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Gold(0) Catalyzed Dehydrogenation of *N*-Heterocycles

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ABSTRACT

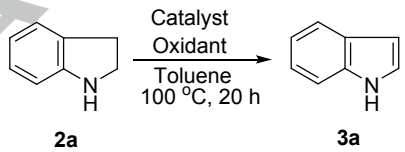
Gold nanoclusters are good catalyst precursors for the catalytic dehydrogenation of indolines, tetrahydroquinazolines, and related *N*-heterocycles. The catalytically active species is presumably Au(0) nanoparticles.

1. **Introduction**

Indoles are one of the most widely distributed heterocyclic compounds in Nature, with many indole alkaloids possessing considerable pharmacological activity.[1] Indoles also feature in agricultural and animal health products, textiles, and perfumes.[2] For these reasons, the synthesis of indole ring derivatives continues to be of interest to synthetic chemists.[3] Among the synthetic methodologies available, the direct dehydrogenation of indolines to indoles is a promising route towards a wide variety of indole derivatives.[4] Indoline dehydrogenation has been achieved *via* electrochemical oxidation,[5] and has also been shown to be catalyzed by a number of transition metals, such as, ruthenium[6] and palladium.[7] More generally, the dehydrogenation of other *N*-heterocycles has been studied with metal complexes based on iron,[8] cobalt,[9] nickel,[10] and iridium,[11] among others.[12]

Following the work of Angelici and co-workers on the use of bulk gold powder (~103 nm particle size) as a catalyst for the aerobic oxidative dehydrogenation of secondary amines to imines, and the fact that this catalytic oxidation likely occurred on the active surface of the heterogeneous gold powder,[13] there has been several reports on gold-catalyzed amine dehydrogenation.[14] Nevertheless, reports on the gold catalysis of indoline dehydrogenation has been sparse, and they include the use of $Au(OAc)_3$ supported on CeO_2,[15] and $KAuCl_4$ supported on graphite,[16] as precursors to active gold nanoparticles. Extension of this reaction to substituted indolines or other *N*-heterocycles has also not been explored. The recent surge in interest regarding thiolate-protected gold nanoclusters led us to consider whether they could be utilized in the catalytic dehydrogenation of indolines. In this study, we have examined a number of thiolate- and the earlier-known phosphine-protected gold nanoclusters in the catalytic dehydrogenation of indoline (Table 1).

Table 1. Optimization study for the oxidative dehydrogenation of indoline.



2a **3a**

Entry	Catalyst (mol%)	Oxidant (1.2 eq.)	Yield **3a** (%)[a]
1	**1** (1)	air	-
2	**1** (1)	pyridine-*N*-oxide	22
3	**1** (1)	H_2O_2	74
4	**1** (1)	TMNO	93
5	-	TMNO	-
6	**1** (1)	-	-
7	**1** (0.5)	TMNO	55
8	**1** (1)	TMNO	60[b]
9	PPh_3AuCl (10)	TMNO	50
10	$Au_{25}(S\text{-hex})_{18}$ (1)	TMNO	23

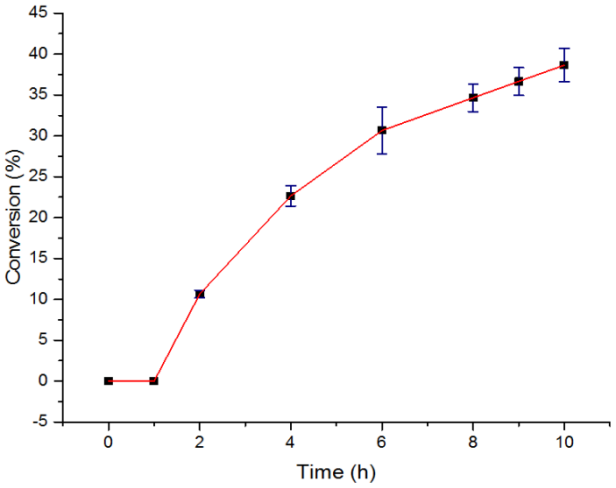
11	$[Au_{25}(SC_2H_4Ph)_{18}]^-$ (1)	TMNO	21
12	$[Au_{11}(PPh_3)_8Cl_2]Cl$ (1)	TMNO	75
13	**1** (1)	TMNO	-[c]
14	**1** (1)	TMNO	-[d]

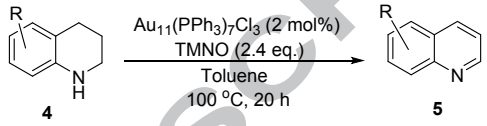
[a] NMR yield. [b] 50 °C. [c] 60 °C in THF. [d] 80 °C in MeCN or DCE.

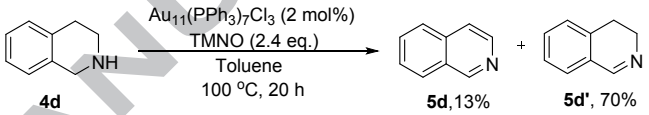
No oxidation occurred when indoline **2a** was heated in air to 100 °C with a catalytic amount (1 mol%) of $Au_{11}(PPh_3)_8Cl_3$ **1** (Entry 1), but the reaction proceeded in the presence of an added oxidant (Entries 2-4), with TMNO giving the best performance. Control experiments showed that both **1** and an oxidant were necessary (Entries 5 and 6), and reducing the amount of catalyst or lowering the temperature led to lower yields (Entries 7 and 8). The Au(I) complex PPh_3AuCl and two thiolate-protected gold nanoclusters showed significantly poorer performance (Entries 9-11), while the cationic form of **1**, *viz*., $[Au_{11}(PPh_3)_8Cl_2]Cl$ showed slightly poorer performance (Entry 12). The reaction failed to proceed in solvents such as tetrahydrofuran, 1,2-dichloroethane and acetonitrile. Monitoring the reaction by $^{31}P\{^1H\}$ NMR spectroscopy showed that the resonance for **1** at 54 ppm was replaced by a new resonance for Ph_3PO at 25 ppm after 1 h, and this remained until reaction completion.

The above observation, together with the results in Table 1, suggests that the active catalyst is probably Au(0) nanoparticles. Indeed, the reaction profile for indoline with **1** as the catalyst shows an induction period of about an hour, consistent with the decomposition of **1** into nanoparticles and hence heterogeneous catalysis (Fig. 1). Phosphine-protected gold nanoclusters having a higher proportion of Au(0) than the thiolate-protected gold nanoclusters may account for the better performance of the former as they form Au(0) nanoparticles more readily.

Figure 1. Reaction profile for the oxidative dehydrogenation of indoline catalyzed by **1**. Reagents and conditions: indoline (0.2 mmol), **1** (1 mol%), TMNO (0.24 mmol), toluene-d_8, 100 °C. 1,3,5-trimethoxybenzene was used as an internal standard to determine conversion.







A substrate scope study using **1** with the optimized conditions proceeded well with indolines possessing a variety of functional groups (Table 2). With 1,2,3,4-tetrahydroquinolines, 2 mol% of **1** and 2.2 equivalents of TMNO were required for reaction completion, while under similar conditions, 1,2,3,4-tetrahydroisoquinoline afforded a mixture of isoquinoline and 3,4-dihydroisoquinoline in 13% and 70% yield, respectively (Scheme 1).

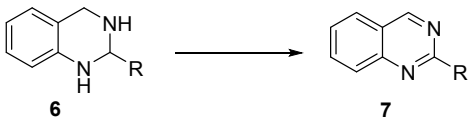
Scheme 1. Oxidative dehydrogenation of 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydroisoquinoline.

Table 2. Substrate scope for the oxidative dehydrogenation of indolines.

The latter reaction conditions also led to the dehydrogenation of 1,2,3,4-tetrahydroquinazolines to quinazolines in good yields (Table 3); substituted quinazolines have potential therapeutic effects.[17]

Entry	R^1	R^2	Product (% isolated yield)
1	H	H	**3a** (79)
2	5-CH_3	H	**3b** (89)
3	5-Br	H	**3c** (75)
4	5-F	H	**3d** (86)
5	5-NO_2	H	**3e** (87)
6	6-NO_2	H	**3f** (71)
7	H	CH_3	**3g** (78)
8	H	CO_2CH_3	**3h** (85)
9	H	$CO_2C_2H_5$	**3i** (83)

Table 3. Substrate scope for the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinazolines.



Entry	R	Product (% isolated yield)
1	H	**7a** (78)
2	C_6H_5	**7b** (76)
3	CH_3-4-C_6H_4	**7c** (87)
4	MeO-4-C_6H_4	**7d** (92)
5	CN-4-C_6H_4	**7e** (91)
6	Cl-4-C_6H_4	**7f** (92)
7	NO_2-4-C_6H_4	**7g** (90)
8	MeO_2C-4-C_6H_4	**7h** (93)
9	Furan-2-yl	**7i** (82)

100

the

A

2 for

Au_2

Reagents and conditions: cluster **1** (2 mol%), TMNO (2.4 eq.), toluene, °C, 20 h.

Quinazolines are also obtainable *via* a one-pot reaction, as exemplified by reaction of 2-aminobenzylamine with 4-methylbenzaldehyde to give 2-(*p*-tolyl)quinazoline, **7c** in good yield (Scheme 2).

Scheme 2. One-pot reaction to synthesize quinazolines.

mechanism involving surface $Au^{\delta+}$ sites has been proposed for the selective oxidation of amines by Au nanoparticles.[16] An alternative, depicted in Figure indoline **2a**, involves oxidative addition of the indoline N-H bond across an unit leading to intermediate **A**. This can then undergo β–hydrogen elimination to give **B** and the hydrido digold species **C**. Intermediate **B** undergoes tautomerization to the indole, whereas **C** reacts with TMNO to regenerate the two Au(0) centres. This pathway parallels that proposed for amine oxidation over the intermetallic Pd_3Pb surface.[18]

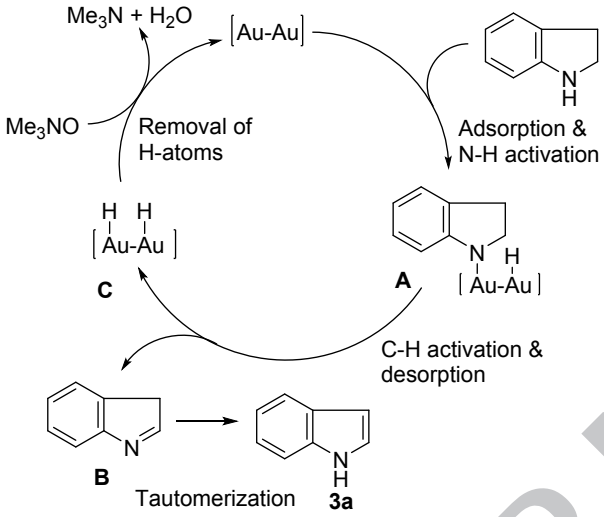


Figure 2. Proposed catalytic cycle for the **1**-catalyzed dehydrogenation of indoline.

In conclusion, we have found that gold nanoclusters are good catalyst precursors for Au(0) nanoparticles which catalyse the dehydrogenation of indolines, tetrahydroquinazolines, and related *N*-heterocycles.

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Supplementary Material

Details of experiments and characterization data of all products.

Highlights

- Gold nanoclusters as pre-catalysts
- Gold nanoparticles as catalysts
- Catalytic oxidative dehydrogenation of N-heterocycles under mild conditions