Reusable and Durable Immobilized-Cationic Gold(I) Catalysts for Environmentally Benign Bond-Forming Reactions

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Abstract: Polystyrene-immobilized cationic gold catalysts 2a and 2b were synthesized for the first time and found to be highly effective catalysts for the bond-forming reactions *via* the activation of the C=C triple bonds. The immobilized 2a was easily and quantitatively recovered from the reaction mixture and reused at least seven times while maintaining the original catalytic activity. Furthermore, a flow reactor containing 2a was developed for a larger scale continuous production.

Keywords: alkynes; bond formation; gold; green chemistry; immobilization

For a long time, gold compounds have scarcely received any attention as a catalyst due to the bias that gold is unreactive. Once it was discovered that gold compounds have a significant affinity to carboncarbon multiple bonds, great strides were made using them in organic synthesis.^[1] Among the gold species, cationic gold(I) complexes have become particularly attractive over the past decade because they are resistant to air and moisture and display a high catalytic reactivity with a small loading to promote a variety of transformations, such as nucleophilic reactions, intramolecular cyclizations, and rearrangements.^[2,3]

Meanwhile, increasing environmental concerns have recently resulted in the development of new protocols that can minimize reagent quantity, prevent waste, or use renewable feedstocks. One of the key technologies to achieve these objectives is the application of the metallic gold immobilized on a support. Until now, the huge effort has focused on the synthesis of gold nanoparticles finely dispersed on either metal oxides or organic polymers; however, their utility has been mainly limited to CO oxidation and the selective oxidation of alcohols,^[4] although there are a few reports on their use for reduction^[5] and the Suzuki–Miyaura cross-coupling reaction.^[6] Therefore. it is highly desirable to develop supported gold catalysts that effectively catalyze bond-forming reactions by activating carbon-carbon multiple bonds.^[7] Described herein are the first synthesis of recyclable and durable cationic gold(I) catalysts immobilized on a polymer and their application to environmentally benign ring forming reactions.

Aiming to synthesize the immobilized gold complexes that can activate unsaturated bonds while retaining high catalytic activities, we considered that the gold-phosphine coordination would be the most convenient and effective for the immobilization. Readily available polystyrene-bound triphenylphosphines were first treated with (Me₂S)AuCl^[8] in CH₂Cl₂ at room temperature (Scheme 1), and the particle size of the supports was found to have a significant influence on the coordination and/or catalytic activities. For in-



Scheme 1. Synthesis of polystyrene-immobilized gold catalysts 1 and 2.

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stance, the polymer resin with a 20-60 mesh poorly coordinated to (Me₂S)AuCl, while the smaller polymer-PPh₂ species were successfully involved in the coordination. Among them, the 100-200 mesh polymer resin^[9] was the most effective and useful in view of easy handling to form the immobilized gold compound 1 with a 0.81 mmol gold composition per 1.0 g of the prepared polymer-bound reagent. Subsequently, stirring the mixture of 1 and silver compounds, such as AgOTf and AgNTf₂, in toluene for 15 min in situ generated the cationic gold catalysts 2a and b immobilized on the polymer. In addition, the nature of the resin was found to be another important factor because a similar gold catalyst immobilized on the more flexible polystyrene JandaJel^{TM[10]} exhibited a low catalytic activity.

As part of our ongoing project on the development of highly potential gold-catalyzed reactions,^[11] we have recently developed an efficient and rapid synthesis of furans and pyrroles 4 via the intramolecular cyclization of readily available compounds 3 using homogeneous cationic gold catalysts.^[11b] We have evaluated the activity of the immobilized gold compounds 2a and **b** for the same intramolecular cyclization of **3** as a test reaction (Table 1). When 3a was treated with either 2a or 2b, each containing 0.5 mol% of the Au component, the expected compound 4a was obtained in 95% and 98% yields, respectively, though their reaction times were longer than those under homogeneous conditions. We have examined a similar reaction in the presence of polystyrene-PPh₂ and AgOTf (0.5 mol%) in toluene at room temperature for 3 h to obtain a trace amount of 4a. The reaction with 5.0 mol% of TfOH did not take place at all. Therefore, the supported cationic gold species has been shown to be the true active catalyst.^[11b] Similarly, the reactions of **3b–e** with **2a** and **b** afforded the furans **4b–d** and the pyrrole **4e** in excellent yields. Thereby, it was found that the polymer-attached **2a** and **b** possessed a sufficient reactivity for the C–O bond formation and that the type of counter anion had little influence on their activities. Another important fact is that the gold pre-catalyst **1** was stable enough to maintain its high catalytic activity in a refrigerator. For example, the combination of **1** (0.5 mol%), stored for at least 1 year, with AgNTf₂ (0.5 mol%) catalyzed the cyclization of **3a** to produce a 95% yield of **4a** in 3 h, which was comparable to that using the freshly prepared **1** (Table 1, entry 2).

The polymer-attached cationic gold catalysts (1 and 2) were also available for other types of Au-catalyzed cyclization reactions. For instance, the oxazolidine-forming reaction, discovered by Carretero using Ph₃PAuCl and AgSbF₆,^[12] similarly proceeded with the combination of the pre-catalyst 1 and AgSbF₆ [Eq. (1)]. The activated **2a** proved to be efficient for Toste's C–C bond forming reaction^[13] to give **6** in 94% yield within only 3 h [Eq. (2)]. Hence, these polymer-bound gold catalysts will be widely applica-

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Table 1. Intramolecular cyclization of 3 into 4 using the immobilized cationic gold(I) catalysts 2a and b.

				$\begin{array}{c} 2^{2} \text{ OH} \\ + \\ 3 \end{array} \begin{array}{c} 2z \\ + \\ 4 \\ 3 \end{array} \begin{array}{c} 2z \\ (A \\ + \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	PPh ₂ Au ⁺ L ⁻ a: L= OTf, 2b : L Au: 0.5 mol %)	- = NTf ₂	R^2 R^1 X R^3 R^3		
Entry	Subst	rate \mathbf{R}^1	\mathbb{R}^2	R ³	Х	2	Time [h]		Product Isolated yield [%]
1	3 a	Н	Me	(CH ₂) ₂ Ph	0	2a	3	4 a	95
2	3a	Η	Me	$(CH_2)_2Ph$	Ο	2b	3	4a	98
3	3b	Н	Me	2-thienyl	Ο	2a	9	4 b	79
4	3b	Н	Me	2-thienyl	Ο	2b	6	4b	88
5	3c	-(C	$H_2)_4$ -	Ph	Ο	2a	6	4 c	92
6	3c	-(C	H_{2}_{4} -	Ph	Ο	2b	6	4 c	95
7	3d	Н	H	Ph	Ο	2a	6	4d	88
8	3d	Н	Н	Ph	Ο	2b	6	4d	92
9	3e	Н	Me	$(CH_2)_2Ph$	NBoc	2a	6	4e	80
10	3e	Н	Me	$(CH_2)_2$ Ph	NBoc	2 b	6	4e	79

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ble to various organic reactions that have been conducted using homogeneous gold-based catalysis.

Having established the high catalytic performance of 2a and b in the ring forming reactions, we next examined their recyclability. Using 2a (0.5 mol% of the Au component), the reaction of 3a was conducted under the conditions described in Table 1. After the reaction, simple decantation allowed the easy and almost quantitative recovery of 2a from the reaction mixture. Catalyst 2a was then dried for 10 min under reduced pressure and reused for the next reaction run without the further addition of AgOTf. Its high catalytic activity was maintained up to the fourth run as shown in Table 2. Moreover, even for the eighth use, the reaction smoothly proceeded to afford **4a** in 94% yield, although it took a longer time for completion. The leaching of the Au components was evaluated by inductively coupled plasma (ICP) spectroscopy of the each crude product which revealed that 0.47% of Au was leached in the first run and 0.12-0.21% for runs 2-8. Thus, the coordination binding between the Au moiety and the phosphine on the polymer has proved to be strong enough during every reaction and recovery process. The lengthening of the reaction time seems to be attributable to the slight deactivation of the immobilized gold catalyst by water formed during these reactions.

It is notable that the cationic catalyst 2a was also applicable for a larger-scale continuous flow reactor system (Scheme 2). After mixing polymer-PPh₂-AuCl 1 (800 mg, 0.65 mmol) with AgOTf (167 mg, 0.65 mmol) in toluene (10 mL) for 15 min at room temperature to generate 2a, the reaction mixture was poured into a glass column with a diameter of 12 mm and a length of 30 mm containing the catalytic phase. Subsequently, a solution of 3a (5.00 g, 25 mmol) in

Table 2. The reuse of 2a for converting 3a into 4a.

	OH (CH ₂) ₂ Ph	O−PPh₂ Au ⁺ OTf [−] 2a (Au: 0.5 mol%) toluene, r.t.	Me H(CH ₂) ₂ Ph
Run	Time [h] ^[a]	Yield [%] of 4a	Au leaching [%] ^[b]
1 st	2	98	0.47
2 nd	2	98	0.18
3 rd	2	94	0.12
4 th	2	98	0.16
5 th	3	97	0.15
6 th	5	99	0.21
7 th	7	98	0.14
8 th	7	94	0.14

^[a] Reaction time to consume **3a**.

^[b] The amount of leached Au based on the starting material **2a**.





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Scheme 2. Flow reactor system for the preparation of 4a.

toluene (60 mL) was passed at a 1.0 mLmin^{-1} flow rate through the column. Concentration of the effluent, followed by flash filtration through a silica gel pad with hexanes as eluent gave **4a** in 92% yield. At the higher flow rate of 2.5 mLmin⁻¹, 4.04 g of **4a** were produced with a similar yield (89%) and purity within 30 min. Therefore, the high efficiency of the flow reactor system was demonstrated in terms of a rapid production and simple operation.

In summary, we have synthesized, for the first time, polymer-supported cationic gold(I) complexes **2a** and **b**, which exhibited high catalytic activities for the intramolecular ring-forming reactions leading to heterocycles (**4** and **5**) and a cycloalkane **6**. The reusability of **2a** was also demonstrated without any significant loss of reactivity over 8 times. Moreover, **2a** was applied to a flow reactor system to achieve a rapid and continuous production with a high quality. Further improvement of the reactivity and durability of these immobilized gold catalysts are now in progress.

Experimental Section

Procedure for the Preparation of 1

To a suspension of polystyrene-supported triphenylphosphine^[9] (170 mg, 0.170 mmol of the phosphine ligand) in CH₂Cl₂ (4.0 mL) was added a solution of (Me₂S)AuCl (50.0 mg, 0.170 mmol) in CH₂Cl₂ (2.5 mL) at 0°C *via* a canula. After stirring at room temperature for 6 h, the precipitate was filtered off, washed with CH₂Cl₂, and dried under vacuum. Based on the weight gain of the resin and a trace amount (<1.0 mg) of the gold compound recovered from the combined filtrates, the Au moiety was found to completely coordinate with the phosphine ligand on the polymer. Thus, the polymer supported-gold catalyst **1** with 0.81 mmol of the Au component per 1.0 g of **1** was obtained.

General Procedure for the Preparation of Furans and Pyrrole (Table 1)

Under a nitrogen atmosphere, to a suspension of 1 (7.5 mg, 0.0060 mmol of the Au component) in toluene (3.0 mL, 0.4M) was added either AgOTf (1.6 mg, 0.0060 mmol) or AgNTf₂ (2.3 mg, 0.0060 mmol) at room temperature. The mixture was stirred for 15 min to generate the cationic catalyst **2a** or **2b**. After the substrate **3** (1.2 mmol) was added, the reaction mixture was stirred at room temperature until the complete consumption of **3** and then filtered through a Celite pad. The filtrate was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, usually hexanes/EtOAc or hexanes) to give the corresponding product **4**.

The spectroscopic data of the obtained products **4** were in good agreement with those in our previous publication.^[11b]

Recovery and Reuse of 2a (Table 2)

To a toluene suspension (2.5 mL) of **2a**, generated from **1** (6.2 mg, 0.0050 mmol) and AgOTf (1.3 mg, 0.0050 mmol), was added **3a** (204 mg, 1.0 mmol) at room temperature, and the mixture was stirred for 2 h under a nitrogen atmosphere. The solution was separated by decantation, and the remaining **2a** was washed with toluene. The combined organic layers were evaporated under vacuum, and the residue was purified by column chromatography as above to give **4a**. After drying under vacuum at room temperature for 10 min, the recovered **2a** was reused for another conversion of **3a** (204 mg, 1.0 mmol) into **4a** under the same conditions.

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