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Gold Catalysis in Micellar Systems**

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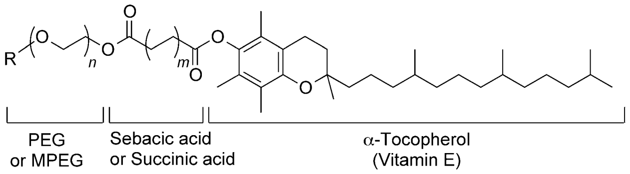
Nowadays, preparative transformations are not only judged by efficiency and stereoselectivity, but also in terms of safety and economic and environmental sustainability.[1] It is mandatory to optimize the use of valuable reagents, recycle precious catalysts, and employ environmentally friendly reaction media. In this context, water offers many advantages, but its use is often hampered by the poor solubility of nonpolar organic substrates and the limited stability and/or reactivity of many transition-metal or organocatalysts. An elegant strategy to solve these issues is micellar catalysis.[2] Micelles formed by addition of amphiphiles to an aqueous reaction medium allow the solubilization of both unpolar and polar substrates, reagents, and catalysts as they exhibit a hydrophilic surface as well as a hydrophobic core. Moreover, a high local concentration of the reactants in the nanometer-sized micelles leads to accelerated transformations and increased selectivities. Compared to traditional "soaps", the vitamin E derived amphiphiles PTS and TPGS (Scheme 1) offer outstanding properties in terms of reactivity, selectivity, and catalyst recycling in many transition-metal-catalyzed transformations,[3] including olefin metathesis,[4] Heck reactions,[5] and Suzuki–Miyaura[6] and Negishi couplings.[7]

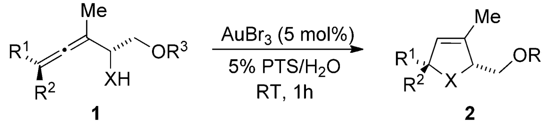


Scheme 1. The structures of poly(oxyethyl)-α-tocopheryl sebacate (PTS; $m=4$, $n\approx13$, R = H) and D-α-tocopherol-polyethyleneglycol-750-succinate monomethyl ether (TPGS-750-M; $m=1$, $n\approx17$, R = Me).

In homogeneous gold catalysis,[8] recycling of the gold(I) or gold(III) catalyst is particularly difficult as it is easily reduced to (catalytically inactive) metallic gold.[9] The few examples of recyclable gold catalysts take advantage of stabilization by ionic liquids[10] or a porphyrin ligand.[11] We now present the first example of gold catalysis in micellar systems using PTS or TPGS-750-M as the amphiphile, which afford gold catalysts with excellent reactivity and recyclability.

Based on our interest[12] in the gold-catalyzed cycloisomerization of functionalized allenes,[13] we started our investigation with the α-hydroxallenes **1a–d**. Treatment of these allenes with 5 mol% of $AuBr_3$ in a 5% aqueous PTS-solution under air for 1 h at room temperature afforded the 2,5-dihydrofurans **2a–d**[14] in 42–88% yield (Table 1, entries 1–4). Not surprisingly,[15] the unprotected α-aminoallene **1e** was very unreactive under these conditions (Table 1, entry 5), whereas the tosylated aminoallene **1f** gave pyrroline **2f** in 60% yield (Table 1, entry 6). The former result is due to deactivation of the gold catalyst by the Lewis basic amine. All cycloisomerizations took place with full axis-to-center chirality transfer. Under the same conditions, but without PTS, the yield of dihydrofuran **2d** was only 42%, whereas the cyclization of aminoallene **2f** did not proceed at all. Other catalysts (AuCl, $AgNO_3$) were less efficient.

Table 1: The gold-catalyzed cycloisomerization of α-functionalized allenes **1** in PTS/water.



Entry	**1**	R^1	R^2	$R^{3\,[a]}$	X	**2** (Yield [%])
1	**1a**	*i*Pr	H	Bn	O	**2a** (42)
2	**1b**	*t*Bu	H	Bn	O	**2b** (62)
3	**1c**	*n*Bu	H	Bn	O	**2c** (48)
4	**1d**	*n*Bu	H	TBS	O	**2d** (88)[b]
5	**1e**	H	*n*Bu	TBS	NH	**2e** (10)[c]
6	**1f**	H	*n*Bu	TBS	NTs	**2f** (60)[d]

[a] TBS = *tert*-butyldimethylsilyl. [b] 42% yield of **2d** in the absence of PTS. [c] Reaction time 24 h. [d] No conversion in the absence of PTS.

Even though these initial results show the feasibility of gold catalysis in micellar systems, optimization of the reaction conditions is required. It is known that the size of PTS-derived micelles can be strongly increased in the presence of NaCl, leading to faster reactions in cross-coupling and ring-closing olefin metathesis.[3] To establish whether this effect can also be utilized in gold catalysis, dynamic light scattering (DLS) measurements of a 2% aqueous PTS solution were carried

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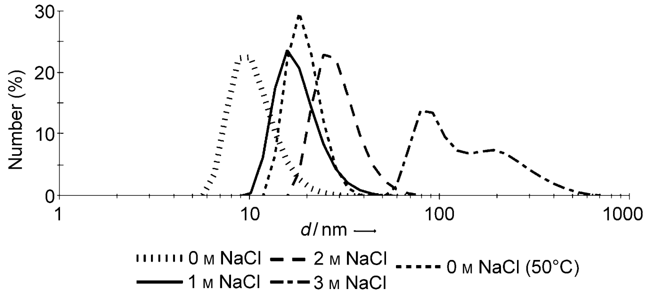
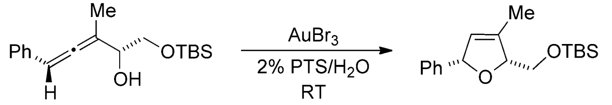


Figure 1. The effect of salt concentration on the average diameter of PTS-derived micelles according to dynamic light scattering (DLS) measurements.

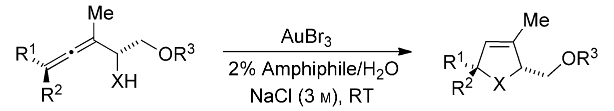
Table 2: The effect of salt concentration on the gold-catalyzed cycloisomerization of allenol **1g** in PTS/water.



1g **2g**

Entry	$AuBr_3$ (mol %)	[NaCl]	t [min]	Yield [%]
1	5	0 M	45	80
2	5	1 M	30	88
3	5	2 M	20	86
4	5	3 M	10	88
5	2	3 M	20	88
6	1	3 M	30	84

Table 3: Gold-catalyzed cycloisomerization of α-functionalized allenes **1** in the presence of PTS or TPGS-750-M and NaCl.



1 **2**

Entry	1	R^1	R^1	R^3	X	$AuBr_3$ [mol %]	Amphiphile	t [min]	**2** (Yield [%])
1	**1d**	*n*Bu	H	TBS	O	2	PTS	30	**2d** (88)
2	**1h**	Ph	H	Bn	O	2	PTS	40	**2h** (84)
3	**1i**	*t*Bu	H	Ac	O	2	PTS	40	**2i** (90)
4	**1f**	H	*n*Bu	TBS	NTs	2	PTS	60	**2f** (76)
5	**1j**	H	Ph	Bn	NTs	2	PTS	80	**2j** (82)
6	**1k**	H	*i*Pr	Bn	NTs	2	PTS	60	**2k** (87)
7	**1g**	Ph	H	TBS	O	1	PTS	70	**2g** (82)
8	**1g**	Ph	H	TBS	O	1	TPGS-750-M	40	**2g** (88)
9	**1l**	*i*Pr	H	TBS	O	1	PTS	30	**2l** (86)
10	**1l**	*i*Pr	H	TBS	O	1	TPGS-750-M	10	**2l** (92)
11	**1b**	*t*Bu	H	Bn	O	1	PTS	60	**2b** (84)
12	**1b**	*t*Bu	H	Bn	O	1	TPGS-750-M	60	**2b** (85)
13	**1c**	*n*Bu	H	Bn	O	1	PTS	80	**2c** (83)
14	**1c**	*n*Bu	H	Bn	O	1	TPGS-750-M	70	**2c** (78)

out, and they showed a strong effect of NaCl on the micelle size (Figure 1). The average diameter increased from about 10 nm in fresh water to about 100 nm with 3 M NaCl.[16] Interestingly, a higher temperature also leads to larger micelles. This effect should allow more catalyst and substrate to migrate into the micellar reaction chamber, resulting in faster conversions. Indeed, the time required for complete conversion of allenol **1g** to 2,5-dihydrofuran **2g** in 2 % aqueous PTS decreases from 45 min at ambient temperature (no NaCl) to just 10 min with 3 M NaCl (Table 2, entries 1–4). Even with lower catalyst loadings of 2 or 1 mol % $AuBr_3$, the reactions are still faster than in the absence of salt (Table 2, entries 5 and 6 versus 1). High yields (80–88 %) were obtained in all cases.

Under these optimized conditions, various α-hydroxy- and α-aminoallenes were converted into the corresponding heterocycles in high yields within 10–80 minutes at room temperature in air (Table 3). The reaction tolerates the presence of acid-sensitive TBS ethers (Table 3, entries 1, 4, 7–10) as well as ester groups (Table 3, entry 3) and sulfonamides (Table 3, entries 4–6). Compared to the corresponding allenols, tosylated α-aminoallenes react slower, but give similar yields (Table 3, entries 4 and 5 versus 1 and 2).

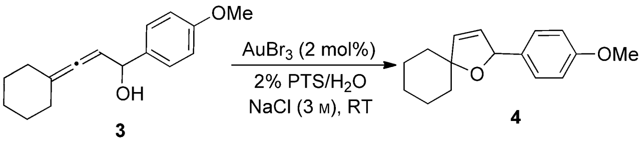
Even though the differences in structure between the amphiphiles PTS and TPGS-750-M are small (Scheme 1), the micelles formed in water have a different size and shape. Cryo-TEM experiments for PTS revealed a mixture of spherical micelles and wormlike structures, whereas TPGS give larger particles.[5] Thus, different properties in transition-metal-catalyzed reactions are expected.[3] Indeed, the cycloisomerization of the allenols **1g** and **1l** bearing a TBS ether proceed faster and with higher yield in the presence of TPGS-750-M (Table 3, entries 8 and 10 versus 7 and 9); in the case of substrate **1l**, only 10 minutes at room temperature were required to afford product **2l** in 92 % yield (Table 3, entry 10). Interestingly, this difference is not observed for the benzyloxy-substituted α-hydroxyallenes **1b** and **1c** (Table 3, entries 11–14).

Whereas most α-functionalized allenes studied so far are oily or liquid and seem to have an appreciable solubility in the aqueous reaction medium, the allenol **3** is solid and appears to be insoluble in aqueous PTS. To convert this substrate into dihydrofuran **4**, it was stirred strongly in a 2 % aqueous PTS solution containing NaCl (3 M) for 30 minutes before $AuBr_3$ (2 mol %) was added. Under these conditions, it took 1 h at room temperature for complete conversion to afford product **4** in 85 % yield (Table 4, entry 1).

With allene **3**, we also examined the recyclability of the micellar gold catalyst. After extraction of the product with *n*-hexane, a decreased reactivity was observed; this decrease is probably due to diffusion of *n*-hexane into the micelles, which leaves less room for the substrate. This problem can be solved either by removal of excess *n*-hexane under reduced pressure or (preferably) by extending the time for phase separation. In the latter case, addition of fresh substrate to the micellar gold catalyst solution afforded product **4** in high yield and an only slightly longer reaction time (Table 4, entries 2–4). This result demonstrates the high stability of the gold catalyst in the PTS micelles.

The recyclability of the micellar gold catalyst was further demonstrated for the acyclic α-hydroxyallene **1g** and the

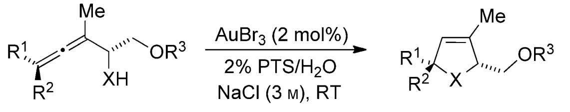
Table 4: Recycling of the $AuBr_3$/PTS-catalyst solution in the cycloisomerization of allenol **3**.



Entry	Run	t [min]	Yield [%]
1	1	60	85
2	2	70	86
3	3	70	84
4	4	70	88

aminoallene **1j** (Table 5). For both substrates, consistently high yields of the heterocycles **2g** (88–91 %) and **2j** (80–83 %) were achieved in 4 runs under air. As for allene **3**, a small drop of the catalyst reactivity was observed after the first run.

Table 5: Recycling of the $AuBr_3$/PTS-catalyst solution in the cycloisomerization of allenes **1g/j**.



1g (R^1 = Ph, R^2 = H, R^3 = TBS, X = O)
1j (R^1 = H, R^2 = Ph, R^3 = Bn, X = NTs)

Entry	Run	1	*t* [min]	2 (Yield [%])	Leaching[a]
1[a]	1	**1g**	40	**2g** (88)	0.08 %
2[a]	2	**1g**	50	**2g** (91)	0.10 %
3[a]	3	**1g**	50	**2g** (88)	0.07 %
4[a]	4	**1g**	50	**2g** (88)	0.04 %
5	1	**1j**	80	**2j** (82)	–
6	2	**1j**	100	**2j** (83)	–
7	3	**1j**	100	**2j** (82)	–
8	4	**1j**	100	**2j** (80)	–

[a] Gold amount in the *n*-hexane extract according to ICP-MS analysis: 1.72 µg (first run), 2.10 µg (second run), 1.40 µg (third run), 0.85 µg (fourth run). Original catalyst loading: 4.60 mg $AuBr_3$ (2.07 mg Au).

Finally, we tested the micellar gold catalyst for metal leaching, which is an important criterion in terms of recyclability and application of the method in the synthesis of pharmacologically active products. Analysis of the *n*-hexane extracts obtained in the cycloisomerization of allenol **1g** with induced coupled plasma mass spectrometry (ICP-MS) revealed a gold content of between 0.04 and 0.10 % of the original catalyst loading (Table 5, entries 1–4). Over the 4 runs, only 0.29 % of the gold catalyst is lost, indicating that the PTS-derived micellar gold catalyst can be recycled several hundred times.

In conclusion, we have established the first example of gold catalysis in micellar systems using PTS or TPGS-750-M as the amphiphile. These afford air-stable aqueous gold catalyst solutions with excellent reactivity and recyclability, which allow the smooth and efficient cycloisomerization of various α-functionalized allenes at room temperature. Addition of NaCl to the reaction mixture affords larger micelles and induces faster reactions. The reaction tolerates the presence of TBS ethers, ester groups, and sulfonamides. For certain substrates, TPGS-750-M offers advantages in terms of reactivity and product yield compared to PTS. The recycling of the micellar gold catalyst solution is possible without compromising reactivity and efficiency by extraction of the product with *n*-hexane. Moreover, the PTS-derived catalyst shows a very low leaching of only 0.29 % over 4 runs. We are continuing to study further applications of this environmentally benign and sustainable micellar catalyst system.

Experimental Section

Representative reaction of **1** to **2**: In a vial, allene **1l** (50.0 mg, 185 µmol) was dissolved in a 2 % aqueous TPGS-750-M solution (1.5 mL) containing NaCl (263 mg, 3 M) and treated with $AuBr_3$ (0.8 mg, 1.85 µmol) under air. After complete conversion (10 min, monitored by TLC), the reaction mixture was extracted with *n*-hexane. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, cyclohexane/ethyl acetate = 10:1) to afford 46.2 mg (92 %) of 2,5-dihydrofurane **2l** as a yellow oil.

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[16] The same trend is observed in the presence of $AuBr_3$ and allene **1l**.

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