ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 4937

Received 30th January 2014,
Accepted 27th March 2014

DOI: 10.1039/c4cc00839a

www.rsc.org/chemcomm

Highly active phosphite gold(I) catalysts for intramolecular hydroalkoxylation, enyne cyclization and furanyne cyclization†

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New and highly active mononuclear phosphite gold(I) catalysts are described. Turn-over numbers up to 37 000 for the furan–yne reaction and up to 28 000 000 for the two-fold hydroalkoxylation of alkynes are reported.

During the last decade, homogeneous gold catalysis has evolved to a highly active and innovative field.[1] The yearly numbers of publications are still increasing; most of them focus on the synthesis of new gold complexes, new methodologies and applications in total synthesis,[2] as well as studies on reaction mechanisms.[3] The high catalyst loading (1–10 mol%), usually employed in gold-catalyzed reactions, indicates the need for the design of more stable and active catalysts able to achieve high turn-over numbers (TONs), which would allow the use of smaller amounts of catalysts.

There are only a few reports in the literature concerning high TON or turnover frequencies (TOFs) with gold catalysts.[4–10] In homogeneous gold catalysis, the highest TONs and TOFs reported so far all cover the addition of alcohols to alkynes. The first study was described by Teles and coworkers,[4] who achieved TONs up to 100 000 and TOFs up to 5400 h^{-1}. In 2004, Hayashi, Tanaka and coworkers reported a TOF to 15 600 h^{-1} using CO and acids as co-catalysts.[5] In 2009, Nolan and coworkers[6] reached a TON of 84 000 and TOF of 4667 h^{-1} even using the less nucleophilic water instead of alcohols. Thieleux and coworkers achieved a TON of 800 000 and a TOF of 294 000 h^{-1} using dissymmetric gold(I) N-heterocyclic carbene complexes.[7] More recently, our group reported a TON of 32 000 000 for the two-fold addition of alcohols to an alkyne, and proved that high TONs can also be achieved in reactions following an entirely different mechanism.[8] That is how a TON of 5720 could be accomplished in the gold(I)-catalyzed furan–yne reaction. On the other hand, the use of gold nanoparticles as catalysts for the oxidation of glucose by oxygen, reported by Rossi and coworkers, allowed a TOF of 50 120 h^{-1}.[9] Small gold clusters (with 3 to 5 gold atoms) have been recently described by Corma and coworkers, who reported a remarkable TON of 10 000 000 and TOF of 100 000 h^{-1} in the ester-assisted hydration of alkynes.[10]

Based on our previous results and in continuation of our efforts to prove that excellent catalytic activity can be achieved using homogeneous and mononuclear gold catalysts,[8] we decided to synthesize, characterize and investigate the catalytic activity of phosphite gold(I) complexes. In earlier work, cationic phosphite gold(I) complexes have been recognized to possess high kinetic activities, but low stabilities due to the easy dissociation of these weak donor ligands.[4] On the other hand, we had assumed that the sterical shielding of the gold(I) center in our highly active NAC–gold(I) complex avoids catalyst decomposition by preventing gold–gold interactions.[8] If this hypothesis is correct, the use of a bulky phosphite ligand instead of a bulky NAC ligand should also lead to high TONs and fast kinetics. Here we report our findings when using such very bulky phosphite ligands.

We synthesized the phosphite gold(I) chlorides **1–3** (Fig. 1) by reaction of DMS–gold chloride (DMS = dimethylsulfide) with the phosphite ligands prepared according to previously described methods.[11] For **1** and **3**, suitable single crystals for X-ray crystal structure analysis could be obtained, which show the different sterical demand of the ligands.[12]

The gold-catalyzed cycloisomerization of 1,6-enynes was first used to study the catalytic activity of phosphite gold(I) complexes. Table 1 summarizes the results for catalysts **2** and **3**, which show high TONs (up to 420) in comparison to best value published so far for the homogeneous gold-catalyzed cycloisomerization of enyne **4** (TON of only 39–41 with 2 mol% of Au).[13] These preliminary results

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 983150 and 983151. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00839a

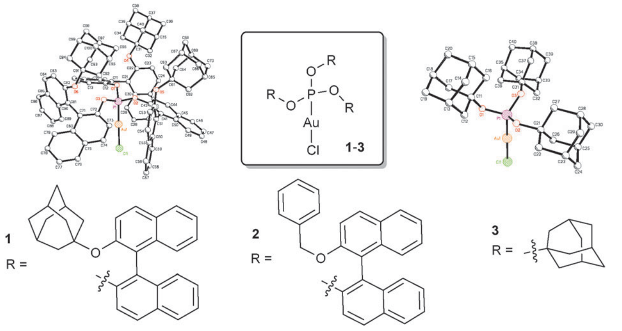
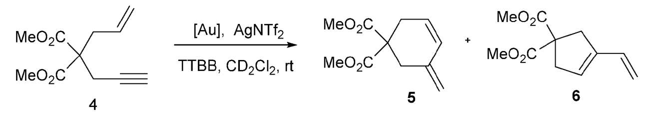


Fig. 1 Phosphite gold(I) complexes **1–3** and solid state molecular structures of **1** and **3**.

Table 1 Gold-catalyzed 1,6-enyne cycloisomerization



Entry	Catalyst	[Au] (mol%)	Conversion^a (%)	Yield **5** : **6**^{a} (%)	TON^b
1	**2**	0.50	72	28 : 40	136
2	**2**	0.10	31	9 : 19	280
3	**3**	0.50	88	17 : 61	156
4	**3**	0.10	47	9 : 33	420
5	$(PhO)_3PAuCl$	0.50	50	10 : 12	44

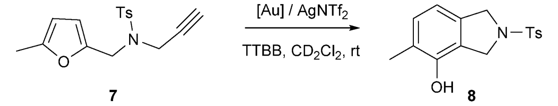
The experiments were carried out in a NMR tube using 0.2 mmol of the substrate in 500 μL of solvent. ^{a} Determined by ^{1}H NMR using TTBB (1,3,5-tri-*tert*-butylbenzene) as internal standard. ^{b} TON: *n*(product)/*n*(catalyst).

of increasing the TON for the reaction of the 1,6-enyne **4** by a factor of ten, already indicated a high potential of this new series of catalysts. The use of sterically less hindered triphenylphosphite ligand gave a much lower TON (entry 5).

Motivated by these results, we decided to investigate the catalytic activity of the phosphite gold(I) complexes **1–3** in the furan–yne reaction.[14] Furan–yne **7** is a very useful substrate among the enyne compounds family, delivering phenols; it has been already used as model substrate for evaluation of new catalysts,[15] achieving a TON of 1180.[15b] When the reaction was performed using 0.1 mol% of the respective catalyst with *in situ* activation according to Gagosz,[16] we were delighted to detect full conversion with TON up to 880 (Table 2). Under the same reaction conditions it was possible to decrease the catalyst loading to 0.001 mol% reaching a remarkable TON of 37 000. The three catalysts **1–3** achieved comparable TONs, which indicated that their stability and catalytic activity is quite similar. With these results a new record for the gold-catalyzed phenol synthesis has been established. Here we did not include the $(PhO)_3P$ ligand in the screening, as in the group there already have been many previous efforts to optimize the ligands for that reaction, including this phosphite, phosphines and carbene ligands as well as heterogeneous gold catalysts.[14b]

As mentioned above, in homogeneous gold catalysis the addition of alcohols to alkynes has reached the highest TONs and TOFs so far reported.[4–10] Thus, we now decided to investigate the catalytic activity of the phosphite gold(I) catalysts **1–3** in the intramolecular two-fold hydroalkoxylation reaction of substrate **9**. This test substrate, which was first studied with Rh and Ir catalysts by Messerle and coworkers,[17] was recently investigated by our group using a highly sterically demanding NAC–gold(I) catalyst, which was able to achieve a TON of 32 000 000.[8] We were curious how the activity of those catalysts bearing a silsesquioxane group compares to that of the new phosphite gold(I) catalysts **1–3**.

Table 2 Gold-catalyzed phenol synthesis



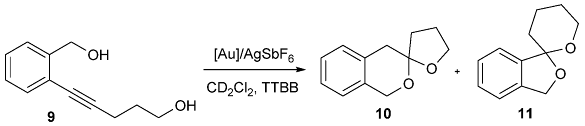
Entry	Catalyst	[Au] (mol%)	Conversion^a (%)	Yield^a (%)	TON^b
1	**1**	0.1	100	73	730
2		0.01	60	42	4200
3		0.001	40	31	31 000
4	**2**	0.1	100	88	880
5		0.01	75	50	5000
6		0.001	50	37	37 000
7	**3**	0.1	100	74	740
8		0.01	85	54	5400
9		0.001	65	34	35 000

Unless otherwise stated, the experiments were carried out in a NMR tube using 0.2 mmol of the substrate in 500 μL of solvent. ^{a} Determined by ^{1}H NMR using TTBB (1,3,5-tri-*tert*-butylbenzene) as internal standard. ^{b} TON: *n*(product)/*n*(catalyst).

Table 3 shows the results obtained for the gold-catalyzed two-fold hydroalkoxylation reaction with substrate **9**, forming the spiro-compounds **10** and **11**. With 0.1 mol% of the catalysts **1–3** (entries 1–3), a complete conversion was observed in less than 2 hours at room temperature; catalyst $(PhO)_3PAuNTf_2$ needed 3 h for the same result (entry 4). A decrease of the catalyst loading to 0.01 mol% (entries 5–7) and 0.001 mol% (entries 9–11) still allowed complete conversions at room temperature, which correspond to TONs up to 9700 and 96 000, respectively. When a catalyst loading of 0.0001 mol% or less was employed,[18] it was necessary to increase the temperature to 40 °C and/or double the concentration of the substrate in the reaction mixture in order to avoid extremely long reaction times. In these entries $(PhO)_3PAuNTf_2$ could not keep up with the other catalysts (entries 8, 12 and 16). Even with a loading of 0.00001 mol% almost complete conversion was accomplished in 72 hours (entries 17–19) achieving TONs up to 9 700 000. Only when the catalyst loading was 0.000001 mol%, the reaction did not proceed to completion, with conversions between 18–29% being observed after 72 hours, reaching TONs between 18 000 000 and 28 000 000, which correspond to TOFs between 250 000 and 380 000 h^{-1} (entries 20–22). No conversion was observed under the same conditions without gold catalysts. Since it was already reported for substrate **9** that, under the same reaction conditions, silver salts alone or Brønsted acids does not show any comparable catalytic activity,[8] the gold catalysts have to be the species responsible for the high TONs reached.

In order to establish the rate by which the catalysts **1–3** convert substrate **9** into the corresponding spiro-compounds **10** and **11**, time/conversion curves for each catalysts were measured using a catalyst loading of 0.0001 mol% at 40 °C. The curves showed that the three catalysts convert the substrate at the same rate, having only a

Table 3 Gold-catalyzed formation of spiro-compounds **10–11**



Entry	[Au] (mol%)	T	Conversion^b (%)	TON^{b,c}
1^a	0.10, **1**	r.t.	100	980
2^a	0.10, **2**	r.t.	100	980
3^a	0.10, **3**	r.t.	100	980
4^a	0.10, $(PhO)_3PAuCl$	r.t.	100	980
5^a	0.01, **1**	r.t.	100	9700
6^a	0.01, **2**	r.t.	100	9700
7^a	0.01, **3**	r.t.	100	9600
8^a	0.01, $(PhO)_3PAuCl$	r.t.	100	9700
9^a	0.001, **1**	r.t.	100	96 000
10^a	0.001, **2**	r.t.	97	94 000
11^a	0.001, **3**	r.t.	98	96 000
12^a	0.001, $(PhO)_3PAuCl$	r.t.	62	60 000
13^a	0.0001, **1**	40 °C	98	960 000
14^a	0.0001, **2**	40 °C	98	940 000
15^a	0.0001, **3**	40 °C	100	980 000
16^a	0.0001, $(PhO)_3PAuCl$	40 °C	14	120 000
17^d	0.00001, **1**	40 °C	98	9 700 000
18^d	0.00001, **2**	40 °C	93	9 200 000
19^d	0.00001, **3**	40 °C	97	9 400 000
20^d	0.000001, **1**	40 °C	25	24 000 000
21^d	0.000001, **2**	40 °C	29	28 000 000
22^d	0.000001, **3**	40 °C	18	18 000 000

[a] In a NMR tube using 0.1 mmol of the substrate in 500 μL of solvent. [b] A ratio of **10** : **11** = 1 : 2 determined by ^{1}H NMR using TTBB (1,3,5-tri-*tert*-butylbenzene) as internal standard. [c] TON: n(product)/n(catalyst). [d] The reaction was carried out with 0.2 mmol of substrate in 500 μL of solvent.

slight difference in the conversion at the end. That is how after 40 hours, catalyst **1** and **2** showed complete conversion (100%) and catalyst **3** reached 97%. The same outcome was observed at 0.000001 mol% catalyst loading when catalyst **3** achieved the lowest TON of 18 000 000, compared to the 28 000 000 obtained with catalyst **2**. In perfect agreement with our initial hypothesis, this difference could be explained in terms of the stabilizing effect of the bulky[19] substituents on the gold catalysts. Therefore catalyst **3**, which is bearing only adamantyl substituents, is the less stabilized catalyst, showing a faster deactivation and achieving lower TONs than the other two phosphite catalysts, bearing bulkier binaphthyl substituents.

Although for this substrate the highest TON reported is 32 000 000 using NAC–gold(I) complex,[8] it was proved that phosphorus-containing gold catalysts can achieve similar high activity by introducing bulky substituents, which stabilize the gold complex.

Our investigation supports the hypothesis that high catalytic activity is not limited to sub-nanoparticles[20] or heterogeneous catalysis; in contrast, it can be achieved not only by NAC–gold(I) complexes but also by homogeneous, mononuclear, phosphorus-containing gold catalysts. The steric bulkiness of the ligand is the crucial factor for achieving long catalyst lifetimes – not the rate of conversion of the substrate is increased, the rate of decomposition of the catalyst becomes slower. Furthermore, a new record for the gold catalyzed phenol synthesis was accomplished with a TON of 37 000.

M. C. Blanco J. is grateful to DAAD for a fellowship. S.A.C. Carabineiro acknowledges financial support from "Investigador FCT" program. M. M. P. and R. M. B. C. thank the financial support from FCT-Portugal and QREN/FEDER (COMPETE – Programa Operacional Fatores de Competitividade, PTDC/QUI-QUI/112913/2009). Authors also thank Fundação das Universidades Portuguesas and DAAD for the bilateral project Ação Integrada Luso-Alemã 2012 – Ref.^{a} A-19/12. Gold salts were generously donated by Umicore AG & Co. KG.

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