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Gold Catalysis

Highly Active Mononuclear NAC–Gold(I) Catalysts**

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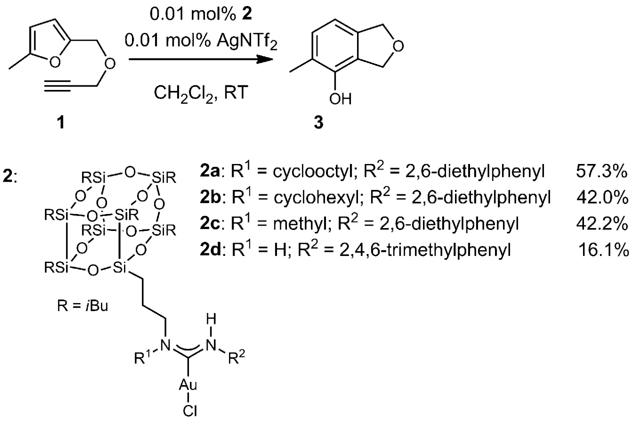
During the last 12 years homogeneous gold catalysis has undergone rapid development, dominated by methodology investigations,[1] research on mechanisms,[2] and applications in total synthesis.[3] With regard to the catalyst, simple complexes like $AuCl_3$[4] were first applied, and subsequent work mainly focussed on known and established ligands for transition-metal catalysis.[1] In most cases catalyst loadings between 1 mol % and 5 mol % (sometimes even more) were used, which correlate to turnover numbers (TONs) of 20 to 50 (or less).[1]

High TONs or turnover frequencies (TOFs) were reported in only a small number of cases. With regard to homogeneous catalysis, in the industrial environment of BASF SE, Teles et al.[5] explored the gold(I)-catalyzed addition of alcohols to alkynes on multi-kilogram scale and achieved an impressive TON of 100000 and a TOF of 5400 h^{-1}. Using CO and acid as promoters and co-catalysts, Hayashi, Tanaka, and co-workers[6] subsequently almost tripled the TOF to 15600 h^{-1}. Nolan et al.[7] recently reported a highly efficient hydration of alkynes; with some substrates a TON of 84000 was reached (TOF of 4667 h^{-1}). With regard to heterogeneous catalysis, Rossi, Della Pina, and co-workers[8] achieved an even higher TOF of 50120 h^{-1} for the gold-catalyzed oxidation of glucose by oxygen, using "naked" gold nanoparticles. Much better results were obtained with a hybrid of homogeneous and heterogeneous gold catalysts, again for the addition of alcohol to alkynes. Only last year Thieleux et al.[9] reported a TON of 800000 and a TOF of 294000 h^{-1}. Now in a recent publication, Corma et al. reported spectacular values (TON 10000000, TOF 100000 h^{-1}) for "sub-nanosized" gold particles in the ester-assisted hydration of alkynes.[10]

In general it seems that these additions of water or alcohol to alkynes, which probably follow the most basic mechanism in gold catalysis,[5,11] allow the lowest catalyst loadings. For other reactions with more complex mechanisms and more delicate intermediates, even much lower TONs are considered as excellent. For example, the gold-catalyzed phenol synthesis, the first gold-catalyzed enyne cycloisomerization reaction, was initially reported with a TON of 48,[12] and even now a TON of 3050[13] is the best reported value. Another example is the cyclization of allenyl ketones to furan heterocycles; here Che et al. reported a very nice TON of 8300 (TOF 1700 h^{-1}).[14]

Some of the catalysts obtained from the modular template synthesis of N-acyclic carbenes (NACs)[13,15] and H-heterocyclic carbenes (NHCs)[16] showed quite promising TONs. Thus we were trying to improve the catalytic activity of gold(I) catalysts for the gold-catalyzed phenol synthesis by testing a broad variety of substituents on the core of these readily accessible systems. Within the context of the gold-catalyzed phenol synthesis, compound **1** is an excellent test substrate for new catalysts,[17] as it reacts quite sluggishly with many gold catalysts and a highly efficient conversion is still a challenge. When investigating different NAC complexes of silsesquioxanes (Scheme 1),[18] we were delighted to detect unprecedented catalytic activity for precatalyst **2a** in the test reaction (Scheme 1, activated in situ according to Gagosz[19] with $AgNTf_2$). We achieved a new record TON of 5720 (0.01 mol % catalyst loading, 57.2 % yield) for this reaction. In addition, when monitoring the kinetics in a ReactIR system, for a catalyst loading of 0.1 mol % we observed an initial TOF of 5 s^{-1} (corresponding to 18000 h^{-1}) (Figure 1). After 120 s the product had been formed in 50 % yield and after 6:20 min in 80 % yield under these conditions. No conversion was observed with $AgNTf_2$ alone, and catalysts **2b–d** with sterically less demanding R groups gave inferior results.



2a: R^1 = cyclooctyl; R^2 = 2,6-diethylphenyl 57.3%
2b: R^1 = cyclohexyl; R^2 = 2,6-diethylphenyl 42.0%
2c: R^1 = methyl; R^2 = 2,6-diethylphenyl 42.2%
2d: R^1 = H; R^2 = 2,4,6-trimethylphenyl 16.1%

Scheme 1. A TON of 5720 was achieved with precatalyst **2a**.

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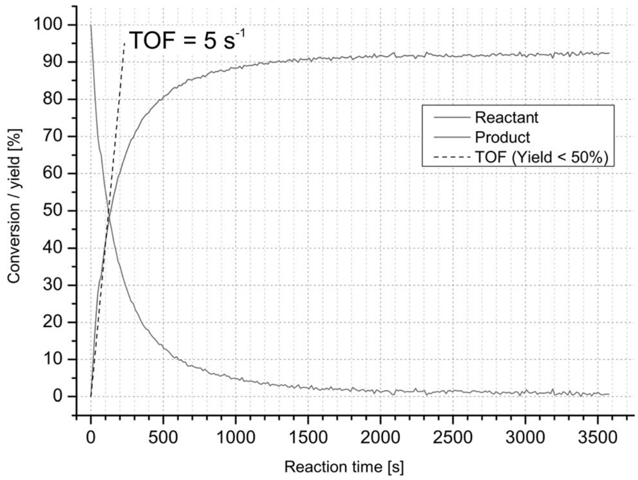
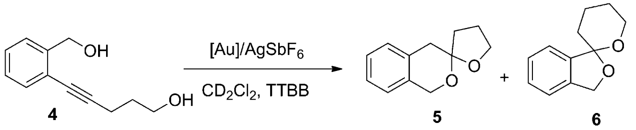


Figure 1. Time/conversion curve for the gold-catalyzed cycloisomerization of **1** with 0.10 mol% of **2a**.

Next, we intended to explore the potential of this catalyst, which set a new record in gold-catalyzed phenol synthesis, in an entirely different type of reaction proceeding by a different mechanism. We applied the new and highly active catalyst **2a** to the reaction of substrate **4**. In preceding work the cyclization of **4** to give isomers **5** and **6** was investigated with Rh and/or Ir catalysts by Messerle et al.,[20] and we were curious whether the superior activity of **2a** in the gold-catalyzed phenol synthesis would also go along with excellent activity in the conversion of **4**.

With 0.5 mol% of catalyst, the gold-catalyzed cyclization of **4** to the spiro compounds **5** and **6** proceeded with complete conversion and the product ratio **5**/**6** was close to 1:1 (Table 1, entry 1). Encouraged by these results, we decreased the amount of catalyst (which is added as a stock solution) by dilution techniques.[21] With 0.3 mol%, 0.1 mol%, 0.05 mol%, and 0.01 mol% of catalyst, complete conversion was still obtained in almost all cases (Table 1, entries 2–5). With a lower catalyst loading (0.001 mol%; Table 1, entry 6) the yield was still high and the substrate was still converted quantitatively; however, the reaction time had to be increased to almost 40 h. Thus, for reactions with lower catalyst loadings, we increased the reaction temperature to 40 °C; even with 0.0001 mol% of catalyst complete consumption of the substrate was still detected (Table 1, entry 7). In order to avoid excessively long reaction times, we increased the amount and concentration of the substrate in the next experiments; with a catalyst loading of 0.00001 mol% quantitative consumption of **4** was still detected (Table 1, entry 9). Only with 0.000001 mol% of catalyst did we reach the limits, and the conversion dropped to 33% and the product was formed in 32% yield (Table 1, entry 10). This corresponds to a TON of 32000000 (reaction time until the conversion stopped was 72 h, TOF 440000 h^{-1}, which is 24 times greater than the TOF for the gold-catalyzed phenol synthesis with the same catalyst and furanyne **1**). This is the best value reported so far for a gold-catalyzed reaction. The last reaction was repeated on a multigram scale and gave the same results. All control experiments conducted under the same conditions but in the absence of the catalyst showed no conversion. The TONs and TOFs achieved with **2a** are by far superior to those reported for Ir and Rh catalysts;[20b] the best values reported so far, for a dinuclear Rh catalyst, were a TON of 1000 and TOF of 13812 h^{-1}.

Table 1: Gold-catalyzed formation of spiro compounds **5** and **6**.[a]



Entry	[Au]	*T* [°C]	Conv.[b] [%]	TON[c]
1	0.5 mol% **2a**	RT	100	200
2	0.3 mol% **2a**	RT	100	327
3	0.1 mol% **2a**	RT	100	980
4	0.05 mol% **2a**	RT	100	1920
5	0.01 mol% **2a**	RT	100	9900
6	0.001 mol% **2a**	RT	100	99000
7	0.0001 mol% **2a**	40	100	9900000
8	0.0001 mol% **7**	40	97	970000
9	0.00001 mol% **2a**	40	100	9700000[d]
10	0.000001 mol% **2a**	40	33	32000000[d]

[a] Unless stated otherwise, the experiments were carried out in an NMR tube using 100 μmol of the substrate in 500 μL of solvent. [b] Determined by ^{1}H NMR analysis using TTBB (1,3,5-tri-*tert*-butylbenzene) as an internal standard. [c] TON = *n*(product)/*n*(catalyst). [d] The reaction was carried out with 1 mmol of substrate in 500 μL of solvent.

Catalyst **7** (Figure 2), which just lacks the silsesquioxane cage, under conditions identical to those used for catalyst **2a** also gave quantitative conversion for catalyst loadings of 0.05 mol%, 0.01 mol%, and 0.001 mol%. A loading of 0.0001 mol% of **7** reached a maximum TON of 970000 (Table 1, entry 8). Then at 0.00001 mol% of **7** no catalytic activity was observed. For all successful conversions with catalyst **7** the **5**/**6** ratio was was close to 1:1 as was observed with **2a**. We measured time/conversion curves at a catalyst loading of 0.0001 mol%: Both **2a** and **7** initially convert the substrate at the same rate, indicating that the difference in the achievable TON is not a consequence of different intrinsic reaction rates, which would allow one catalyst to outpace catalyst deactivation/decomposition more efficiently. This means that for the two catalysts the rates of deactivation/decomposition are different and the bulky siloxane cage must have a stabilizing effect on the catalysts, that is, kinetic stabilization by the bulky substituents. Electronically, as the identical initial rates show and one would assume, the catalysts are essentially the same.

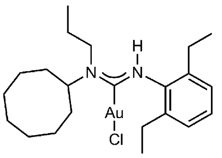


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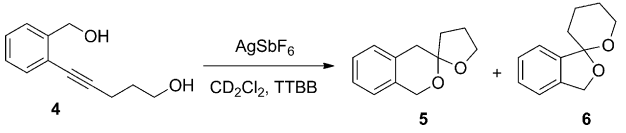
Figure 2. Catalyst **7**.

When we tested the bulky trimesitylphosphane gold(I) complex, which bears a ligand we had successfully used before,[22] only 150000 turnovers were achieved under the same conditions.

Since the stock solution of the catalyst was activated by a silver(I) salt, we also had to investigate the intrinsic activity of silver(I) in these reactions.[23] The results are shown in Table 2; silver(I) indeed shows some activity. Even with 1 mol% of $AgSbF_6$ at room temperature a conversion of only about 69% was reached after a long reaction time (36 h, more than ten times the reaction time required with the gold catalyst; Table 2, entry 1). In addition the chemoselectivity changed: instead of the 1:1 ratio of the two products observed with gold, in the case of silver, product **5** dominated. At 40 °C with 1 mol% of $AgSbF_6$ indeed the substrate was completely consumed, **5** was detected in 97% yield and no **6** was formed under these conditions (Table 2, entry 2). And once more the reaction is much slower than in the case of the gold catalysis. The limit is then reached with 0.01 mol% of $AgSbF_6$: only 14% conversion of the substrate and 10% yield of **5** are detected. This clearly proves that the silver salt cannot be responsible for the high catalytic activity observed in Table 1. Control experiments with *p*-toluenesulfonic acid showed no conversion.[24]

Table 2: Control experiments with silver(I).[a]



Entry	$AgSbF_6$	*T* [°C]	Conv.[b] [%]	Yield **5/6** [%][b]
1	1.0 mol%	RT	69	56/12
2	1.0 mol%	40 °C	97	60% yield of **5**, no **6**
3	0.01 mol%	40 °C	14	10% yield of **5**, no **6**

[a] In analogy to Table 1 the experiments were carried out in an NMR tube using 100 μmol of the substrate in 500 μL of solvent. [b] Determined by ^1H NMR analysis using TTBB as an internal standard.

In order to exclude spontaneous formation of gold sub-nanoparticles during the reaction, we investigated both our catalyst and our reaction mixture of catalyst **2** and substrate **4** by in situ ESI-MS. No particles with more than one gold atom could be detected.

In conclusion, our investigation proves that excellent catalytic activity is not restricted to sub-nanoparticles[10a] and surface-bound complexes:[9] also homogeneous, mononuclear gold catalysts can possess excellent catalytic activities. Furthermore, this investigation supports the assumption that the TON that can be achieved depends significantly on the reaction type investigated.

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[21] The stock solutions were prepared by stepwise dilution in volumentric flasks. According to the analysis by ICP (inductively

coupled plasma), for example, the lowest concentration sample, which was 0.000001 M in catalyst (which is 1.3764 mg L^{-1} of catalyst and should correspond to 196.97 μg L^{-1} of gold), showed 188 μg L^{-1} (the detection limit of the instrument was 1.7 μg $L^{-1,}$ measuring limit 5.3 μg L^{-1}); when another 100 μg L^{-1} was added to this sample, the value measured as expected was 291 μg L^{-1}.

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[23] In a number of reactions gold and silver are known to be active, see: A. S. K. Hashmi in *Silver in Organic Chemistry* (Ed.: M. Harmata), Wiley, Hoboken, **2010**, pp. 357 – 379.

[24] With 0.01 mol% as well as 0.1 mol% of *p*-toluenesulfonic acid even after 24 h no conversion could be detected under conditions identical to those of the gold-catalyzed case.