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Thiolate-Protected Gold Nanoclusters Au_{25}(phenylethanethiol)$_{18}$: an Efficient Catalyst for the Synthesis of Propargylamines from Aldehydes, Amines, and Alkynes

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Thiolate-Protected Gold Nanoclusters Au_{25}(phenylethanethiol)$_{18}$: an Efficient Catalyst for the Synthesis of Propargylamines from Aldehydes, Amines, and Alkynes

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In this study, we report thiolate-protected Au nanocluster, Au_{25}(phenylethanethiol)$_{18}$ [$Au_{25}(PET)_{18}$] serves as an efficient catalyst by a three-component coupling reaction (A^3 reaction) of aldehydes, amines, and alkynes to give the corresponding propargylamines in good to excellent yields.

Keywords: gold nanocluster catalyst, propargylamine, amine, alkyne

Amines are fundamental and important substrates in organic transformations.[1] The conversion of amines to more complex functionalized amines containing unsaturated substructures is valuable.[2] In particular, propargylamine derivatives, amines containing a C≡C bond, are important nitrogen-containing scaffolds in organic transformations.[3]

Some examples of metal-catalysed synthesis of propargylamine derivatives have been reported.[3] In particular, three-component coupling reactions (A^3 reactions), i.e. one-pot synthesis of propargylamine derivatives from amines, aldehydes, and alkynes, have been achieved using various metal catalysts such as Cu, Ag, and Au species.[4] This method has been proceeded by the use of immobilized supported catalyst systems.[5]

Au is an effective low-toxic catalyst for organic synthesis, and much research has focused on their use as nanocatalysts.[6] Au nanoparticles (AuNPs) are used in a range of applications, e.g. emitting materials,[7] inks,[8] and biomedical materials.[9] Au nanoclusters (AuNCs), which are aggregates of Au atoms, of size less than 2 nm, have received particular attention as new nanocatalysts because of their high catalytic activity.[10–16] The size-dependent-structures and discrete electronic states in metal nanoclusters can be used to catalyse various reactions, e.g. oxidation and hydrogenation.[10]

In 1987, Haruta and co-workers first showed that CO could be oxidized using small (<2 nm) AuNCs supported on metal oxides.[11] As a result of this work, heterogeneously supported AuNC-catalysed reactions have received considerable attention.[12]

Many approaches have been used for the atomically precise synthesis of AuNCs. Some groups have synthesized thiol-protected AuNCs with precise size control.[13] Tsukuda and co-workers first reported the preparation of precisely sized thiol-protected AuNCs [$Au_{25}(SR)_{18}$] on hydroxyapatite, and used them to catalyse styrene epoxidation.[14a] In 2012, they converted $Au_{25}(SR)_{18}$ to $Pd_1Au_{24}(SR)_{18}$.[14b] Here, the metallic part (Pd_1Au_{24}) was immobilized on multi-walled carbon nanotubes (CNTs) by calcination (Pd_1Au_{24}/CNTs). The catalytic activity of the Pd_1Au_{24}/CNTs in the oxidation of alcohols was higher than that of Au_{25}/CNTs. In 2008, Jin and co-workers reported the synthesis and separation of phenylethanethiol-protected AuNCs [$Au_{25}(PET)_{18}$] using a size-focusing method.[15a] In 2012, they reported metal oxide-supported $Au_{25}(PET)_{18}$ as a heterogeneous catalyst for the Ullmann homocoupling of phenols and aryl iodides.[15b]

AuNCs enable the use of reduced catalyst loadings; this increases the specific surface area and improves the catalytic activity, and reduces costs. Although the activity of supported $Au_{25}(PET)_{18}$ has been well explored,[16] its use in colloidal form (homogeneous catalysis) has not been exploited.[15b,c] Homogeneous catalysts show high activity under mild conditions because of their large surface areas. Recently, unsupported (homogeneous) colloidal NPs have been used as catalysts, and we have developed dimethylformamide (DMF)-stabilized colloidal Pd and Cu NPs using a DMF reduction method.[17] These catalysts have high catalytic activities in Mizorok–Heck,[17a] Suzuki–Miyaura,[17a] and Ullmann coupling reactions.[17b]

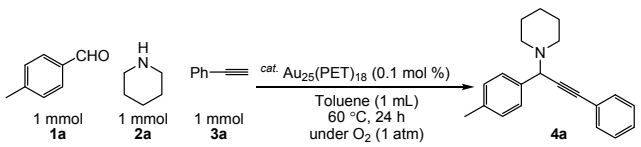
In this study, we used thiolate-protected colloidal AuNCs [$Au_{25}(PET)_{18}$] as an efficient catalyst for synthesizing propargylamine derivatives from aldehydes, amines, and alkynes using an environmentally friendly, low-toxicity A^3 reaction. We also investigated the behaviour of $Au_{25}(PET)_{18}$ in solution and its function as an unsupported homogeneous catalyst.

First, we investigated the behaviour of $Au_{25}(PET)_{18}$ in various solutions, as it is important to understand any solvent-dependent behaviour. $Au_{25}(PET)_{18}$ is highly soluble in DMF, dichloroethane, and dioxane, but complete dissolution in dichloromethane (DCM) takes a long time. $Au_{25}(PET)_{18}$ is insoluble in hexane.

Next, $Au_{25}(PET)_{18}$ oxidation was investigated by stirring under O_2 in the desired solvent. In 2008, Jin and co-workers observed structural changes in $Au_{25}(PET)_{18}$ under O_2 in DCM using ultraviolet-visible spectroscopy.[18] We observed similar changes in the absorption patterns of $Au_{25}(PET)_{18}$ at 400, 450, and 670, and 700 nm under O_2 in toluene, DCM, and tetrachloroethane (TCE), indicating oxidation of $Au_{25}(PET)_{18}$ [see the Supporting Information (SI)].

Based on the solution behaviour, we performed an A^3 homogeneous catalytic reaction of an aldehyde, amine, and alkyne in toluene.

Table 1. Optimization of $Au_{25}(PET)_{18}$ catalyzed A^3 reaction[a]



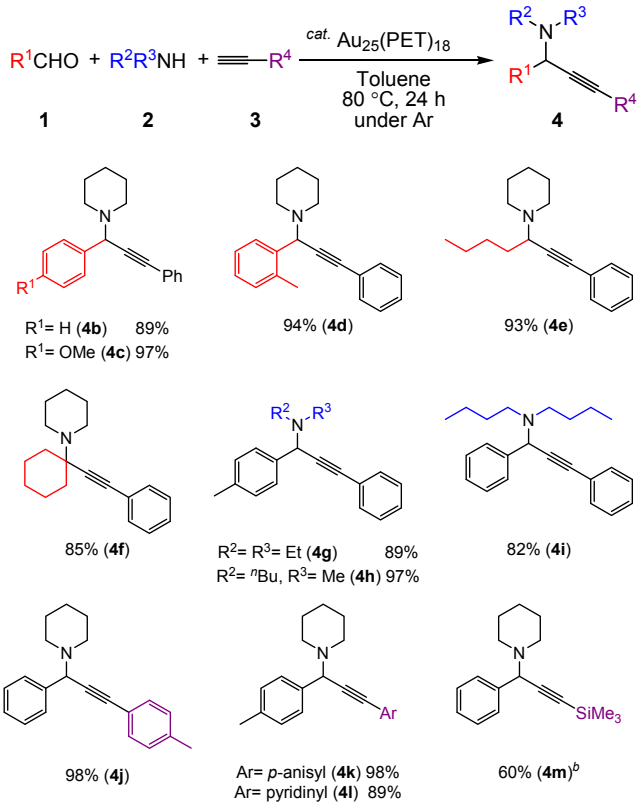
Entry	Conditions	Yield/%[b]
1	Standard conditions	56
2	DMF-protected AuNCs used as catalyst	n.d.[c]
3	DMF-protected PdNCs used as catalyst	n.d.[c]
4[d]	DCM as solvent	2
5	TCE as solvent	1
6	DMF as solvent	26
7	THF as solvent	22
8	DMA as solvent	15
9	**Ratio of 1a**:**2a**:**3a**=1:1:2	76
10	**Ratio of 1a**:**2a**:**3a**=1:2:3	95(93)
11	**Ratio of 1a**:**2a**:**3a**=1:3:3	56
12	**Ratio of 1a**:**2a**:**3a**=1:3:2	14
13	**1a**:**2a**:**3a**=1:2:3, under Ar, 80 °C	>99
14	**1a**:**2a**:**3a**=1:2:3, $Au_{25}(PET)_{18}$(0.01 mol %)	68

[a] Standard conditions: **1a** (1 mmol), **2a** (1 mmol) and **3a** (1 mmol) in toluene (1 mL) with $Au_{25}(PET)_{18}$ (0.1 mol %) at 60 °C. [b]GC yields. The number in parenthesis shows isolated yield. [c]Not detected by GC. [d]At 35 °C, 6 h.

The reaction of tolualdehyde (**1a**), piperidine (**2a**), and phenylacetylene was selected as a test reaction and was performed under various conditions (Table 1), with $Au_{25}(PET)_{18}$ as an unsupported homogeneous catalyst. The standard A^3 reaction gave the desired propargylamine derivative **4a** in in 56% yield (entry 1). This reaction did not proceed with DMF-protected metal NCs (Au and Pd), which were previously reported by our group (entries 2 and 3).[17a,19] Thiolate ligands strongly bind on Au, which is an advantage the $Au_{25}(PET)_{18}$ cluster over the DMF-protected Au NCs with regard to retain the cluster's stability in the catalytic conditions.[19] In addition, it is reported that the single crystal X-ray analysis of the $Au_{25}(PET)_{18}$ clusters possesses open sites, unblocked by thiolates. The open sites might serve as an active sites in the catalytic reactions.[15,20] Next, the effect of the solvent was examined. The reaction was sluggish in DCM and TCE (entries 4 and 5). The yield of **4a** was more than halved when solvents other than DMF (entry 6) were used, with tetrahydrofuran (THF) and dimethylacetamide (DMA) giving **4a** in 15% (entry 7) and 22% (entry 8), yields, respectively.

The effect of the initial substrate ratios was examined (entries 9–12). The yield improved with increasing amount of alkyne. In contrast, increasing the amount of amine inhibited the reaction. The best substrate ratios were aldehyde:amine:alkyne = 1:2:3 (entry 10). This reaction may need excess alkyne to compensate for slow activation through reaction of the alkyne and $Au_{25}(PET)_{18}$ active sites. The amine is needed for enamine formation and alkyne activation (see the SI). This reaction gave an excellent yield (>99%) under Ar at 80 °C (entry 13). As shown in entries 10 and 13, this reaction proceeded smoothly under O_2 and Ar. It is therefore assumed that Au_{25}^- species are involved in the reaction, but we could not clearly discuss the difference in the catalytic activity between the anionic Au and the neutral Au clusters. This reaction proceeded even in the presence of small amounts of catalyst, i.e. 0.01 mol% (68% yield) and 0.001 mol% (14% yield).

Table 2. Scope of aldehydes, amines, and alkynes applicable to $Au_{25}(PET)_{18}$ catalyzed A^3 reaction reaction[a]



[a] Conditions: **1** (0.5 mmol), **2** (1 mmol) and **3** (1.5 mmol) in toluene (0.5 mL) with $Au_{25}(PET)_{18}$ (0.1 mol %) at 80 °C. All yields are isolated yields. [b] At 50 °C.

We investigated the range of substrates that can be used in this reaction. The aldehyde was varied first. The desired products **4b**–**4e** and **4i** were obtained in good to excellent yields from benzaldehyde (**4b**) and anisaldehyde (**4c**). *o*-Tolualdehyde (**4d**) gave an excellent yield, despite the increased steric hindrance. Valeraldehyde (**4e**), an aliphatic aldehyde, also gave an excellent yield. Ketones were also tested instead of aldehydes. The corresponding product **4f** was obtained in excellent yield from a cyclic ketone, namely cyclohexanone, but acetophenone gave only a trace of the desired product. However, the reaction of diethyl ketone under these conditions did not give the product. Next, the amine was varied. Aliphatic amines, i.e. diethylamine, *N*-methylbutylamine, and dibutylamine, gave the desired products **4g**, **4h**, and **4i**, respectively, in good to excellent yields The reaction with aniline, diphenylamine, and *N*-methylaniline were unsuccessful and gave no product. It is important to use secondary amines. When the reaction was attempted with primary amines such as hexylamine or

butylamine, the reaction did not reach completion because the enamine intermediate was too stable and the reaction terminated at this step. Finally, a number of alkynes were tested. Functionalized aromatic alkynes, namely 4-ethynyltoluene and 4-ethynylanisole, gave the corresponding products **4j** and **4k** in excellent yields. 3-Ethynylpyridine, an alkyne containing a heterocycle, gave the corresponding product **4l** in good yield. In contrast, 1-decyne, an aliphatic alkyne, gave the desired product in only 8% yield, and trimethylsilylalkyne gave the desired product **4m** in 60% yield.

Next, we investigated the turnover number (TON) of $Au_{25}(PET)_{18}$ in this reaction. The catalyst loading was reduced in stages (entry 15) to determine its effects. The TON rose gradually to a maximum of 1.4×10^4.

We investigated catalyst reuse. The catalyst was placed in toluene under O_2 at 60 °C; it did not aggregate after 24 h (Table 1, entry 9). After reaction, the solvent was evaporated from the quenched mixture, and hexane (about 7 mL) was added to form a solid. The recovered catalyst was filtered off and redissolved in toluene for reuse. This material was used in the A^3 model reaction and gave 64% yield.

In conclusion, we have shown that thiolate-protected AuNCs, $Au_{25}(PET)_{18}$, have high catalytic activity in the production of propargylamine derivatives from aldehydes, amines, and alkynes by a three-component coupling reaction. Further studies to achieve a detailed understanding of the reaction and its overall scope are currently underway in our laboratory.

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