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# The first Au-nanoparticles catalyzed green synthesis of propargylamines *via* a three-component coupling reaction of aldehyde, alkyne and amine†

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Recyclable Au-nanoparticles provide an efficient, economic, novel route for multi component A<sup>3</sup> coupling reaction of aldehyde, amine and alkyne. This method provides the wide range of substrate applicability. This protocol avoids the use of heavy metals, co-catalyst and gives the propargylamine in excellent yields.

## Introduction

Propargylamines are major skeletons<sup>1</sup> or synthetically versatile and key intermediates<sup>2</sup> for the preparation of many nitrogen-containing biological active compounds, such as  $\beta$ -lactams, oxotremorine analogues, conformationally restricted peptides, isosteres and important structural elements of natural products and therapeutics drug molecules.<sup>3</sup> Propargylamines were synthesized by three component one-pot coupling reaction (A<sup>3</sup> coupling) of aldehydes, alkynes and amines.

One-pot multi component coupling reactions (MCRs) are an attractive strategy in organic synthesis<sup>4</sup> and are highly valued among synthetic methodologies, as several elements of diversity can be introduced in a single step into a molecule. There are several transition metal catalysts able to carry out multi component A<sup>3</sup> coupling reactions of aldehyde, alkynes and amines *via* C–H activation. These include Ag(I) salts,<sup>5</sup> Au(I)/Au(III) salts,<sup>6</sup> Au(III) salen complexes,<sup>7</sup> Cu(I) salts,<sup>8</sup> iridium complexes,<sup>9</sup> Hg<sub>2</sub>Cl<sub>2</sub><sup>10</sup> and a Cu/Ru<sup>11</sup> bimetallic system under homogenous conditions.

Recently, an A<sup>3</sup> coupling reaction has been reported through C–H activation in water using Au(I) salts,<sup>6</sup> immobilization of Ag salts in ionic liquid,<sup>12</sup> and Cu-supported hydroxyapatite,<sup>13</sup> although the scope is generally limited for cyclic amines. In addition, more sophisticated alternative energy sources like microwave<sup>8,14</sup> and ultrasonic<sup>15</sup> radiation have been used in the presence of a Cu(I) salt.

However, these reagents, used in stoichiometric amounts, are highly moisture sensitive, and require strictly controlled reaction conditions. Using the above-mentioned protocol, reactions were carried out either in toxic solvent like toluene<sup>5</sup> or in the presence of expensive solvents, such as ionic liquids<sup>16</sup> or required drastic

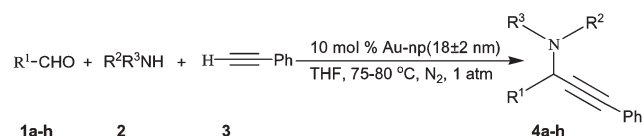
reaction conditions. It is a considerable drawback that an expensive metal catalyst is often lost at the end of the reaction, as there were no reports on the recyclability of catalyst. Metal nanoparticles are employed as a heterogenous catalyst and could be recycled, which overcomes the serious limitation of the non-recyclability of the catalyst.

In continuation of our studies on the development of new synthetic methods<sup>17</sup> and the role of transition metal nanoparticles<sup>18</sup> in organic transformations, we report here in an efficient recyclable A<sup>3</sup> coupling reaction (*via* C–H activation) catalyzed by Au-nanoparticles (An-np).

## Result and discussion

Initially, to examine the catalytic activity of Au-nanoparticles on the traditional Mannich reaction, benzaldehyde (1 mmol), piperidine (1 mmol) and phenylacetylene (1.5 mmol) in methanol (5 ml) were stirred under a nitrogen atmosphere at 35 °C in the presence of 10 mol% of Au-nanoparticles for 12 h (Scheme 1). 91% conversion of phenylacetylene was found on the basis of <sup>1</sup>H-NMR analysis of the crude reaction mixture, and propargylamine was isolated in 78% yield.

Increasing the loading of Au-nanoparticles up to 50 mol% gave desired propargylamine in 96% yield (Table 1, entry 5) with 93%



**Scheme 1** Gold nanoparticles catalysed A<sup>3</sup> coupling reaction of aldehyde, secondary amines, and alkyne.

**Table 1** Optimization of Au-nanoparticles for A<sup>3</sup> coupling<sup>a</sup>

| Entry | Au-np (18 ± 2 nm)/mol% | Time/h | Conversion (%) <sup>b</sup> | Yield (%) <sup>c</sup> |
|-------|------------------------|--------|-----------------------------|------------------------|
| 1     | 0                      | 18     | 54                          | 0                      |
| 2     | 5                      | 12     | 66                          | 83                     |
| 3     | 10                     | 5      | 97                          | 92                     |
| 4     | 30                     | 3.5    | 88                          | 95                     |
| 5     | 50                     | 2      | 93                          | 96                     |

<sup>a</sup> Reaction conditions: 1.0 equiv. of benzaldehyde, 1.0 equiv. of piperidine, 1.5 equiv of phenylacetylene, x mol% Au-np (18 ± 2 nm); solvent MeOH; temperature 75–80 °C; N<sub>2</sub>; 1 atm. <sup>b</sup> Conversions were determined by <sup>1</sup>H NMR of crude reaction mixture. <sup>c</sup> Isolated and unoptimized yields.

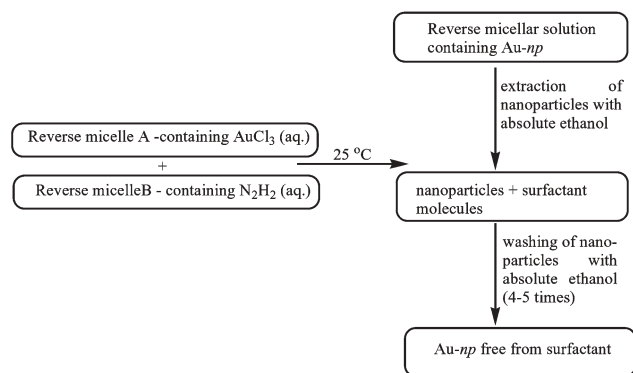
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**Scheme 2** Preparation of Au-nanoparticles.

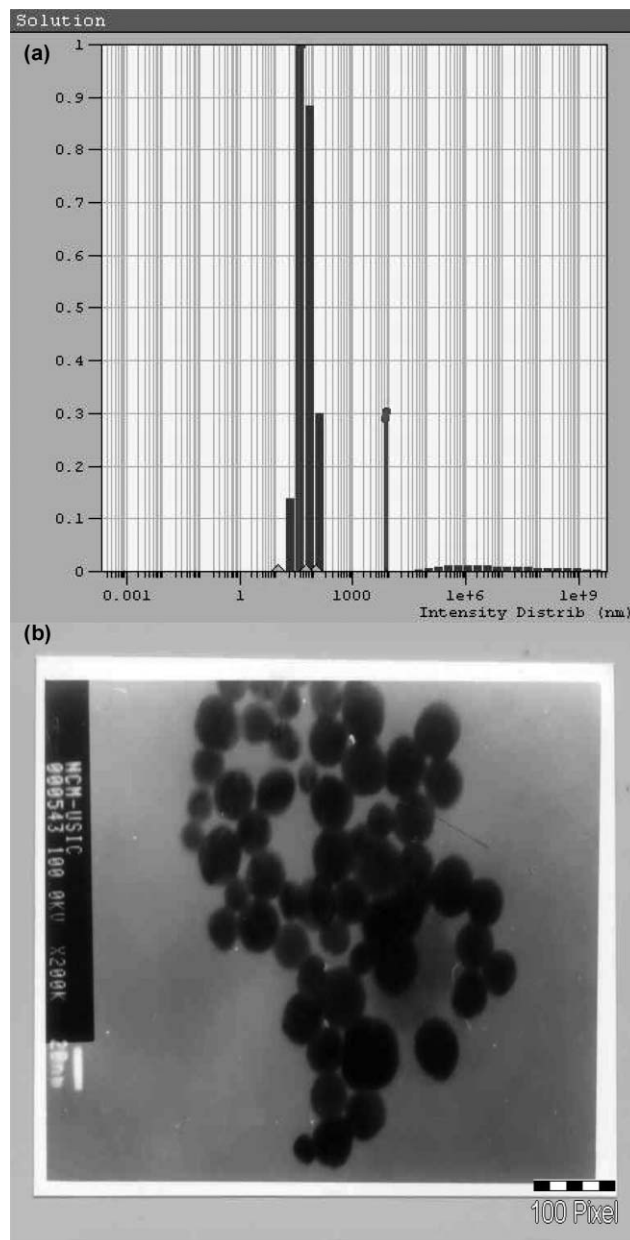
conversion. However, the increase in the concentration of catalyst not only promotes the reaction but also results in an increase of the yield.

In addition, it was found that at higher temperatures Au-np show good catalytic activity; at 75–80 °C, a 92% yield were obtained, however at room temperature lower yields are obtained even after longer reaction times. Comparable results were obtained when the reaction was carried out at 75–80 °C with 10 mol% of Au-np. Thus, to reduce the amount of catalyst, all optimizations are carried out at 75–80 °C with 10 mol% of Au-np. Further, to optimize the reaction conditions, Au-nanoparticles of different sizes, ranging from 15 nm to 70 nm in diameter, were prepared in an aqueous core of reverse micellar droplets (Scheme 2)<sup>19–21</sup> and size was confirmed as 10–17 nm through quasi elastic light scattering data (QELS) (Fig. 1a) and transmission electron microscopy (TEM) (Fig. 1b). The studies shows that mechanism of catalytic action nanoparticles is dependent on the nanoparticles size (Table 2).

The maximum reaction rate has been observed for an average particle of diameter of about 20 nm. With a decrease in a particle size, a trend of decreasing reaction rate has been found for particles with a diameter of less than 20 nm, while those above this diameter shows a steady decline of reaction rate with increasing size. It has been postulated that in the case of particles of average size less than a 20 nm, a downward shift of the Fermi level takes place, with a consequent increase of band gap energy. As a result, the particles require more energy to pump electrons to the adsorbed ions for electron transfer reaction. This leads to a reduction in reaction rate when catalysed by smaller particles. On the other hand, for nanoparticles >20 nm in diameter, the change of Fermi level is not appreciable. As these particles exhibit less surface area for adsorption with increased particle size, a decrease in catalytic efficiency results.

It is important to stress that the catalyst was recycled and reused for five or seven runs with only slight drop in activity. Additional starting material was added into the reaction mixture and the reaction proceeded for an additional 10 h, and it results in the formation of **4a** (Table 5) in 80% yield. The results in Table 3 showed that after every run the yield was excellent while the reaction time was delayed.

We supposed that this result was induced by conglomeration of Au-nanoparticles, which was size dependent. Au-nanoparticles were separated from the reaction mixture by mild centrifugation at 2000–3000 rpm, at 10 °C for 5 min. QELS data (Figure 2) clearly



**Fig. 1** (a) QELS data of Au-nanoparticles: plot of population distribution in percentile versus size distribution in nanometres (nm); (b) TEM image of Au-nanoparticles. The scale bar corresponds to 100 nm in the TEM image.

**Table 2** Size screening of Au-nanoparticles on A<sup>3</sup> coupling of benzaldehyde, phenylacetylene, and piperidine<sup>a</sup>

| Entry | Particle size (±2)/nm | Time/h | Conversion (%) <sup>b</sup> | Yield (%) <sup>c</sup> |
|-------|-----------------------|--------|-----------------------------|------------------------|
| 1     | 10                    | 11     | 94                          | 87                     |
| 2     | 20                    | 5      | 97                          | 92                     |
| 3     | 30                    | 8      | 87                          | 85                     |
| 4     | 50                    | 12     | 91                          | 73                     |
| 5     | 70                    | 15     | 78                          | 67                     |

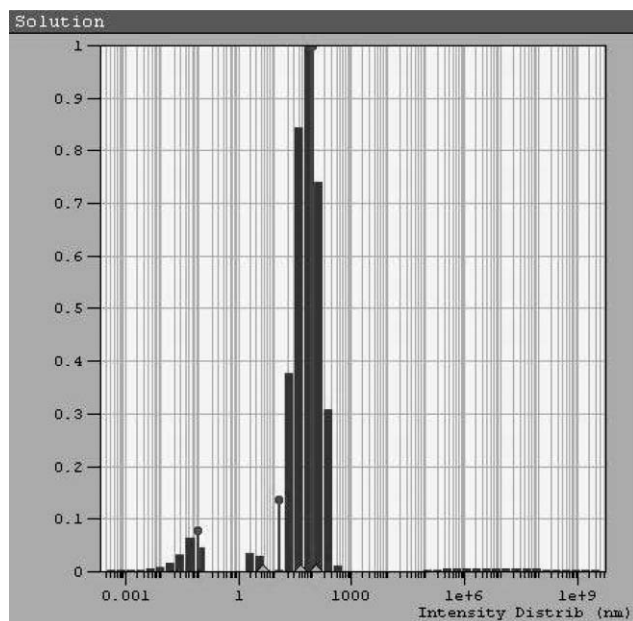
<sup>a</sup> Reaction conditions: 1.0 equiv. of benzaldehyde, 1.0 equiv. of piperidine, 1.5 equiv. of phenylacetylene, 10 mol% Au-np ( $x \pm 2$  nm); solvent MeOH; temperature 75–80 °C; N<sub>2</sub>; 1 atm.

<sup>b</sup> Conversions were determined by <sup>1</sup>H NMR of crude reaction mixture. <sup>c</sup> Isolated and unoptimized yields.

**Table 3** Recycling of Au-nanoparticles

| No. of cycles <sup>a</sup> | Fresh | Run 1 | Run 2 | Run 3 | Run 4 |
|----------------------------|-------|-------|-------|-------|-------|
| Yield (%) <sup>b</sup>     | 92    | 87    | 81    | 72    | 63    |
| Time/h                     | 5     | 7     | 10    | 12    | 18    |

<sup>a</sup> Reaction conditions: 1.0 equiv. of benzaldehyde, 1.0 equiv. of piperidine, 1.5 equiv of phenylacetylene, 10 mol% Au-np (18 ± 2 nm); solvent MeOH; temperature 75–80 °C; N<sub>2</sub>; 1 atm. <sup>b</sup> Isolated and unoptimized yields.

**Fig. 2** QELS data of recycled Au-nanoparticles: plot of population distribution in percentile versus size distribution in nanometres (nm).

showed that there was conglomeration of Au-nanoparticles. In addition, the reaction remained very clean without side product formation, thus Au-nanoparticles are 'green'.

The nature of reaction media has an important role in A<sup>3</sup> coupling reactions in the presence of Au-nanoparticles (10 mol%). Among the various solvent investigated, CH<sub>3</sub>CN was found to be the best solvent of choice (Table 4, entry 1), and no products were obtained when the reaction was carried out in C<sub>6</sub>H<sub>12</sub> or CH<sub>2</sub>Cl<sub>2</sub>. This may be due to the high polarity associated with CH<sub>3</sub>CN, which may result in the stabilization of the alkenyl–Au intermediate.

After all the standardisation, we chose a variety of structurally different aldehydes, and amines possessing a wide range of

**Table 4** Effect of polarity of the solvent on A<sup>3</sup> coupling<sup>a</sup>

| Entry | Solvent         | Time/h | Yield (%) <sup>b</sup>   |
|-------|-----------------|--------|--------------------------|
| 1     | Acetonitrile    | 5      | 96                       |
| 2     | Methanol        | 5      | 92                       |
| 3     | Tetrahydrofuran | 5      | 87                       |
| 4     | Dichloromethane | 5      | 0 (unidentified product) |
| 5     | Cyclohexane     | 5      | 0 (unidentified product) |

<sup>a</sup> Reaction conditions: 1.0 equiv. of benzaldehyde, 1.0 equiv. of piperidine, 1.5 equiv of phenylacetylene, 10 mol% Au-np (18 ± 2 nm); temperature 75–80 °C; N<sub>2</sub>; 1 atm. <sup>b</sup> Isolated and unoptimized yields.

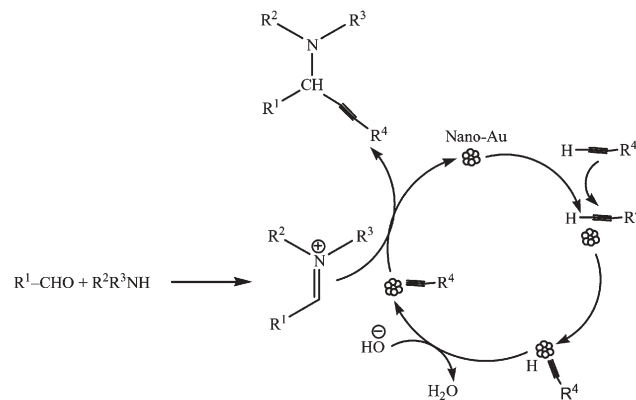
**Table 5** A<sup>3</sup> coupling of aldehyde, alkynes and secondary amines by Au-nanoparticles as catalyst<sup>a</sup>

| Entry | Aldehyde R <sup>1</sup>              | Amines     | Product   | Time/h | Conv. (%) <sup>b</sup> | Yield (%) <sup>c</sup> |
|-------|--------------------------------------|------------|-----------|--------|------------------------|------------------------|
| 1     | C <sub>6</sub> H <sub>5</sub> –      | Piperidine | <b>4a</b> | 5      | 97                     | 94                     |
| 2     | 4-MeC <sub>6</sub> H <sub>4</sub> –  | Piperidine | <b>4b</b> | 11     | 76                     | 81                     |
| 3     | 4-MeOC <sub>6</sub> H <sub>4</sub> – | Piperidine | <b>4c</b> | 8      | 78                     | 87                     |
| 4     | 3-ClC <sub>6</sub> H <sub>4</sub> –  | Piperidine | <b>4d</b> | 4      | 94                     | 96                     |
| 5     | 4-Br C <sub>6</sub> H <sub>4</sub> – | Piperidine | <b>4e</b> | 7      | 92                     | 95                     |
| 6     | 2-Furfuryl                           | Piperidine | <b>4f</b> | 3      | 85                     | 84                     |
| 7     | 2-Thiophenyl                         | Piperidine | <b>4g</b> | 5      | 88                     | 96                     |
| 8     | 3-Pyridinyl                          | Piperidine | <b>4h</b> | 6      | 91                     | 93                     |
| 9     | C <sub>6</sub> H <sub>5</sub> –      | Morpholine | <b>5a</b> | 7      | 79                     | 82                     |
| 10    | 4-MeC <sub>6</sub> H <sub>4</sub> –  | Morpholine | <b>5b</b> | 8.5    | 73                     | 88                     |
| 11    | C <sub>6</sub> H <sub>5</sub> –      | Pyrolidine | <b>6a</b> | 6      | 82                     | 67                     |
| 12    | 4-MeC <sub>6</sub> H <sub>4</sub> –  | Pyrolidine | <b>6b</b> | 13     | 88                     | 71                     |

<sup>a</sup> Reaction conditions: 1.0 equiv. of aldehyde, 1.0 equiv. of secondary amine, 1.5 equiv of phenylacetylene, 10 mol% Au-np (18 ± 2 nm); solvent: CH<sub>3</sub>CN; temperature 75–80 °C; N<sub>2</sub>; 1 atm.; <sup>b</sup> Conversions were determined by <sup>1</sup>H NMR of crude reaction mixture. <sup>c</sup> Isolated and unoptimized yields.

functional group to understand the scope and generality of the Au-nanoparticles promoted A<sup>3</sup> coupling reaction. A variety of aromatic aldehydes were coupled with a piperidine and phenylacetylene and it was found that aryl aldehydes possessing electron withdrawing groups (Table 5, entries 4, 5) afforded a better yield, with good reactivity, than that with an electron donating group (Table 5, entry 2, 3) bound to the benzene ring, which required longer reaction times. Heterocyclic aldehydes (Table 5, entry 6,7,8) also displayed high reactivities with good yields. To expand the scope of amine substrate, we used phenylacetylene as a model substrate and examined various amines with different aldehydes. The coupling proceeded smoothly with morpholine and pyrolidine to afford the corresponding propargylamine in good yields under standard conditions, and it was found that piperidine gave better results in term of yields and reaction time than morpholine.

In general, the formation of propargylamine via A<sup>3</sup> coupling proceeded smoothly to afford the corresponding propargylamine via A<sup>3</sup> coupling proceeding through C<sub>sp</sub>–H bond activation of terminal alkynes. A tentative mechanism (Figure 3) was proposed involving the activation of the C–H bond of alkyne by Au-nanoparticles. The alkenyl–Au intermediate thus formed reacted with the iminium ion generated *in situ* from aldehyde and secondary amines to give the corresponding propargylamine and

**Fig. 3** Tentative mechanism of Au-nanoparticles catalysed A<sup>3</sup> coupling.

regenerated the Au-nanoparticles for further reaction. In the literature it was reported that metal nanoparticles act as a redox catalyst by a free radical mechanism<sup>22</sup> and thus the reaction may proceed by a free radical mechanism.

## Conclusions

Overall this methodology offers the competitive advantages of recyclability of the catalyst without significant loss of catalytic activity; ready availability; it can be used or reused without further purification, and without using additives or cofactor; it requires lower catalyst loading, has broad substrate applicability, gives high yields in short reaction times, and is simple and easy to carry out.

In conclusion, we have successfully developed a novel, facile, economic, practical and green method for the synthesis of propargylamines. The catalyst can be readily recovered and reused, thus making this procedure more environmentally acceptable and no catalyst has widespread use in organic synthesis for preparation of propargylamines.

## Experimental

In a 50 ml round bottom flask, aromatic aldehydes/heterocyclic aldehydes **1a–h** (1 mmol), secondary amine (1 mmol) and phenylacetylene (1.5 mmol) in CH<sub>3</sub>CN (5 ml) were mixed and stirred under a nitrogen atmosphere. To this, Au-nanoparticles (10 mol%, 18 ± 2 nm) were added. The resulting solution was refluxed at 75–80 °C for the appropriate time mentioned in Table 5. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was centrifuged at 2000–3000 rpm, at 10 °C for 5 min. The organic layer was decanted out and remaining Au-nanoparticles were reused for further reactions. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo*. The crude product was subjected to purification by silica gel column chromatography using 15% ethyl acetate, 5% methanol and 80% petroleum ether as an eluent to yield the propargylamine **4a–h**. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, <sup>1</sup>H NMR and GC/MS mass spectral data). All the products are known compounds (see ESI).†

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