Heterogeneous Cross-Coupling over Gold Nanoclusters

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Abstract: Au clusters with the precise numbers of gold atoms, a novel nanogold material, have recently attracted increasing interest in the nanoscience because of very unique and unexpected properties. The unique interaction and electron transfer between gold clusters and reactants make the clusters promising catalysts during organic transformations. The Au nL m nanoclusters (where L represents organic ligands and n and m mean the number of gold atoms and ligands, respectively) have been well investigated and developed for selective oxidation, hydrogenation, photo-catalysis, and so on. These gold clusters possess unique frameworks, providing insights into the catalytic processes and an excellent arena to correlate the atomic frameworks with their intrinsic catalytic properties and to further investigate the tentative reaction mechanisms. This review comprehensively summarizes the very latest advances in the catalytic applications of the Au nanoclusters for the C–C cross-coupling reactions, e.g., Ullmann, Sonogashira, Suzuki cross-couplings, and A 3−coupling reactions. It is found that the proposed catalytically active sites are associated with the exposure of gold atoms on the surface of the metal core when partial capping organic ligands are selectively detached under the reaction conditions. Finally, the tentative catalytic mechanisms over the ligand-capped Au nanoclusters and the relationship of structure and catalytic performances at the atomic level using computational methods are explored in detail.

Keywords: gold nanocluster; cross-coupling; Ullmann hetero-coupling; Sonogashira coupling; Suzuki coupling; A 3−coupling; catalytic mechanism; ligand removal

1. Introduction

Since the work of Haruta’s group in the late 1980s [1], supported gold nanoparticles with a particle size in the range of 3–20 nm have played a central role in a variety of reactions such as selective oxidation [2–5], hydrogenation [6–8], and photocatalysis [9,10]. These conventional gold catalysts have been realized via deposition–precipitation and co-precipitation impregnation with oxides by controlling the pH of the synthetic system. These obtained gold nanoparticles are usually polydisperse, which is a major issue in fundamental catalysis and investigations [11]. For example, the size-hierarchy of Au nanoparticles are often averaged out in polydispersion. It is difficult to correlate the relationship between the catalytic properties and the structure of the nanoparticles. Therefore, developing nanostructured catalysts with specific morphology (e.g., nanosheet, nanocube, and nanorod) is highly desirable to overcome this issue, further promoting the development of crystal-identified model catalysts [12,13].

On the other hand, the remarkable developments in the synthesis of atomically precise gold nanoclusters have been achieved in recent decades, which opens a new burgeoning area.
in nanoscience [14,15]. These gold nanoclusters are comprised of a few dozen to a few hundred gold atoms and protecting organic ligands (e.g., thiolate, phosphine, and alkyne), and the size is ultra-small, usually ca. 0.6–2 nm. Some gold nanoclusters are identifiable by X-ray crystallography technology. It offers a big opportunity for in-depth understanding of the relationship of the catalytic properties and the active-site structure at the atomic level [16].

It is observed that these gold nanoclusters exhibit good catalytic performance in heterogeneous catalysis (e.g., selective oxidation and hydrogenation) [16–18]. Sometime, the gold clusters show better catalytic behavior (e.g., activity and product selectivity) than the corresponding Au nanoparticles, because of their high surface-to-volume ratio (reaches up to ~100%), surface geometric effect (e.g., low-coordinated Au$^{6+}$ atoms, $0 < \delta < 1$), and the unique electronic properties and the quantum size effect. Furthermore, the protecting organic ligands can improve the product selectivity due to their electronic factors and steric hindrance and weak interaction (e.g., $\pi$-$\pi$ interaction) between the reactants and cluster surface ligands during the catalysis process. In the recent decade, these gold nanoclusters exhibited good catalytic activity in the cross C–C couplings, e.g., Ullmann hetero-coupling, Suzuki and Sonogashira coupling, and A$^3$-coupling [19,20]. Traditionally, these catalyzed C–C coupling reactions are over the Cu, Pd, and Pt complexes and particles in the previous literatures [21–23].

In this review, we aim to provide an overview focused on the Au nanocluster-catalyzed coupling reactions, e.g., Ullmann hetero-coupling of Ar–I, Suzuki cross-coupling of PhB(OH)$_2$ and Ph–I (IB), Sonogashira cross-coupling of IB and Ph–C≡C–H (PA), and A$^3$-coupling (Scheme 1). The pathway of the selective detachment of the surface protecting ligands (under the reaction conditions), giving the catalytically active sites, is well discussed. Moreover, the proposed reaction pathway and mechanisms of these carbon–carbon coupling reactions were thoroughly summarized based on the precise framework of gold nanoclusters (e.g., two Au$_2$S) as the mode theoretical calculations.

2. Activation of Ph–B(OH)$_2$, Ph–I, and C≡C–H Bonds over Au: Theoretical Simulation

The activation of the Ph–B(OH)$_2$, Ph–I, and C≡C–H bonds over the gold clusters plays an important role and step in the cross-coupling reactions, e.g., Ullmann hetero-coupling, Sonogashira coupling, Suzuki coupling, and A$^3$–coupling. The adsorption and activation process of the reactants over the different well-defined gold facets and sites are distinct [24–27]. The density functional theory (DFT) calculations should be a feasible and fast method to explore the activation of Ph–B(OH)$_2$, C–I, and C≡C–H bond by gold nanoclusters.

Firstly, the shape controlled Au nanoparticles (e.g., Au nanorod) with well-defined surfaces and morphologies are well investigated [28,29], providing a platform to establish site–activity relationships and to pursue the understanding of heterogeneous processes. Therefore, the gold nanorod is chosen for the theoretical simulation of the activation of Ph–I and C≡C–H bonds. DFT studies showed that
the Ph–I reactant adsors onto the Au(100) and Au(111) with Au–I distance 2.95 and 2.86 Å. The C–I bond is more elongated on the Au(111) compared to Au(100) (2.17 Å vs. 2.13 Å) [26]; the C–I length of the free IB is 2.09 Å. Furthermore, the phenyl group is located on an Au atom. The iodine atom is strongly chemisorbed on the bridging and hollow sites. Regarding the activation of alkyne, the Ph–C≡C–fragment is also adsorbed on bridging and 3-fold hollow sites of Au(100) and Au(111). The coordination number of one Ph–C–unit is 3 and 4 for Au(100) and Au(111) facets during the cross-coupling reaction, respectively, Figure 1, and the activation energy of cross-coupling is comparable [26].

![Figure 1. Proposed pathway for the cross-coupling on the (A) Au(100) and (B) Au(111). Reproduced with permission from [26]. Elsevier, 2015.](image1)

Next, the activation of Ph–B(OH)$_2$, Ph–I, and C≡C–H also was explored on a model cluster (Au$_{38}$ and partially oxidized Au$_{38}$O$_2$) [30–32]. It is worthy to note that the model clusters of the Au$_{38}$ and Au$_{38}$O$_2$ are somewhat different from the real catalyst in terms of the real structure. The Au$_{38}$O$_2$ cluster contains metallic Au$^0$ and cationic Au$^{5+}$ species, and each O atom bonds to three Au atoms. In the activation process of phenylboronate, DFT showed that the phenylboronate reactant is preferentially adsorbed on the Au$^0$ species rather than on the Au$^{5+}$ sites [30], leading to formation of the final product- biphenyl (Figure 2B). Meanwhile, DFT simulation also found that the interaction between the Au$^{5+}$ sites and Ph–I is weaker and the adsorption of C≡C–H on Au$^{5+}$ sites is relatively strong. Further, the proton of alkyne was detached with aid of O atom in the deprotonation step (Figure 2A). Therefore, a very low activation energy is required when the cross-coupling reactions occurred over the Au$_{38}$O$_2$ cluster. Of note, the cross-coupling step of the activated PA and –Ph on the Au$_{38}$O$_2$ should be the rate-determining step [32].

![Figure 2. Calculated energy of the dissociation of PhB(OH)$_3$– anion (A) and deprotonation of PA (B) on the Au$_{38}$O$_2$ cluster. Reproduced with permission from [30]. American Chemical Society, 2012.](image2)
3. Physical Property of Au Nanoclusters

3.1. Framework

The gold clusters with crystal structure can be employed as the practical simulation models for mechanism study. In this Review, we only focus on the two cluster structures of the nanorod-shaped \([\text{Au}_{25}(\text{PPh}_3)_{10}\text{L}_5\text{Cl}_2]^{2+} (\text{L} = \text{-SR and PA})\) and the nanosphere \([\text{Au}_{25}(\text{SR})_{18}]^x (x = -1, 0, +1, \text{etc}.)\), used as the real model for DFT studies (vide infra). The \(\text{Au}_{25}(\text{SR})_{18}\) cluster comprises an \(\text{Au}_{13}\) core \([33]\) and six staples of \(\text{Au}_{2}(\text{SR})_{3}\) \([34]\). \([\text{Au}_{25}(\text{PPh}_3)_{10}\text{L}_5\text{Cl}_2]^{2+}\) is composed of two \(\text{Au}_{13}\) cores by sharing one common vertex to form the waist sites \([35]\), connected by thiolate or alkyne ligands \([36]\) (Figure 3).

![Figure 3](image_url)

**Figure 3.** Framework of \(\text{Au}_{25}(\text{SR})_{18}\) (A) and \(\text{Au}_{25}(\text{PPh}_3)_{10}\text{L}_5\text{Cl}_2\) (B). The orange areas in are are the \(\text{Au}_3\) and the waist active sites during the catalysis. Reproduced with permission from \([36]\). American Chemical Society, 2008 and Springer, 2019.

3.2. Redox Property of Au cluster

\(\text{Au}_{38}\text{S}_2(\text{SAdm})_{20}\) (\(\text{SAdm} = \text{adamantanethiolate}\)) nanoclusters exerted photosensitizing properties to give singlet oxygen (\(\cdot\text{O}_2\)) under visible light irradiation (e.g., 532 and 650 nm) \([37]\). The \(\text{Au}_{38}\text{S}_2(\text{SAdm})_{20}\) is intact during the whole photocatalysis process, evidenced by UV-vis tracing and mass spectroscopy analysis. The cyclic voltammetry analysis showed that the \(\text{Au}_{38}\text{S}_2(\text{SAdm})_{20}\) cluster had good charge transfer capacity to the redox \(\text{K}_3\text{Fe(CN)}_6\) probe, Figure 4 \([38]\). However, the redox property of the cluster disappeared when beta-cyclodextrins (\(\beta\text{-CDs}\)) was introduced in the THF solution. After detailed analysis, the huge \(\beta\text{-CDs} \) “umbrella” can trap the adamantane groups and then completely cover windows of the \(\text{Au}_{38}\text{S}_2(\text{SAdm})_{20}\) nanoclusters, thereby blocking direct interaction with foreign molecules and then quenching the charge transfer process (Figure 4B). It indicated that these gold nanoclusters have good redox properties and electron transfer (ET) capacity during the catalytic reactions \([39]\).

Further, Kumar and coworkers studied the \(\text{Au}_{25}(\text{SG})_{18}\) catalyst in an electrochemical oxidation \([40]\). The \(\text{Au}_{25}(\text{SG})_{18}\) on the electrode gave good electro-activity during the oxidation of ascorbic acid and dopamine over a wide linear range from 0.71 to 44.4 \(\mu\text{M}\). And pH dependent electrocatalytic activity was observed, attributed to the consequence of pH-dependent electrostatic attraction/repulsion between the charged \(\text{Au}_{25}(\text{SG})_{18}\) clusters and the charged analytes. Moreover, an amperometric sensing method for other compounds was developed. Next, Kauffman et al. investigated the electron transfer between \(\text{CO}_2\) and \(\text{Au}_{25}(\text{PET})_{18}\) in solution \([41]\). Upon the DMF solution (containing \(\text{Au}_{25}(\text{SR})_{18}\)) was saturated with \(\text{CO}_2\) gas, the optical absorbance features showed the oxidized state of \(\text{Au}_{25}(\text{SR})_{18}\). Meanwhile, the photoluminescence increases and blue-shift. The \(\text{CO}_2^{-}\) induced optical changes can be simply reversed by purging the solution with \(\text{N}_2\) gas to remove the \(\text{CO}_2\), indicating an interaction between \(\text{Au}_{25}(\text{SR})_{18}\) and \(\text{CO}_2\). DFT calculations revealed that the \(\text{CO}_2\) molecule interacts with three \(\text{S}\) atoms of the \(\text{Au}_3\) site of the \(\text{Au}_{25}(\text{SR})_{18}\) cluster, prompting the \(\text{CO}_2\) electrochemical reduction. These observed unique
interactions and electron transfers between gold clusters and reactants make the clusters promising catalysts during the organic transformations.

Figure 4. (A) Cyclic voltammograms (CV) for the redox reaction in potassium ferricyanide solution on Au38S2(SAdm)20 clusters and Au38S2(SAdm)20-(β-CD)2 conjugates. (B) Schematic illustrations of the Au38S2(SAdm)20-(β-CD)2 formation and the charge transfer between Fe(CN)63− and the Au clusters and conjugates. Reproduced with permission from [38]. The Royal Society of Chemistry, 2016.

4. Catalytic Properties

4.1. Ullmann Coupling

At the beginning, the catalytic activity of the Au nanoclusters was examined in the Ullmann homo-coupling reactions of aryl iodides, which are generally catalyzed by palladium, nickel, and copper catalysts [42]. The supported gold cluster catalysts were simply prepared by a vortex-mixing of supports and a solution containing gold clusters at room temperature, and an annealing at 150 °C. The supported Au clusters were intact after the 150 °C annealing process (higher than the reaction temperatures), evidenced by UV−vis and scanning transmission electron microscopy (STEM) [43]. The X-ray photoelectron spectroscopy (XPS) analysis shows the chemical state of Au species in the oxide-supported cluster catalysts is positively charged (Auδ+) [44], where 0 < δ < 1, consistent with the free gold nanoclusters. The catalytic processes were carried out at 130 °C in the presence of base, which is similar with these catalyzed by Pd/Cu complexes or nanoparticles. The Au25(SR)18/CeO2 showed the best catalytic activity, and the test was then expanded to a serial of substituents with functional side-groups (Table 1) [45]. Of note, the efficiency of gold nanoclusters was not as good as the palladium, nickel, and copper nanocomposites in the Ullmann homo-coupling reactions of aryl chlorides and aryl bromides.
Table 1. The catalytic results over the Au25(PET)18/CeO2 catalysts in Ullmann homo-coupling. Reaction conditions: 0.2 mmol iodobenzene, 0.6 mmol K2CO3, 100 mg Au25(PET)18/CeO2 (1 wt% cluster loading), 1 mL DMF, 130 °C, 2 day.

| Entry | Substrate | Product | Conversion (%) |
|-------|-----------|---------|----------------|
| 1     |           |         | 99.8           |
| 2     | MeO-       | MeO-    | 99.5           |
| 3     | O2N-       | O2N-    | 67.5           |
| 4     | OHC-       | OHC-    | 78.2           |
| 5     |           |         | 99.7           |

Later, these Au cluster were studied in the Ullmann hetero-coupling reactions. The catalytic conditions over the Au25(SR)18/CeO2 catalysts were the same with the homo-coupling reactions (Table 1 vs. Table 2). The aromatic and aliphatic thiolate-capped Au25 nanoclusters (e.g., naphthalenethiolate (-SNap), benzenethiolate (-SPh), hexanethiolate (-SC6H13), and 2-phenylethanethiolate (PET)) were chosen for comparison and exploration in the Ullmann hetero-coupling of 4-MeC6H4I and 4-NO2C6H4I [46]. Intriguingly, the aromatic thiolate ligated Au25 clusters gave much better catalytic performance (both the conversion of NO2C6H4I and selectivity for the hetero-coupling product (4-methyl-4′-nitrobiphenyl) than these protected by alkyl thiolate ligands. The Au25(SNap)18 cluster gave an 82% selectivity toward the hetero-coupling product, which was much higher than the Cu, Pd, and Au complexes (the selectivity: <30%, Table 2). Unfortunately, both of the conversion and selectivity decreased in the 2nd and 3rd cycles, which was due to the removal of the capping surface ligands and hence the decomposition of Au clusters, evidenced by the TEM images. These large gold nanoparticles jeopardized the catalytic performance in this coupling reaction. Thus, the protecting ligands on the clusters’ surface play a key influence on their catalytic properties.

Table 2. The catalytic results over the Au25(SR)18/CeO2 catalysts in Ullmann hetero-coupling. Reaction conditions: 0.06 mmol 4-methyl iodobenzene, 0.05 mmol 4-nitroiodobenzene, 0.3 mmol K2CO3, 100 mg Au25(SR)18/CeO2 (~1 wt% cluster loading), 1 mL DMF, 130 °C, 24 h.

| Catalyst       | Conversion (%) | Selectivity (%) |
|----------------|----------------|-----------------|
| Au25(SC6H13)18 | 69             | 16              |
| Au25(PET)18    | 72             | 19              |
| Au25(SPh)18    | 80             | 50              |
| Au25(SNap)18   | 91             | 82              |
DFT simulations were applied to explain the catalytic results. It is worthy to note that the reactants of both 4-MeC₆H₄I and 4-NO₂C₆H₄I cannot interact well with the intact Au₂₅(SR)₁₈ clusters, because of the steric effect of the protecting thiolate ligands on the clusters’ surface. In the first step, one “-SR” unit on the Au₂₅(SR)₁₈ cluster was surmised to be detached under the reaction conditions in the presence of a K₂CO₃ base. Then the gold atoms on the motif were exposed to reactants and were associated with the catalytic sites [44]. Further, the activation energy for the homo- and hetero-couplings over the Au₂₅ protected by “-SCH₃” thiolate were compared by the nudged elastic band (NEB) approach (Figure 5). Intriguingly, the activation energy in the hetero-coupling was less than in the homo-coupling in the case of Au₂₅-SNap clusters, (Figure 4). It implied that the aromatic thiolate-capped gold cluster can not only improve the conversion rate but can also favor the hetero-coupled process [46].

**Figure 5.** Interaction of 4-NO₂C₆H₄I with the exposed Au atoms on the Au₂₅(SCH₃)₂(SH)₁₅ (A) and Au₂₅(SNap)₂(SH)₁₅ (B). Energy vs. reaction coordinate with “-SCH₃” (C) and “-SNap” ligands (D) during the homo- and hetero-coupling reactions. Reproduced with permission from [46]. American Chemical Society, 2016.

DFT simulations were applied to explain the catalytic results. It is worthy to note that the reactants of both 4-MeC₆H₄I and 4-NO₂C₆H₄I cannot interact well with the intact Au₂₅(SR)₁₈ clusters, because of the steric effect of the protecting thiolate ligands on the clusters’ surface. In the first step, one “-SR” unit on the Au₂₅(SR)₁₈ cluster was surmised to be detached under the reaction conditions in the presence of K₂CO₃ base. Then the gold atoms on the motif were exposed to reactants and were associated with the catalytic sites [44]. Further, the activation energy for the homo- and hetero-couplings over the Au₂₅ protected by “-SCH₃” thiolate are comparable by the nudged elastic band (NEB) approach (Figure 5). Intriguingly, the activation energy in the hetero-coupling less than in the homo-coupling in the case of Au₂₅-SNap clusters, (Figure 4). It implied that the aromatic thiolate-capped gold cluster not only can improve the conversion rate but also can favor the hetero-coupled process [46].
4.2. Suzuki Coupling

Further, the titania-supported Au\textsubscript{25} clusters are studied in the Suzuki coupling in the presence of ionic liquids (ILs), which are catalyzed over palladium catalysts [42]. The Suzuki cross-coupling run at 90 °C using different solvents (e.g., ethanol, xylene, toluene, \(N,N'\)-dimethylformamide (DMF), ILs, etc.). The imidazolium-based ILs exerted a large effect on the MeOC\textsubscript{6}H\textsubscript{4}I conversion to the desire products. A very low conversion (<5%) is observed when using the ethanol, toluene, o-xylene, and DMF as solvents in the Au\textsubscript{25}/TiO\textsubscript{2} catalyzed coupling reactions (Table 3). Interestingly, the iodoanisole conversion over Au\textsubscript{25}/TiO\textsubscript{2} drastically increased to 89%–99% when BMIM-X (BMIM: 1-butyl-3-methylimidazolium, X = Br or Cl or BF\textsubscript{4}) solvents are introduced to the reaction system (Table 3). The catalytic results indicate that the imidazolium-based ILs acts as a promoter for the cross-coupling reactions [47]. Of note, only the BMIM cation (i.e., the acidic proton at position 2 of the imidazolium ions) play an important role during the reactions, as no activity is found in the presence of BDiMIM-BF\textsubscript{4} (BDiMIM: 1-butyl-2,3-dimethylimidazolium) solvent, which is further supported by the DFT calculations. It is worthy to note that the efficiency of gold nanoclusters was not as good as the palladium nanocomposites, however, the gold nanoclusters exhibited much better selectivity toward the target cross-coupling products.

Table 3. Catalytic results over the Au\textsubscript{25}/TiO\textsubscript{2} catalysts in the Suzuki cross-coupling reactions of iodoanisole and phenylboronic acid using the imidazolium-based ionic liquids. Reaction conditions: 0.1 mmol iodoanisole, 0.12 mmol phenylboronic acid, 0.36 mmol K\textsubscript{2}CO\textsubscript{3}, 100 mg Au\textsubscript{25}(SR)\textsubscript{18}/TiO\textsubscript{2} (~1 wt % cluster loading), solvents (1 mL EtOH or EtOH:H\textsubscript{2}O (10:1, v/v), and 0.2 mL IL or other organic solvents), 90 °C, 18 h.

| Solvent                  | Conversion (%) |
|--------------------------|----------------|
| o-xylene + EtOH:H\textsubscript{2}O | <0.5           |
| DMF + EtOH:H\textsubscript{2}O       | 4              |
| BMIM·Br + EtOH           | 89             |
| BMIM·Cl + EtOH           | 90             |
| BMIM·BF\textsubscript{4} + EtOH   | 94             |
| BMIM·BF\textsubscript{4} + EtOH:H\textsubscript{2}O | >99           |
| BDiMIM·BF\textsubscript{4} + EtOH  | <0.5           |

To explore the active species during the coupling reactions, the free Au\textsubscript{25}(PET)\textsubscript{18} was mixed with the BMIM-BF\textsubscript{4} under the same reaction conditions [43]. Except the molecular peak of Au\textsubscript{25}(PET)\textsubscript{18} cluster, four new mass peaks are clearly detected in the matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). These new appeared mass peaks belonged to the Au\textsubscript{25-n}(SR)\textsubscript{18-n} (where, \(n = 1–4\)) species (Figure 6). Of note, these new species are not the fragments caused by laser of the MALDI method. These species also were observed in the ESI-MS method [48]. The imidazolium-based ILs indeed assist the yield of Au\textsubscript{25-n}(SR)\textsubscript{18-n} species under the reaction conditions, which may be the active sites for the cross-coupling reactions. The other explanation is that the Au-NHC complex (NHC: N-heterocyclic carbene) with the Au\textsubscript{25-n}(SR)\textsubscript{18-n} species could be responsible for the active sites during the Suzuki cross-coupling reactions, although it needs further investigation. Of note, the Au-NHC complex was the product of the reaction of BMIM cations with the gold nanoclusters.
were using DMF as a solvent and K$_2$(~1 wt % loading) with a 150 °C annealing. The catalytic performance of the Au$_{25}$(PET)$_{18}$ cluster (supported on oxides) was studied. The supported catalyst was prepared by impregnating oxide powders (such as TiO$_2$, CeO$_2$, SiO$_2$, and MgO) in a CH$_2$Cl$_2$ solution of Au$_{25}$(PET)$_{18}$ (~1 wt % loading) with a 150 °C annealing. STEM and TG analyses showed that the protecting thiolate ligands were intact on the surface of gold clusters after thermal treatment. Then these Au$_{25}$/oxide catalysts were applied to the Sonogashira cross-coupling reaction. The optimized reaction conditions in the Sonogashira cross-coupling reaction was studied [49]. The supported catalyst was prepared by impregnating oxide powders (such as TiO$_2$, CeO$_2$, SiO$_2$, and MgO) in a CH$_2$Cl$_2$ solution of Au$_{25}$(PET)$_{18}$ (~1 wt % loading) with a 150 °C annealing. STEM and TG analyses showed that the protecting thiolate ligands were intact on the surface of gold clusters after thermal treatment. Then these Au$_{25}$/oxide catalysts were applied to the Sonogashira cross-coupling reaction. The optimized reaction conditions were using DMF as a solvent and K$_2$CO$_3$ as a base under an N$_2$ atmosphere at 160 °C, which is harsher than those for the above Suzuki and Ullmann couplings. The Au$_{25}$/CeO$_2$ catalyst showed the best activity (96.1% iodoanisole conversion with 88.1% selectivity toward the target product) (Table 4). The solvent and base can also influence the product selectivity. The size-dependent catalytic performance also was studied.

Table 4. The catalytic performance of Au$_{25}$(SR)$_{18}$/oxides in the Sonogashira cross-coupling reaction of p-iodoanisole and phenylacetylene. DMBP and MPEB stand for homo-coupling product of 4,4’-dimethoxy-1,1’-biphenyl and cross-coupling product of 1-methoxy-4-(2-phenylethynyl)benzene, respectively. Reaction conditions: 100 mg catalyst (1 wt % Au$_{25}$(SR)$_{18}$ or AuNC 2–3 nm (SC$_6$H$_{13}$)$_x$ loading), 0.1 mmol p-iodoanisole, 0.15 mmol phenylacetylene, 0.3 mmol K$_2$CO$_3$, 1 mL DMF, 160 °C, 40 h. n.r. = no reaction. Conv. = conversion.

| Entry | Catalyst | Conv. (%) | Selectivity (%) |
|-------|----------|-----------|-----------------|
|       |          |           | MPEB | DMBP |
| 1     | Au$_{25}$(SR)$_{18}$/CeO$_2$ | 96.1 | 88.1 | 11.9 |
| 2     | Au$_{25}$(SR)$_{18}$/TiO$_2$ | 92.8 | 82.9 | 17.1 |
| 3     | Au$_{25}$(SR)$_{18}$/SiO$_2$ | 90.8 | 79.3 | 20.7 |
| 4     | Au$_{25}$(SR)$_{18}$/MgO | 93.3 | 80.6 | 19.4 |
| 5     | AuNC 2–3 nm (SC$_6$H$_{13}$)$_x$/CeO$_2$ | 65.5 | 57.2 | 42.8 |
| 6     | CeO$_2$ | n.r. | 57.2 | 42.8 |
| 7     | TiO$_2$ | n.r. | 57.2 | 42.8 |

Figure 6. Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) of the fresh Au$_{25}$(PET)$_{18}$ clusters and samples treated with the ionic liquid (IL) of BMIM·BF$_4$; the (n, m) presents the number of the Au$_n$(PET)$_m$ species. Reproduced with permission from [47]. American Chemical Society, 2015.

4.3. Sonogashira Coupling

As the IB and alkyne can be activated over gold clusters, hence, the catalytic performance of the gold nanoclusters may extend to Sonogashira cross-coupling reactions, often catalyzed over palladium catalysts [42]. The catalytic performance of the Au$_{25}$(PET)$_{18}$ cluster (supported on oxides) in the Sonogashira cross-coupling reaction was studied [49]. The supported catalyst was prepared by impregnating oxide powders (such as TiO$_2$, CeO$_2$, SiO$_2$, and MgO) in a CH$_2$Cl$_2$ solution of Au$_{25}$(PET)$_{18}$ (~1 wt % loading) with a 150 °C annealing. STEM and TG analyses showed that the protecting thiolate ligands were intact on the surface of gold clusters after thermal treatment. Then these Au$_{25}$/oxide catalysts were applied to the Sonogashira cross-coupling reaction. The optimized reaction conditions were using DMF as a solvent and K$_2$CO$_3$ as a base under an N$_2$ atmosphere at 160 °C, which is harsher than those for the above Suzuki and Ullmann couplings. The Au$_{25}$/CeO$_2$ catalyst showed the best activity (96.1% iodoanisole conversion with 88.1% selectivity toward the target product) (Table 4). The solvent and base can also influence the product selectivity. The size-dependent catalytic performance also was studied.

The catalytic performance of small-sized Au$_{25}$(PET)$_{18}$ cluster catalysts was much better than large-sized of gold clusters of 2–3 nm and Au/CeO$_2$ (~20 nm). Support effects were studied in the...
cross-coupling, and no distinct effect of the oxide supports was observed (i.e., CeO$_2$, SiO$_2$, TiO$_2$, and MgO). The conversion was no obvious decrease, but the selectivity decreased from 88.1% to 64.5% after 5 cycles. It is noteworthy that TEM analysis shows that the gold clusters grow into larger nanoparticles (>3 nm), meaning that the gold clusters capped by organic ligands cannot stay intact under harsh reaction conditions (160 °C in the presence of a base). The gradual degradation of gold clusters leads to a decrease in selectivity, as the larger Au clusters showed a much lower selectivity. It is worthy to note that the efficiency of gold nanoclusters is much worse than the palladium-based catalysts, and the selectivity for the cross-coupling products over Au clusters is also worse.

DFT calculation found that the reactants (i.e., IB and PA) prefer to adsorb on the open facet (Au$_{13}$) of the Au$_{25}$ cluster with the phenyl ring facing a surface Au atom (Figure 7). A total adsorption energy reaches $-0.90$ eV when the two reactants co-adsorb on the Au$_{25}$(SR)$_{18}$ catalyst. While, the IB/IB pair has an adsorption energy of $-1.05$ eV, indicating that the IB/IB pair interacts strongly with the cluster and the homocoupling of IBs is the dominant side-reaction competing with the cross-coupling between IB and PA. DFT results suggested that the catalytic active sites is associated with the Au$_{25}$(SR)$_{18}$ clusters, which is consistent with the experimental results.

The structure of the 25-atom cluster is similar [50], but the electronic property and the catalytic activity of the bimetallic clusters can be largely regulated by the foreign dopants [50–55]. Recently, Li et al. [56] studied the doping effects of the Au$_{25}$(SR)$_{18}$ nanoclusters in the Sonogashira cross-coupling reaction base on the experiment and DFT simulations. The obtained results suggested that the Cu and Ag atoms are preferentially occupied at the cluster’s kernel (Au$_{13}$) rather than the Au$_2$(SR)$_3$ staple motif, while a single Pt atom only can be doped individually and locates in the center of the cluster. The overall performance of Ag$_x$Au$_{25-x}$(SR)$_{18}$ was similar to that of Au$_{25}$(SR)$_{18}$ and Pt$_1$Au$_{24}$(SR)$_{18}$,
which showed a decrease in catalytic activity (Table 5). The catalytic activity was from AgxAu25−x(SR)18 ≈ Au25(SR)18 > Cu1Au24−x(SR)18 > Pt1Au24(SR)18. Interestingly, the Cu1Au24−x(SR)18 produced a homo-coupling product base on the Ullmann homo-coupling pathway, which is contrary to the other three cluster catalysts. However, DFT calculations showed that the adsorption energy of one PA molecule on the Pt1Au24(SR)18, Cu1/2Au24/23(SR)18, and Au25(SR)18 nanoclusters was very similar (−0.50 to −0.52 eV, Table 6). The adsorption energy of one IB molecule onto the Pt1Au24(SR)18, Ag1/2Au24/23(SR)18 and Au25(SR)18 was also very similar (−0.59 to −0.61 eV, Table 6). These results suggested that the adsorption process of the PA and IB onto the alloy clusters is not the key step during the coupling reactions. Generally, the catalytic activity is largely affected by the electronic effect in the core of bimetallic clusters (i.e., Pt1Au12, Cu2Au13−x, AgxAu13−x, and Au13), and the selectivity of product is primarily turned by the atomic type on the shell of M1Au12−x [51,57].

The structure of the 25-atom cluster was similar [50], but the electronic property and the catalytic activity of the bimetallic clusters could be largely regulated by the foreign dopants [50–55]. Recently, Li et al. [56] studied the doping effects of the Au25(SR)18 nanoclusters in a Sonogashira cross-coupling reaction based on an experiment and DFT simulations. The obtained results suggested that the Cu and Ag atoms were preferentially occupied at the cluster’s kernel (Au13) rather than the Au2(SR)3 staple motif, while a single Pt atom only can be doped individually and locates in the center of the cluster. The overall performance of AgxAu25−x(SR)18 was similar to that of Au25(SR)18 and Pt1Au24(SR)18, which showed a decrease in catalytic activity (Table 5). The catalytic activity was AgxAu25−x(SR)18 ≈ Au25(SR)18 > Cu1Au24−x(SR)18 > Pt1Au24(SR)18. Interestingly, the Cu1Au24−x(SR)18 produced a homo-coupling product base on the Ullmann homo-coupling pathway, which was contrary to the other three cluster catalysts. However, DFT calculations showed that the adsorption energy of one PA molecule on the Pt1Au24(SR)18, Cu1/2Au24/23(SR)18, and Au25(SR)18 nanoclusters was very similar (−0.50 to −0.52 eV, Table 6). The adsorption energy of one IB molecule onto the Pt1Au24(SR)18, Ag1/2Au24/23(SR)18, and Au25(SR)18 was also very similar (−0.59 to −0.61 eV, Table 6). These results suggested that the adsorption process of the PA and IB onto the alloy clusters was not the key step during the coupling reactions. Generally, the catalytic activity was largely affected by the electronic

### Table 5. Catalytic performance of TiO2-supported MxAu25−x(SR)18 catalysts in the C–C coupling reaction between MeOC6H4I and PA. Reaction conditions: 100 mg catalyst, 1 wt % MxAu25−x(SR)18 loading, 0.1 mmol MeOC6H4I, 0.1 mmol PA, 0.3 mmol K2CO3, 1 mL DMF, 160 °C, 40 hr.

| Entry | Catalysts | Conversion (%) | Selectivity (%) |
|-------|-----------|----------------|-----------------|
|       |           |                | Selectivity (%) |
|       |           |                | MPEB | DMBP |
| 1     | Au25(SR)18| 79.5           | 65.7 | 34.3 |
| 2     | AgxAu25−x(SR)18 | 83.0 | 55.4 | 44.6 |
| 3     | Cu1Au24−x(SR)18 | 52.4 | 28.3 | 71.7 |
| 4     | Pt1Au24(SR)18 | 48.5           | 67.2 | 32.9 |

### Table 6. Adsorption energy of the PA and IB on the Au3 site of the M1Au24(SR)18 (M: Pt, Ag, and Cu, and noted as M1Au24) and M2Au23(SR)18 (M: Ag and Cu, M2Au23) cluster models, respectively.

| Adsorption Energy (eV) | MxAu25−x(SR)18 Cluster |
|------------------------|------------------------|
| One PA                 | Au25 | Pt1Au24 | AgxAu24 | Ag2Au23 | Cu1Au24 | Cu2Au23 |
| One IB                 | −0.51 | −0.50 | −0.61 | −0.60 | −0.52 | −0.52 |
| “PA + IB” pair         | −0.60 | −0.61 | −0.59 | −0.59 | −0.54 | −0.58 |
| “IB + IB” pair         | −1.11 | −1.11 | −1.20 | −1.19 | −1.06 | −1.10 |

The structure of the 25-atom cluster was similar [50], but the electronic property and the catalytic activity of the bimetallic clusters could be largely regulated by the foreign dopants [50–55]. Recently, Li et al. [56] studied the doping effects of the Au25(SR)18 nanoclusters in a Sonogashira cross-coupling reaction based on an experiment and DFT simulations. The obtained results suggested that the Cu and Ag atoms were preferentially occupied at the cluster’s kernel (Au13) rather than the Au2(SR)3 staple motif, while a single Pt atom only can be doped individually and locates in the center of the cluster. The overall performance of AgxAu25−x(SR)18 was similar to that of Au25(SR)18 and Pt1Au24(SR)18, which showed a decrease in catalytic activity (Table 5). The catalytic activity was AgxAu25−x(SR)18 ≈ Au25(SR)18 > Cu1Au24−x(SR)18 > Pt1Au24(SR)18. Interestingly, the Cu1Au24−x(SR)18 produced a homo-coupling product base on the Ullmann homo-coupling pathway, which was contrary to the other three cluster catalysts. However, DFT calculations showed that the adsorption energy of one PA molecule on the Pt1Au24(SR)18, Cu1/2Au24/23(SR)18, and Au25(SR)18 nanoclusters was very similar (−0.50 to −0.52 eV, Table 6). The adsorption energy of one IB molecule onto the Pt1Au24(SR)18, Ag1/2Au24/23(SR)18, and Au25(SR)18 was also very similar (−0.59 to −0.61 eV, Table 6). These results suggested that the adsorption process of the PA and IB onto the alloy clusters was not the key step during the coupling reactions. Generally, the catalytic activity was largely affected by the electronic
effect in the core of bimetallic clusters (i.e., Pt$_x$Au$_{12}$, Cu$_x$Au$_{13-x}$, Ag$_x$Au$_{13-x}$, and Au$_{13}$), and the selectivity of the product is primarily turned by the atomic type on the shell of M$_x$Au$_{12-x}$ [51, 57].

4.4. $A^3$-Coupling

$A^3$-coupling reactions, where three reactants (aldehydes, amines, and alkynes) react each other in one-pot to yield only one product, have attracted overwhelming interest in the past decade. The $A^3$-coupling is favorable from environmental and economic perspectives: more efficient and less waste [58–61]. The $A^3$-coupling reactions involve new C–C and C–N bond formation in one procedure. The alkyn activation was deemed as the key step for the $A^3$-coupling; the aldehydes could react with amines spontaneously. Hence, the gold clusters should be active in this reaction, because the cluster catalyst has exhibited the capacity of the alkyn activation in the semi-hydrogenation of terminal alkynes [36].

The catalytic performance of the Au$_{25}$(PPh$_3$)$_{10}$(PA)$_5X_2$ was investigated in different solvents and reaction temperatures [62]. The most prominent feature was that the polarity of the solvent had a great influence on catalytic activity. The TiO$_2$-supported Au$_{25}$ catalyst gave higher activity in the polar solvents. The gold clusters also showed good recyclability. Interestingly, the cluster catalyst showed no conversion using ketones as reactants (Figure 8), which was completely different from the catalytic behaviors of the gold complexes and bare gold nanoparticles. Therefore, the electronic factors and steric hindrance of the substituents had significant effects on the reaction conversion rate.

![Figure 8](image_url)

**Figure 8.** Catalytic results over the Au$_{25}$(PPh$_3$)$_{10}$(PA)$_5X_2$ ([Au$_{25}$/TiO$_2$] catalysts in the $A^3$-coupling reaction. Reaction conditions: 100 mg catalyst (1 wt.% cluster loading), 1.0 mmol benzaldehyde, 1.2 mmol piperidine, 1.3 mmol phenylacetylene, 5 mL water, 100 °C, 18 h, under a N$_2$ atmosphere.

An induction period (0 to 3 h) appeared and the conversion slightly increased during the induction period. After the induction period, the reaction conversion of gold clusters significantly increased in the time evolution for $A^3$-coupling [62]. The results showed that some phosphine ligands are removed to generate catalytic active sites, which associates with the surface gold atoms. Further research found that the capped phosphine ligands can be selectively removed in the case of Au$_{11}$(PPh$_3$)$_7X_3$ with the aid of base (e.g., pyridine), evidenced by UV-vis and ESI-MS analyses [63].

Finally, the catalytic mechanism over the gold clusters was studied by DFT calculations. Firstly, the phosphine ligand is detached in the presence of the reaction system, and then the uncovered Au atoms are exposed to the reactants. Next, the PA molecules are adsorbed onto the M1 site via the interaction of Au···whole triple bond, Figure 9. Further, a terminal hydrogen deprotonation occurs in
the presence of amine (e.g., HN(CH₃)₂). The iminium ion (H₂C=N(CH₃)₂⁺) interacts with the PhC≡C– on site M1 and finally give rise to the final product (i.e., propargylamine) [62].

**Figure 9.** Proposed mechanism for the [Au₂₅(PH₃)₁₀(PA)₅Cl₂]²⁺-catalyzed A³-coupling reaction. Reproduced with permission from [62]. Elsevier, 2016.

Further, Jin et al. reported Au₁₃ nanocluster-catalyzed the A³-coupling reaction [64]. They argued that the synergistic effect of the partial positive charged Au surface (Au⁵⁺, 0 ≤ δ ≤ 1) and the electron-rich Au₂₃ kernel were responsible for the catalytic behaviors. Li et al. found that cadmium doped Au₁₃ nanocluster also showed catalytic activity in the A³-coupling [65]. The cooperation between the exerted cadmium atoms and the neighbor gold atoms on the surface of Au₁₃ icosahedron are tentatively deemed as the active sites in the cross-coupling reactions.

5. Summary and Outlook

In the past decade years, remarkable advances have been made in developing catalytic applications of gold nanoclusters, which is a new perspective for gold nanocatalysis, especially in carbon–carbon cross-coupling reactions. These gold nanoclusters were more efficient in the cross C-C coupling reactions in this Review. The higher catalytic activity was mainly because of the distinctive frame structure and electronic properties of the gold nanoclusters and the protecting ligands. However, some of the gold nanoclusters with the protection of thiolate/phosphine could not stay intact under the harsh reaction conditions during the catalysis processes, leading to a decrease or even disappearance of catalytic activity due to the increasing size of formed particles. How to maintain the stability of gold nanoclusters during the catalysis has become a major challenge and subject for future research.

The present review demonstrated that CeO₂ and TiO₂ oxides have been observed to be excellent supports for gold nanoclusters [66]. Few studies have been done on other oxides. Developing new types of supports is another significant issue for substances such as zeolite [67,68], carbon materials (e.g., graphene or graphite oxide) [69,70], and MOFs [71]. For example, mesoporous materials, e.g., MOFs and zeolite, exhibited regular tunnels and cages and improved the stability of the Au clusters during the catalytic processes [72]. The tunnels and cages, by enriching concentration of the reactants, can also improve the catalytic activity. The steric effects of MOFs organic linker can improve the selectivity of products. In addition, the sites of Lewis acids and Bronstein acids in zeolites also can change the catalytic performance of the catalysts.

In a word, gold nanoclusters will be expected to be used into carbon–heteroatom cross-coupling reactions, which are not yet well investigated. The formed C–O and C–N bonds are very useful
drug intermediates [73]. Recently, some attempts have been reported in these categories, such as the cross-aldol condensation and Michael addition (forming C=C bonds) and photo-oxidation of amines to imines (C=N bonds) [10,74]. Future research on gold nanoclusters will contribute to fundamental researches and provide clues for the new design of efficient catalysts for other specific chemical processes.

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