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# Introduction

Aryl-aryl bond formation reactions are one of the most important reactions in organic synthesis as they give rise to many naturally occurring biologically and pharmaceutically active products.<sup>1</sup> Though this area has been mainly dominated by transition metal based catalysts like iron,<sup>2</sup> copper,<sup>3</sup> nickel,<sup>4</sup> rhodium<sup>5</sup> and palladium,<sup>6</sup> gold nanoparticles have surprisingly shown excellent catalytic activity as well as selectivity for carbon-carbon bond formation reactions like homocoupling of phenylboronic acid,<sup>7</sup> Suzuki Miyaura coupling,8 as well as Sonogashira reactions.9 Other than these reactions, the Ullmann coupling of aryl halides to yield symmetrical biaryls is a very important carbon-carbon bond forming reaction for organic synthesis.<sup>10</sup> Traditionally this reaction is catalyzed with an excess of copper at elevated temperatures of about 200 °C.11 Although several new methodologies for the synthesis of biaryls have been developed, the century old Ullmann reaction still remains important because of its efficiency and simplicity.12

Literature reports involving homocoupling of aryl iodides catalyzed by nano-gold are very scarce and to date, only a couple of reports exist. For example, gold nanoparticles supported on periodic mesoporous silica has been demonstrated to be catalytically active for the Ullmann homocoupling of aryl iodides.<sup>13</sup> Another example is that of Ullmann homocoupling catalyzed by gold nanoparticles in water and ionic liquid, which has been reported very recently.<sup>14</sup> In our previous works we have successfully synthesized, characterized and employed gold nanoparticles stabilized on nanocrystalline magnesium oxide, NAP-Mg-Au(0), for the one pot synthesis of propargylamines<sup>15</sup> as well as for the reduction of nitroarenes.<sup>16</sup> In an endeavor to further explore the catalytic efficiency of this catalyst for carbon–carbon bond forming reactions, we herein

# Ullmann coupling of aryl iodides catalyzed by gold nanoparticles stabilized on nanocrystalline magnesium oxide

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Gold nanoparticles stabilized on nanocrystalline magnesium oxide is shown to be an efficient heterogeneous catalytic system for the synthesis of symmetrical biaryls *via* homocoupling of aryl iodides.



Scheme 1 Ullmann coupling of aryl iodides catalyzed by the NAP-Mg-Au(0) catalyst.

show NAP-Mg-Au(0) as an active heterogeneous catalyst for the Ullmann coupling of aryl iodides (see Scheme 1). This work forms the focus of this paper.

# **Results and discussion**

Nanocrystalline magnesium oxide commercially available as NAP-MgO (NanoActive<sup>TM</sup> Magnesium Oxide Plus) was selected as a support for heterogenizing gold nanoparticles. NAP-MgO is a superior support compared to other supports because of certain unique physical and chemical features associated with it.<sup>17</sup> For example, the Lewis acidic (Mg<sup>2+</sup>) and Lewis basic (O<sup>2-</sup>) sites along with other cationic and anionic vacancies enable it to possess a high concentration of reactive surface ions that may play a role in stabilizing the reaction intermediates during the course of the reaction. Also the high surface area of NAP-MgO enhances the catalytic activity of the support.

First, reaction was carried out between HAuCl<sub>4</sub> and NAP-MgO to obtain NAP-Mg-Au(III) species, which was subsequently reduced by excess of sodium borohydride to yield gold nanoparticles that are deposited on the surface of NAP-MgO as in the NAP-Mg-Au(0) catalyst. The transmission electron microscopy (TEM) image of the NAP-Mg-Au(0) catalyst shows a homogeneous distribution of gold nanoparticles on the MgO support with an average particle diameter of 5–7 nm (see Fig. 1).

To determine the optimum loading of gold in the NAP-Mg-Au(0) catalyst required for the homocoupling reaction as well as to determine the most appropriate solvent and base, a

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Fig. 1 TEM image of the NAP-Mg-Au(0) catalyst

 
 Table 1
 Optimization of reaction conditions for the Ullmann homocoupling of aryl iodides catalyzed by the NAP-Mg-Au(0) catalyst<sup>a</sup>

Entry	Mol% of Au in NAP-Mg-Au(0) catalyst	Solvent	Base	$\operatorname{Yield}^{b}(\%)$
1	0.75	DMF	K <sub>3</sub> PO <sub>4</sub>	70
2	0.75	Toluene	K <sub>3</sub> PO <sub>4</sub>	55
3	0.75	$H_2O$	K <sub>3</sub> PO <sub>4</sub>	Traces
4	0.75	DMSO	$K_2CO_3$	50
5	0.75	DMF	$K_2CO_3$	73
5	0.75	DMF	$Na_2CO_3$	65
7	1	DMF	$K_2CO_3$	78
8	1	DMF	K <sub>3</sub> PO <sub>4</sub>	73
9	1	DMF	Nil	No reaction
10 <sup>c</sup>	_	DMF	$K_2CO_3$	No reaction
$11^d$	1	DMF	K <sub>2</sub> CO <sub>3</sub>	68
$12^e$	1	DMF	K <sub>2</sub> CO <sub>2</sub>	63

<sup>*a*</sup> Reaction conditions: 4-iodoanisole (1 mmol), base (2 mmol), solvent (3 mL) and catalyst (with the given mol% of Au) was stirred at reflux temperature (140 °C for DMF) for 48 hours. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> 100 mg of NAP-MgO was used as the catalyst. <sup>*d*</sup> *meso*-CeO<sub>2</sub>-Au(0) was used as the catalyst.

series of reactions were carried out by employing 4-iodoanisole as the model substrate (see Table 1). All the reactions were carried out at the reflux temperature of the solvent (140 °C for DMF) and were monitored for 48 hours duration. Among the various solvents and bases that were subjected to screening, DMF was the solvent of choice, whereas K<sub>2</sub>CO<sub>3</sub> proved to be the most efficient base. The NAP-Mg-Au(0) catalyst with 1 mol% of Au was found to be the optimum loading required for the homocoupling of 4-iodoanisole. No reaction occurred in the absence of either base or gold nanoparticles. This proves that the presence of both gold nanoparticles and base is essential for the reaction. It is to be noted here that though NAP-MgO is highly basic in nature, yet the basicity of the NAP-Mg-Au(0) catalyst is much less compared to that of 2 mmol of K<sub>2</sub>CO<sub>3</sub>, hence the requirement of base is essential for the reaction. Other supported gold catalysts like meso-CeO<sub>2</sub>-Au(0) and meso-HAP-Au(0) were also catalytically active for this reaction though the yields were lower when compared to the NAP-Mg-Au(0) catalyst under similar experimental conditions. This further

 Table 2
 Ullmann coupling of various aryl iodides catalyzed by NAP-Mg-Au(0)<sup>a</sup>



 $^a$  Reaction conditions: aryl iodide (1 mmol), NAP-Mg-Au(0) (1 mol% Au), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), DMF (3 mL) stirred at 140  $^\circ C$  for 48 hours.  $^b$  Isolated yields.  $^c$  Reaction time 72 hours.

demonstrates that the unique features that are associated with the NAP-MgO support enhance the catalytic activity of the gold nanoparticles heterogenized onto it.

Having optimized reaction conditions in hand, we now evaluated the catalytic activity of our NAP-Mg-Au(0) catalytic system for the homocoupling of various aryl iodides. As can be seen from Table 2, iodobenzene afforded an excellent yield of the biaryl product (Table 2, entry 1). 4-Iodoanisole and 4-iodotoluene also afforded decent yields of the product under our optimized experimental conditions (Table 2, entries 2 and 3). 1-Chloro, 4-iodobenzene exclusively yielded 4,4'-dichlorobiphenyl (Table 2, entry 4). 3-Iodotoluene gave good yields for the corresponding biaryl product under these conditions (Table 2, entry 5). Interestingly, ortho-substituted substrates viz. 2-iodotoluene and 2-iodoanisole afforded relatively poor yields of the corresponding coupled product (Table 2, entries 6 and 7). This demonstrates that our NAP-Mg-Au(0) catalytic system is sensitive to steric effects. When bromobenzene was employed as the substrate under our optimized experimental conditions no product formation was observed. Even on prolonging the duration of reaction only traces of biphenyl were observed (Table 2, entry 8) with the bromobenzene substrate. This clearly demonstrates that the present catalytic system is unsuitable for the homocoupling of aryl bromides.

The recyclability of the NAP-Mg-Au(0) catalyst was also examined by the Ullmann coupling of 4-iodoanisole used as a

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Table 3 Recyclability studies on the Ullmann homocoupling of 4-iodoanisole using NAP-Mg-Au(0) catalyst  $^{\rm d}$ 

Reaction cycle	1st	2nd	3rd	4th
$\operatorname{Yield}^{b}(\%)$	78	73	70	66

 $^a$  4-Iodoanisole (1 mmol), NAP-Mg-Au(0) (fresh catalyst containing 1 mol% Au), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), DMF (3 mL) stirred at 140  $^\circ$ C for 48 hours.  $^b$  Isolated yield after column chromatography.

model substrate and it was observed that the yield of the product gradually dropped with each reaction cycle (see Table 3). To verify whether any leaching occurs, the gold content in the used NAP-Mg-Au(0) catalyst (after three reaction cycles) was analyzed by ICP-OES and it revealed the loss of about 9.5% of the initial amount of gold that was originally present in the fresh catalyst. This may be the underlying cause for the gradual drop in the yield of the product with each cycle. That the leached gold was not active for the coupling reaction was also verified by performing a heterogeneity test. For this study, two batches of reactions were carried out simultaneously. For the first batch, the solid catalyst was separated from the reaction mixture after 20 hours. The yield of the product obtained was about 40%. At this point, the catalyst was also separated from the second batch and the filtrate was allowed to stir for another 28 hours. There was no improvement in the yield of the product in the latter case as deduced both by TLC and column chromatographic studies. As seen in Table 2, with 4-iodoanisole, we have obtained 78% yield for the biaryl product when the reaction was allowed to continue for 48 h. This result demonstrates that the leached gold is not active for the reaction, and the reaction truly followed a heterogeneous pathway.

#### Probable reaction mechanism

A probable reaction mechanism is proposed for the Ullmann coupling of aryl iodides catalyzed by gold nanoparticles stabilized on nanocrystalline magnesium oxide<sup>14</sup> (Scheme 2). First, aryl iodide molecules get adsorbed onto the surface of gold nanoparticles. Release of the biaryl product and iodide ions takes place with the oxidation of the catalytic gold species. It is to be noted that DMF, which acts as a solvent in this case, is well known to be a good reducing agent for both silver and gold salts.<sup>18</sup> Therefore, it is



Scheme 2 Proposed reaction mechanism for the Ullmann coupling of aryl iodides catalyzed by the NAP-Mg-Au(0) catalyst.

proposed that DMF, containing water as impurity, reduces the cationic gold back to metallic gold, thereby regenerating the active catalytic surface. DMF gets oxidized to carbamic acid which then further decomposes to dimethylamine and CO<sub>2</sub> at high reaction temperature.<sup>18</sup> Notably, the introduction of DMF based half reaction ensures smooth release of iodide ions as hydroiodic acid (HI) in the mechanistic cycle.

### Conclusion

We have shown that the gold nanoparticles stabilized on a nanocrystalline magnesium oxide support is an efficient heterogeneous catalytic system for the Ullmann homocoupling of aryl iodides. The catalytic system requires low reaction temperatures as compared to traditional copper based catalysts, and the catalyst can be separated by simple centrifugation and reused for further reaction cycles.

### **Experimental section**

#### General

NAP-MgO (commercial name: NanoActive™ Magnesium Oxide Plus) was purchased from NanoScale Corporation (Manhattan, USA). All chemicals were purchased from commercial sources, and were used as received. All solvents used for experiments were dried using standard procedures (except water), and distilled prior to use. The particle size and external morphology of NAP-Mg-Au(0) were observed by a Transmission Electron Microscope (JEOL JEM-2100 in ISSP, Univ. Tokyo) operating at 200 kV. Energy dispersive X-ray (EDX) spectroscopy was performed on a Hitachi SEM S-520, EDX-Oxford Link ISIS-300 instrument. An inductively coupled plasma optical emission spectrometer (ICP-OES, Intrepid II XDL, Thermo Jarrel Ash) was used for determining the gold content in the used catalyst. <sup>1</sup>H and <sup>13</sup>C Nuclear Magnetic Resonance (NMR) spectra were recorded on an Avance 300 (300 MHz for <sup>1</sup>H-NMR and <sup>13</sup>C-NMR) spectrometer in CDCl<sub>3</sub> solvent using TMS as an internal standard. ACME SILICA GEL was used for column chromatography purposes using ethyl acetate/hexane as eluting agents, and thin layer chromatography was performed on Merck precoated silica-gel 60-F254 plates.

#### Synthesis of the NAP-Mg-Au(0) catalyst

The NAP-Mg-Au(0) catalyst was synthesized according to a procedure reported earlier.<sup>16</sup> Commercial NAP-MgO was calcined at 450 °C for four hours in air. This NAP-MgO support (3.5 g) was treated with chloroauric acid solution (1 g, 2.54 mmol; dissolved in 100 mL of double distilled water), and stirred at 25 °C for 12 h under a nitrogen atmosphere to give NAP-Mg-Au( $\square$ ) species. To this reaction mixture, excess of sodium borohydride (3.5 g, 92.5 mmol) was slowly added and the contents were allowed to stir under a nitrogen atmosphere for another 12 h. The solid catalyst was then filtered through a G-3 sintered glass funnel, washed thoroughly with double distilled water and then with acetone. It was then oven dried at 70 °C to obtain NAP-Mg-Au(0) as a dark purple coloured

powder (1.34% Au by EDX). Similar synthetic procedures were adopted for *meso*-HAP-Au(0) and *meso*-CeO<sub>2</sub>-Au(0) catalysts.<sup>19</sup>

# Representative procedure for the Ullmann homocoupling of 4-iodoanisole using NAP-Mg-Au(0) catalyst

1 mmol of 4-iodoanisole, 2 mmol of K<sub>2</sub>CO<sub>3</sub>, 150 mg of the NAP-Mg-Au(0) catalyst (1 mol% of Au) and 3 mL of the DMF solvent were taken in a sealed pressure tube and heated at 140 °C for 48 hours. The contents were then allowed to cool to room temperature and the reaction mixture was centrifuged to separate the catalyst. The solid residue was first washed with distilled water and then with acetone to remove any traces of organic material. It was then dried in air at room temperature and used as it is for further reactions. The filtrate containing the reaction mixture was diluted with ethyl acetate (10 mL) and extracted multiple times with water to remove DMF. It was then washed with brine solution (10 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Then the solvent was evaporated under reduced pressure to yield the crude product, which was then purified by column chromatography using silica gel and hexane/ ethyl acetate as an eluent to afford the pure 4,4'-dimethoxybiphenyl product. Spectral data: <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 3.24 (s, 6H), 6.93–6.96 (d, J = 8.876 Hz, 4H), 7.45–7.48 (d, J = 8.876 Hz, 4H); <sup>13</sup>C-NMR (300 MHz, CDCl<sub>3</sub>, TMS): 55.682, 114.505, 128.062, 133.794, 159.015.

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