ C and 120 $^{\circ}$ C. It was observed that this reaction was susceptible to temperature changes. The results show clearly that a temperature of 65 $^{\circ}$ C was needed for the reaction to occur. At

room temperature and 40 °C the yield of product was very low (Table 1, entries 8-10), but increased to 53% at 65 °C (Table 1, entries 6 and 7). This may be attributed to the fact that the reaction is slower at low temperatures, however, an increase in temperature generates a high pressure inside the reaction vessel, resulting in a higher reaction rate. $^{55.57}$

The optimum reaction conditions adopted are: phenylacetylene (2.0 mmol), diethylamine (2.2 mmol), CH_2Cl_2 (23.5 mmol), DABCO (2.0 mmol), 2% Au/CeO₂ (80 mg), CH_3CN (3 mL), 65 °C, 24 h.

In order to show that the method can be used to produce different propargylamines, we varied the nature of the amine while keeping phenylacetylene as the terminal alkyne. Thus, various secondary amines (**2a-d**) were used in the AHA three-component coupling reaction with CH_2Cl_2 and phenylacetylene using the optimum reaction conditions (Table 2). Propargylamine yields of up to 60% were obtained. These results are very significant compared with the studies on AHA couplings using homogeneous catalysts.

The reusability of the catalyst was studied in the AHA coupling reaction of phenylacetylene, dichloromethane and diethylamine using the optimized conditions. The catalyst was separated from the reaction mixture by centrifugation, washed with CH_2Cl_2 and water, dried at room temperature and reused. The results in Table 3 show that the yields were similar until the third cycle. The decrease of the catalyst activity is probably due to HCl being released during the reaction, which probably modifies the ceria and therefore the interaction between gold nanoparticles and ceria.

Mechanism

According to studies reported in the literature^{49,50,57} and our results, the catalytic mechanism for the AHA three-component coupling reaction with CH_2Cl_2 , phenylacetylene and amines is proposed in Scheme 2.

The reaction of CH_2Cl_2 and amine **2** gives a chloro-*N*,*N*-R¹R²methammonium chloride salt **4**, which is known as a Mannich reaction intermediate.⁵⁵ This compound produces chloro-*N*,*N*-R¹R²-methanamine **5** by elimination of HCl. Finally, **5** reacts with an adsorbed molecule of phenylacetylene **1** on the catalyst surface to give the corresponding propargylamine.

Ph — — +	CH ₂ Cl ₂	+ $HNR^{1}R^{2}$	2% CH ₃ CN, I	6 Au/CeO₂ DABCO, 65 °C, 24 h	Ph
1a		2a-2d			3a-3d
Entry		Amine		Product	Yield (%)
1	2a	Et ₂ NH	3a	Ph	53
2	2b	$\left({ \atop {}_{H}^{N}} \right)$	3b		55
3	2c	$\left< \sum_{\substack{\mathrm{N} \\ \mathrm{H}}} \right>$	3c		53
4	2d	$\bigcap_{\substack{\mathrm{N}\\\mathrm{H}}}$	3d		59-60 ^a

Table 2: Three-component coupling between phenylacetylene, CH₂Cl₂ and amines catalyzed by 2% Au/CeO₂

Reaction conditions: phenylacetylene (2.0 mmol), amine (2.2 mmol), CH_2Cl_2 (23.5 mmol), DABCO (2.0 mmol), CH_3CN (3 ml), Au/CeO₂ (80 mg), 65 °C, 24 h. ^a Yield after 48 h

Table3: Reusability of the 2% Au/ CeO₂ catalyst

Run	Yield (%)
1	53
2	50
3	30





Scheme 2: A plausible mechanism for the synthesis of propargylamines via the coupling of amines, CH₂Cl₂, and terminal alkynes using 2% Au/CeO₂

In conclusion, a heterogeneous supported nano gold catalyst has been used for the first time to synthesize propargylamines via a one-pot, three-component coupling reaction of phenylacetylene, CH_2Cl_2 (instead of aldehydes) and different secondary amines. Indeed, supported gold nanoparticles can activate the C-H bond of a terminal alkyne and the C-Cl bond of CH_2Cl_2 . The catalyst can be reused up to three times

References

- 1 Singh, M. S.; Chowdhury, S. RSC Adv. 2012, 2, 4547.
- 2 Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790.
- 3 Indrani B.; Atsushi O.; Bimal K. B. Heterocycl. Lett. 2011, Vol. 1 83.
- 4 Bolea, I.; Gella, A.; Unzeta, M. J. Neural Transm. 2013, 120, 893.
- 5 Carvell, H. W.; Lawson, J. Biochem. Pharm 1974, 23, 629.
- 6 Li, P.; Wang, L. Tetrahedron 2007, 63, 5455.
- 7 Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Sreedhar, B. *Tetrahedron Lett.* **2004**, *45*, 7319.
- 8 Gommermann, N.; Knochel, P. Tetrahedron 2005, 61, 11418.
- 9 Sreedhar, B.; Reddy, P. S.; Krishna, C. S. V.; Babu, P. V. *Tetrahedron Lett.* 2007, 48, 7882.
- 10 Kantam, M. L.; Laha, S.; Yadav, J.; Bhargava, S. *Tetrahedron Lett.* **2008**, *49*, 3083.

- 11 Sharghi, H.; Khalifeh, R.; Moeini, F.; Beyzavi, M. H.; Beni, A. S.; Doroodmand, M. M. J. Iran. Chem. Soc. 2011, 8, S89.
- 12 Luz, I.; Llabres i Xamena, F. X.; Corma, A. J. Catal. 2012, 285, 285.
- 13 Jose Albaladejo, M.; Alonso, F.; Moglie, Y.; Yus, M. Eur. J. Org. Chem. 2012, 3093.
- 14 Ramu, V. G.; Bordoloi, A.; Nagaiah, T. C.; Schuhmann, W.; Muhler, M.; Cabrele, C. Appl. Catal., A 2012, 431, 88.
- 15 Naeimi, H.; Moradian, M. Appl. Catal., A 2013, 467, 400.
- 16 Srinivas, M.; Srinivasu, P.; Bhargava, S. K.; Kantam, M. L. Catal. Today 2013, 208, 66.
- 17 Dulle, J.; Thirunavukkarasu, K.; Mittelmeijer-Hazeleger, M. C.; Andreeva, D. V.; Shiju, N. R.; Rothenberg, G. Green Chem. 2013, 15, 1238.
- 18 Li, Z. G.; Wei, C. M.; Chen, L.; Varma, R. S.; Li, C. J. *Tetrahedron Lett.* 2004, 45, 2443.
- 19 Reddy, K. M.; Babu, N. S.; Suryanarayana, I.; Prasad, P. S. S.; Lingaiah, N. *Tetrahedron Lett.* 2006, 47, 7563.
- 20 Yan, W.; Wang, R.; Xu, Z.; Xu, J.; Lin, L.; Shen, Z.; Zhou, Y. J. Mol. Catal. A: Chem. 2006, 255, 81.
- 21 Li, P.; Wang, L.; Zhang, Y.; Wang, M. Tetrahedron Lett. 2008, 49, 6650.
- 22 Maggi, R.; Bello, A.; Oro, C.; Sartori, G.; Soldi, L. *Tetrahedron* **2008**, *64*, 1435.
- 23 Zhou, Y.; He, T.; Wang, Z. ARKIVOC 2008, (xiii), 80.

- 24 Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R. *Tetrahedron Lett.* **2007**, *48*, 7184.
- 25 Kantam, M. L.; Balasubrahmanyam, V.; Kumar, K. B. S.; Venkanna, G. T. *Tetrahedron Lett.* 2007, 48, 7332.
- 26 Mukhopadhyay, C.; Rana, S. Catal. Commun. 2009, 11, 285.
- 27 Satyanarayana, K. V. V.; Ramaiah, P. A.; Murty, Y. L. N.; Chandra, M. R.; Pammi, S. V. N. *Catal. Commun.* **2012**, *25*, 50.
- 28 Eagalapati, N. P.; Rajack, A.; Murthy, Y. L. N. J. Mol. Catal. A: Chem. 2014, 381, 126.
- 29 Samai, S.; Nandi, G. C.; Singh, M. S. Tetrahedron Lett. 2010, 51, 5555.
- 30 Sreedhar, B.; Kumar, A. S.; Reddy, P. S. *Tetrahedron Lett.* 2010, 51, 1891.
- 31 Zeng, T.; Chen, W.-W.; Cirtiu, C. M.; Moores, A.; Song, G.; Li, C.-J. *Green Chem.* 2010, 12, 570.
- 32 Chen, W.-W.; Nguyen, R. V.; Li, C.-J. *Tetrahedron Lett.* 2009, *50*, 2895.
- 33 Teimouri, A.; Chermahini, A. N.; Narimani, M. Bull. Korean Chem. Soc. 2012, 33, 1556.
- 34 Lo, V. K.-Y.; Kung, K. K.-Y.; Wong, M.-K.; Che, C.-M. J. Organomet. Chem. 2009, 694, 583.
- 35 Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. Tetrahedron 2008, 64, 2755.
- 36 Price, G. A.; Brisdon, A. K.; Flower, K. R.; Pritchard, R. G.; Quayle, P. *Tetrahedron Lett.* **2014**, *55*, 151.
- 37 Hashmi, A. S. K.; Hutchings, G. J. Angew. Chem. Int. Ed 2006, 45, 7896.
- 38 Zhang, X.; Corma, A. Angew. Chem. Int. Ed. 2008, 47, 4358.
- 39 Abahmane, L.; Koehler, J. M.; Gross, G. A. Chem. Eur. J. 2011, 17, 3005.
- 40 Layek, K.; Chakravarti, R.; Kantam, M. L.; Maheswaran, H.; Vinu, A. *Green Chem.* **2011**, *13*, 2878.
- 41 Karimi, B.; Gholinejad, M.; Khorasani, M. *Chem. Commun.* **2012**, *48*, 8961.
- 42 Liu, L.; Zhang, X.; Gao, J.; Xu, C. Green Chem. 2012, 14, 1710.
- 43 Gonzalez-Bejar, M.; Peters, K.; Hallett-Tapley, G. L.; Grenier, M.; Scaiano, J. C. *Chem. Commun.* **2013**, *49*, 1732.
- 44 Stromeyer, S. A.; Winkelbauer, W.; Kohler, H.; Cook, A. M.; Leisinger, T. Biochem. Pharm 1991, 2, 129.
- 45 Yu, D.; Zhang, Y. Adv. Synth. Catal. 2011, 353, 163.
- 46 Lin, Z.; Yu, D.; Zhang, Y. Tetrahedron Lett. 2011, 52, 4967.
- 47 Rahman, M.; Bagdi, A. K.; Majee, A.; Hajra, A. *Tetrahedron Lett.* 2011, *52*, 4437.
- 48 Gao, J.; Song, Q.-W.; He, L.-N.; Yang, Z.-Z.; Dou, X.-Y. Chem. Commun. 2012, 48, 2024.
- 49 Chen, X.; Chen, T.; Zhou, Y.; Au, C.-T.; Han, L.-B.; Yin, S.-F. Org. Biomol. Chem. 2014, 12, 247.
- 50 Aguilar, D.; Contel, M.; Urriolabeitia, E. P. Chem. Eur. J. 2010, 16, 9287.
- 51 Ameur N. ; Berrichi A. ; Bedrane S.; Bachir R. Adv. Mater. Res. 2014, 856, 48.
- 52 Ameur, N.; Bedrane, S.; Bachir, R.; Choukchou-Braham, A. J. Mol. Catal. A: Chem. 2013, 374, 1.
- 53 Zhu, L.; Letaief, S.; Liu, Y.; Gervais, F.; Detellier, C. Appl. Clay Sci. 2009, 43, 439.
- 54 Rawat, V. S.; Bathini, T.; Govardan, S.; Sreedhar, B. Org. Biomol. Chem. 2014, 12, 6725.
- 55 Nevstad, G. O.; Songstad, J. Acta Chem. Scand. B Org. Chem. Biochem 1984, 38, 469.
- 56 Hallett-Tapley, G. L.; Crites, C. O. L.; González-Béjar, M.; McGilvray, K. L.; Netto-Ferreira, J. C.; Scaiano, J. C. J. Photochem. Photobiol. A Chem. 2011, 224, 8.
- 57 Anand, N.; Ramudu, P.; Reddy, K. H. P.; Seeth, K.; Rao, R.; Jagadeesh, B.; Babu, V. S. P.; Burri, D. R. *Appl. Catal.*, A 2013, 454, 119.

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