

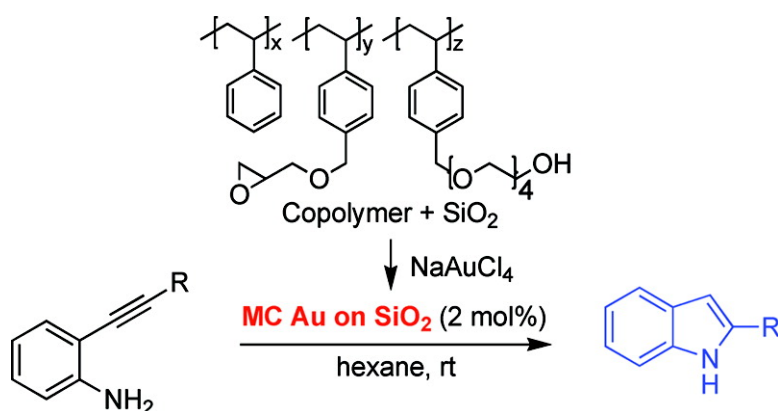
Report

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Report

Novel Gold(III) Polymer-Supported Catalyst for Indole Library Synthesis

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Immobilized catalysts provide among the most effective tools for chemical library synthesis because the procedures are simple and applications to automated systems are feasible. In recent years, use of gold catalysts in organic synthesis has expanded rapidly,¹ and accordingly, development of immobilized gold catalysts is strongly demanded. In the course of our program to develop new methods for library synthesis, we focused on indole ring formation with a gold(III) catalyst reported by Marinelli et al. (Scheme 1).^{2,3} While we and other groups have reported immobilized gold catalysts,^{4,5} most of them are gold(0), and only one approach for immobilizing gold(III) was reported by Corma and Hashmi et al., in which cerium(IV) oxide was used as inorganic support and a mixture of gold(0), gold(I), and gold(III) was obtained.^{4c} Since we have already reported novel immobilization methods for metal catalysts, microencapsulation and polymer-incarcerated methods,⁶ we decided to try these methods for gold(III) immobilization.

First we attempted to prepare polymer-incarcerated (PI) Au(III) from copolymer A and sodium tetrachloroaurate(III) via coacervation in THF–hexane and cross-linking by heating according to the standard method (Table 1).^{5,6} Unexpectedly, this potential catalyst had no activity toward the reaction for the conversion of alkynyl aniline **1a** to the indole **2a** (entry 1). Next cross-linking by acid treatment was tried. Although after treatment with hydrochloric acid the catalyst worked well for the indole synthesis, serious gold leaching into the reaction mixture was observed (entry 2). Cross-linking with other acids under various conditions also failed. We then prepared a microencapsulated gold(III) catalyst (MC Au) without the cross-linking step and applied it to indole synthesis. To our delight, **2a** was obtained in 45% yield without significant gold leaching. Moreover, the MC Au was reused at least three times (entries 3–5), and characteristically displayed lower yields with fresh catalyst rather than in reuse. Further investigations revealed that **2a** was retained in the catalyst. To prevent this retention, MC Au catalysts on various inorganic supports were prepared

and tested (Table 2). Among these inorganic supports, silica gel (SiO₂) afforded the best result in term of the yield, gold leaching, and reusability (entry 8). We decided to use MC Au on SiO₂ in subsequent experiments.

We next investigated the ratio of the three components of the copolymer: styrene, styrene with an epoxide moiety, and styrene with a tetraethylene glycol moiety (Table 3). After careful examination, the best ratio of styrene, styrene with epoxide unit, and styrene with tetraethylene glycol unit was

Scheme 1. Mild and Efficient Indole Synthesis Catalyzed by Gold(III)^{2,3}

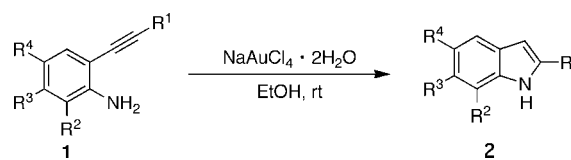
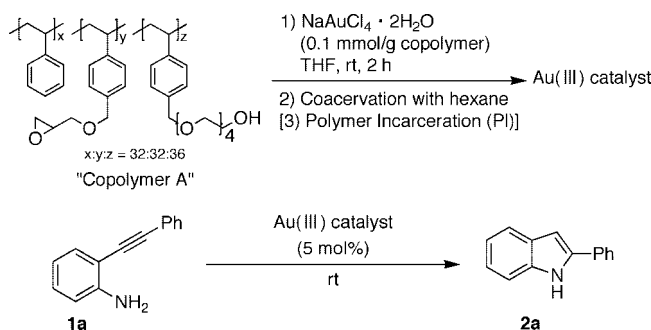


Table 1. Indole Synthesis Catalyzed by PI Au and MC Au



| entry | MC Au (second use) | solvent | time (h) | yield (%) ^a | leaching (%) ^b |
|-------|--------------------|---------|----------|------------------------|---------------------------|
| 1 | heat (120 °C) | THF | 20 | no reaction | not determined |
| 2 | aq HCl | THF | 20 | 81 | 40 |
| 3 | no PI, MC Au | hexane | 20 | 45 | not detected |
| 4 | MC Au (second use) | hexane | 12 | 63 | not detected |
| 5 | MC Au (third use) | hexane | 20 | 88 | 0.6 |

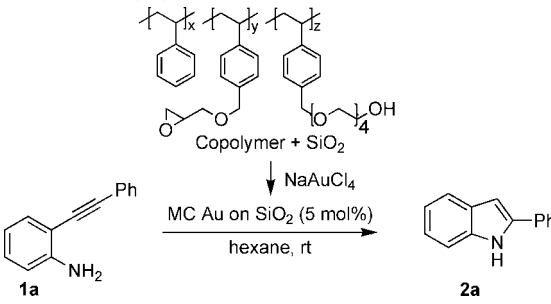
^a Determined by NMR analysis. ^b Determined by ICP analysis.

Table 2. MC Au(III) on Metal Oxides

| entry | metal oxide | time (h) | yield (%) ^a | leaching (%) ^b |
|-------|---|----------|------------------------|---------------------------|
| 1 | none | 20 | 45 | not detected |
| 2 | Al ₂ O ₃ (basic) ^c | 24 | 90 | 1.9 |
| 3 | Al ₂ O ₃ (neutral) ^c | 12 | 82 | 1.1 |
| 4 | TiO ₂ | 24 | 96 | 11 |
| 5 | ZrO ₂ | 96 | 50 ^d | 0.8 |
| 6 | MgO | 12 | 0 ^e | not determined |
| 7 | Hydroxyapatite | 12 | 85 | 7.3 |
| 8 | SiO ₂ ^f | 12 | 84 | 1.2 |

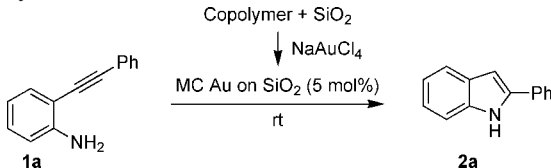
^a Determined by NMR analysis. ^b Determined by ICP analysis. ^c Not reusable. ^d Recoverd SM, 25%. ^e No reaction. ^f Silica gel 60, Merck Reusable.

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Table 3. MC Au(III) on SiO₂ with Different Monomer Ratio


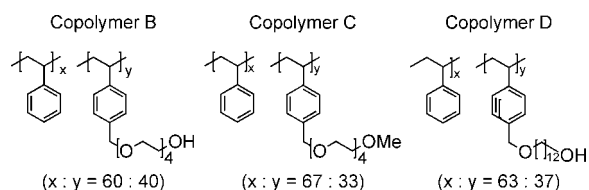
| entry | monomer ratio (x:y:z) | time (h) | yield (%) ^a | leaching (%) ^b |
|-------|--|----------|------------------------|---------------------------|
| 1 | 32:32:36 | 12 | 84 | 1.2 |
| 2 | 100:0:0 | 1 | 92 | 4.3 |
| 3 | 81:0:19 | 2 | 84 | 2.4 |
| 4 | 60:0:40 | 3 | quant | 0.4 |
| 5 | 31:0:69 | 24 | 67 ^c | 0.9 |
| 6 | 0:0:100 | 40 | 87 | 0.6 |
| 7 | 67:37:0 | 1 | 83 | 12 |
| 8 | no polymer | 1 | 97 | 9.3 |
| 9 | no polymer, no SiO ₂ ^d | 96 | 44 | 8.7 |

^a Determined by NMR analysis. ^b Determined by ICP analysis. ^c Recovered SM, 15%. ^d Only NaAlCl₄ was used. ^e Recovered SM, 38%.

Table 4. MC Au(III) on SiO₂ Prepared from Various Copolymers


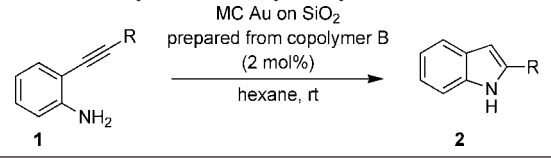
| entry | copolymer | solvent | time (h) | yield (%) ^a | leaching (%) ^b |
|-------|-----------|---------|----------|------------------------|---------------------------|
| 1 | B | hexane | 3 | quant | 0.4 |
| 2 | C | hexane | 1 | 95 | 6.5 |
| 3 | D | hexane | 1 | 82 | 20 |
| 4 | B | toluene | 12 | 86 | 0.8 |
| 5 | B | THF | 40 | 98 | 1.3 |

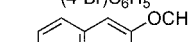
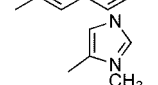

^a Determined by NMR analysis. ^b Determined by ICP analysis.



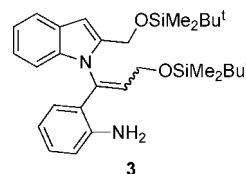
found to be 60:0:40 (entry 4). If the ratio of styrene was increased, the reaction rate was faster, but leaching of gold was also higher (entries 2 and 3). When the ratio of styrene was decreased, the reaction rate proportionally decreased (entries 5 and 6). It is noteworthy that a large amount of gold leaching was observed without the tetraethylene glycol unit (entry 7), and that leaching was also observed without polystyrene or silica gel (entries 8 and 9).

To clarify the effect of the tetraethylene glycol moiety, further modification of this unit was performed (Table 4). Etherification of the hydroxyl group led to more leaching (entry 2, copolymer C), while the conversion of the tetraethylene glycol moiety to the polyalkyl alcohol group resulted in serious gold leaching (entry 3, copolymer D). These results suggested that interaction between gold(III) and the tetraethylene glycol unit played a crucial role in the immobilization. Interestingly, the best catalyst from copolymer B could

Table 5. Indole Synthesis Catalyzed by MC Au on SiO₂


| Entry | R | Time/h | Yield/% ^a | Leaching/% ^b |
|----------------|--|--------|----------------------|-------------------------|
| 1 | Ph | 9 | 88 | 0.8 |
| 2 ^c | (4-MeO)C ₆ H ₅ | 12 | 86 | 0.6 |
| 3 | (4-Me)C ₆ H ₅ | 15 | 93 | not detected |
| 4 | (4-Br)C ₆ H ₅ | 48 | 95 | not detected |
| 5 |  | 16 | 82 | not detected |
| 6 |  | 72 | trace ^d | 0.5 |
| 7 |  | 160 | trace ^e | not determined |
| 8 | <i>n</i> -pentyl | 2 | 86 | 1.3 |
| 9 | 1-Cyclohexenyl | 12 | 81 | 1.1 |
| 10 | CH ₂ CH ₂ Ph | 12 | 96 | 1.5 |
| 11 | (CH ₂) ₃ CN | 16 | 84 | 0.5 |
| 12 | (CH ₂) ₄ Cl | 12 | 88 | not detected |
| 13 | (CH ₂) ₄ OH | 12 | 90 | not detected |
| 14 | Trimethylsilyl | 240 | 5 ^f | 1.0 |
| 15 | CH ₂ OSiMe ₂ Bu [†] | 48 | 3 ^g | 9.5 |

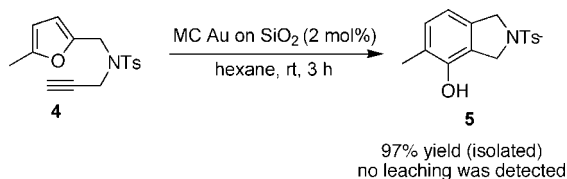
^a Isolated yield. ^b Determined by ICP analysis. ^c Recovered catalyst was used. ^d Recovered SM, 76%. ^e Recovered SM, 75%. ^f Recovered SM, 27%; Indole; 15%. ^g Dimer 3, 24%.



be used not only in hexane but in toluene (entry 4) and even in THF (entry 5) with only a small amount of gold leaching despite of solubility of copolymer B in THF.

The best catalyst from copolymer B was then applied to indole library synthesis (Table 5). The substrates were prepared by Sonogashira reactions of *o*-iodoaniline and acetylene derivatives.⁷ The reactions were conducted in hexane at room temperature in the presence of 2 mol % of the catalyst. In cases of aromatic R substituents with various functional groups, the catalyst worked effectively to give the desired indoles in high yields with little or no leaching of gold (entries 1–5). When the substituent R was a basic heterocycle, the reactions did not proceed, and the starting materials were recovered (entries 6 and 7). After the reaction, the catalyst was recovered by simple filtration, and it is noted that the recovered catalyst also worked well without loss of activity (entry 2). Substrates with aliphatic R were also employed under the same reaction conditions. In most cases, the reactions proceeded smoothly to afford the desired products in high yields (entries 8–13). Cyano, chloro, and hydroxy groups were tolerated under the conditions. When R was trimethylsilyl group, the reaction rate was very slow, presumably because of the steric hindrance, to give the desired product in low yield, and the desilylated indole was

Scheme 2. Synthesis of Phenol from Alkynyl Furan with MC Au on SiO₂



obtained as a side product (entry 14). Interestingly, dimeric compound **3** was the major product when R was *tert*-butyldimethylsilyloxymethyl (entry 15).

Finally, to evaluate the catalysis ability of the MC Au on SiO₂, another gold(III) catalyzed reaction was evaluated. An immobilized gold catalyst on cerium oxide had been applied to the synthesis of phenol **5** from the alkynyl furan **4**.^{4c,8} The MC Au on SiO₂ catalyzed the same reaction efficiently (Scheme 2). The reaction proceeded in hexane at room temperature without any detectable leaching of gold to give **5** in almost quantitative yield. On the other hand, the immobilized gold catalyst on cerium oxide required higher temperature (60 °C) to afford **5**.^{4c} From these results, we deduce that the MC Au on SiO₂ has higher activity than the previously reported gold catalyst immobilized on cerium oxide.

In summary, a novel polystyrene-silica gel-supported gold(III) catalyst (MC Au(III) on SiO₂) has been developed and successfully applied to indole library synthesis. The reactions proceeded smoothly to afford products in high yields at room temperature with little or no detectable gold leaching. Further investigations to obtain more active catalysts and applications to other reactions catalyzed by gold(III) are now in progress.

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Supporting Information Available. Experimental Section. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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