Towards sustainable homogeneous gold catalysis: cycloisomerization of functionalized allenes in water†

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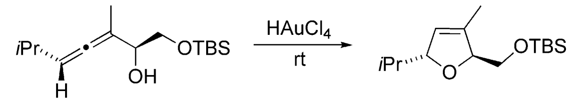
In this study, chloroauric acid ($HAuCl_4$) is used as a catalyst in water for the stereoselective cycloisomerization of various functionalized allenes to five- or six-membered oxygen- or nitrogen-containing heterocycles. Compared to traditional gold catalysts in organic solvents, this new catalytic system is more environmentally friendly, and the gold catalyst can be reused after complete conversion of the substrate.

In recent years, efforts in preparative chemistry have focused not only on the development of new processes, but also on improving the sustainability of existing transformations.[1] In transition metal catalysis, this involves decrease of the catalyst loading, recycling of the catalyst, and use of environmentally friendly reaction media. One of the most benign solvents is water, but it is rarely used in transition metal catalysis since many catalysts are highly sensitive towards moisture. Even though this is not true for many gold catalysts, homogeneous gold catalysis (which is currently at the center of interest in transition metal catalysis)[2] is usually carried out in hazardous organic solvents like dichloromethane or toluene.[3] So far, there are only a few gold-catalyzed transformations which are performed in the presence of water[4] or tolerate the use of hydrated precatalysts like $NaAuCl_4 \cdot 2\ H_2O$.[3b,5,6] The number of examples for gold-catalyzed reaction in water as the bulk solvent seems to be even smaller.[6] Due to our interest in gold-catalyzed cycloisomerizations of functionalized allenes,[2e,3c,7–10] we intended to adapt these transformations (which are usually carried out in dichloromethane, toluene, or THF) for the use of water as the solvent.

Initial experiments were carried out using the readily available α-hydroxyallene **1**[7] as a model substrate. Since many traditional gold precatalysts are either unstable ($AuCl_3$) or hardly soluble in water ($AuBr_3$, AuCl *etc.*), we concentrated on chloroauric acid ($HAuCl_4$) which happens to be the precursor for most gold salts since it is easily obtained by dissolving metallic gold in aqua regia. Gratifyingly, treatment of **1a** (50 mg) with 5 mol% of chloroauric acid in 10 mL of pure water delivered the desired 2,5-dihydrofuran **2a** after 2.5 h reaction time at room temperature (78% isolated yield after extractive workup and chromatographic purification; Table 1, entry 1). A decrease of the amount of water caused an acceleration, but at the cost of more pronounced side reactions (presumably polymerization), so that the product yield fell to 66% and 61%, respectively (Table 1, entries 2, 3). In contrast to this, performing the reaction without any solvent gave only 45% yield of the heterocycle; under these conditions, the reaction was complete after a few seconds (Table 1, entry 4). The use of water/THF mixtures in order to improve the solubility of the substrate accelerated the reaction, but hardly changed the yield of **2a** (Table 1, entries 5 and 6 *vs.* entry 1). Interestingly, an increase of the catalyst loading from 5 mol% to 10 mol% (Table 1, entry 7) lowered the yield, as did a decrease of loading to 1 mol% (Table 1, entry 8). All cyclizations took place with complete axis-to-center chirality transfer.[7]

Table 1 Cycloisomerization of α-hydroxyallene **1a** catalyzed by chloroauric acid in water[a]



1a (*dr* = 85:15) **2a** (*dr* = 85:15)

Entry	Solvent	Catalyst loading (mol%)	Time	Yield (%)[b]
1	Water (10 mL)	5	2.5 h	78
2	Water (5 mL)	5	1 h	66
3	Water (2 mL)	5	30 min	61
4	None	5	<1 min	45
5	Water–THF (10 mL, 100 : 1)	5	2 h	69
6	Water–THF (10 mL, 10 : 1)	5	1 h	77
7	Water (10 mL)	10	1 h	58
8	Water (10 mL)	1	5 h	43

[a] Reaction conditions: 50 mg of **1a** in 10 mL of water, $HAuCl_4$, room temperature. Product **2a** was obtained with full chirality transfer in all cases. [b] Isolated yields.

The biggest obstacle for the recycling of homogeneous gold catalysts is their high tendency to decomposition by reduction to metallic gold which is formed either as a black precipitate or metal mirror (usually immediately after completion of the reaction). Thus, there are only few examples for the recycling of homogeneous gold catalysts.[3,4c] Unfortunately, this behavior was also observed for chloroauric acid which is stable in water only as long as the reaction is proceeding. Once the starting material is consumed, the typical yellow color of the solution turns either purple or colorless with subsequent formation of a metal mirror. With the aim to develop a reusable catalyst system, we tried to stabilize the chloroauric acid solution with additives.

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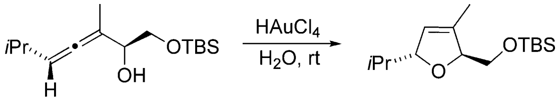
Table 2 Influence of additives on the cycloisomerization of α-hydroxyallene **1a** with $HAuCl_4$ in water[a]

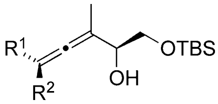
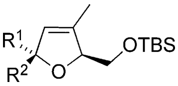
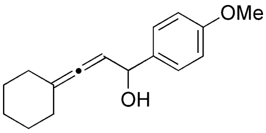
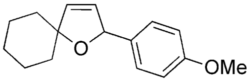
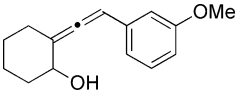
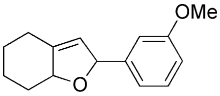


1a (*dr* = 85:15) **2a** (*dr* = 85:15)

Entry	Additive	Equiv.	Time/h	Yield (%)	Note
1	MeCN	1.0	1.5	76	Purple solution
2	$HO(CH_2)_2CN$	0.1	2	82	Purple solution
3	LiCl	10.0	5	75	Yellow solution, no metal mirror
4	LiCl	1.0	3.5	68	Yellow solution, no metal mirror
5	LiCl	0.5	3	77	Metal mirror
6	LiCl	0.1	2.5	68	Metal mirror

[a] Reaction conditions: 50 mg of **1a** in 10 mL of water, 5 mol% of $HAuCl_4$, equivalents of additive relative to **1a**, room temperature. Product **2a** was obtained with full chirality transfer in all cases.

Table 3 Cycloisomerization of α-hydroxyallenes **1** to dihydrofurans **2** with $HAuCl_4$ in water[a]

Entry	Allene			Time	Product	Yield (%)[b]
						
1	**1a**	$R^1 = i\text{Pr}$	$R^2 = H$	3.5 h	**2a**	68
2	**1b**	$R^1 = H$	$R^2 = i\text{Pr}$	1.5 h	**2b**	90
3	**1c**	$R^1 = H$	$R^2 = n\text{Hex}$	3.5 h	**2c**	81
4	**1d**	$R^1 = H$	$R^2 = \text{Et}$	10 min	**2d**	66
5	**1e**	$R^1 = H$	$R^2 = 4\text{-FC}_6H_4$	2 h	**2e**	56
6	**1f**	$R^1 = H$	$R^2 = H$	10 min	**2f**	0
7[c]	 **1g**			3 h	 **2g**	68
8	 **1h**			1.5 h	 **2h**	59

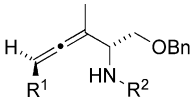
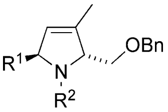
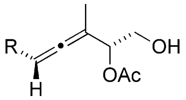
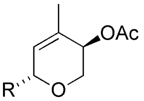
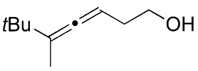
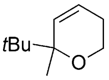
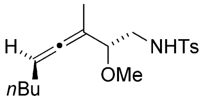
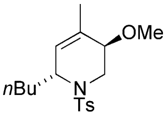
[a] The reactions were performed in water using 5 mol% of $HAuCl_4$ and 1 equiv. of LiCl. [b] Isolated yields; full chirality transfer was observed in all cases. [c] A mixture of water–Et_2O (20 : 1) was used.

Unfortunately, both weak donors like THF (Table 1, entries 5, 6) and stronger ligands such as acetonitrile (Table 2, entry 1) or 3-hydroxypropionitrile (Table 2, entry 2) are not able to prevent decomposition of the catalyst. Better results were obtained with lithium chloride which is well known for its stabilizing effect on organocopper compounds.[11] In the presence of 10 equiv. of LiCl, the yellow color of the catalyst solution was maintained after full conversion of the substrate **1a** (which was obtained with 75% yield), and no metal mirror was formed (Table 2, entry 3). The amount of the lithium salt could be decreased to 1 equiv. with a similar result (Table 2, entry 4), whereas the use of substoichiometric amounts of LiCl was not sufficient to stabilize the catalyst (Table 2, entries 5, 6). In contrast to THF and nitriles which seem to accelerate to cyclization of **1a**, the reaction is slightly slower in the presence of lithium chloride, compared to pure water (Table 2, entries 3–6 *vs.* Table 1, entry 1).

The stabilizing effect of lithium chloride on chloroauric acid in water makes it possible to reuse the gold catalyst. Thus, under the conditions of entry 4 in Table 2, fresh substrate **1a** was added to the reaction mixture after complete conversion of the previous batch. After 3 runs, extractive workup and chromatographic purification afforded product **2a** with 70% isolated yield, indicating that the $HAuCl_4$/LiCl catalyst is sufficiently stable for repeated use. However, extraction of the product with an organic solvent (*n*-hexane, toluene, or diethyl ether) was accompanied by considerable leaching of the catalyst, so that a recycling of the catalytic system is not possible.

Table 3 shows the implementation of these optimized reaction conditions to a variety of α-hydroxyallenes **1** producing the

Table 4 Cycloisomerization of α-aminoallenes **3**, β-hydroxyallenes **5** and β-aminoallene **7** with $HAuCl_4$ in water[a]

Entry	Allene			Time	Product	Yield (%)[b]
						
1	**3a**	R^1 = Ph	R^2 = Boc	1 h	**4a**	82
2	**3b**	R^1 = *i*Pr	R^2 = Ts	25 min	**4b**	89
3	**3c**	R^1 = *i*Pr	R^2 = H	20 h	**4c**	0
						
4	**5a**	R = *n*Bu		3 h	**6a**	57
5	**5b**	R = Bn		1 h	**6b**	50
6	 **5c**			1.5 h		0
7	 **7**			1.5 h	 **8**	16[c]

[a] The reactions were performed in water–THF (20 : 1) using 5 mol% of $HAuCl_4$ and 1 equiv. of LiCl. [b] Isolated yields; full chirality transfer was observed in all cases. [c] 62% of starting material was recovered.

corresponding 2,5-dihydrofurans **2** with 56–90% yield. Only the terminal allene **1f** (Table 3, entry 6) failed to afford the desired cyclization product; rather, a rapid decomposition of the catalyst solution was observed. It is interesting to note that allene **1b** reacted much faster than its diastereomer **1a** and gave the *cis*-disubstituted dihydrofuran **2b** in higher yield of 90% (Table 3, entry 2 *vs.* 1). The method is not only applicable to various alkyl-substituted α-hydroxyallenes **1a-d** (Table 3, entries 1–4), but also to substrates **1e** and **1h** bearing an aromatic substituent at the allene moiety (Table 3, entries 5, 7). Moreover, the bicyclic products **2g** and **2h** are also accessible with the new procedure (Table 3, entries 7, 8). In the former case, the best yield of 68% was obtained in the presence of 5 vol% of diethyl ether as cosolvent.

In order to explore the scope of the $HAuCl_4$/LiCl catalyst, we also investigated the cycloisomerization of α-aminoallenes, as well as of β-hydroxy- and β-aminoallenes, which has been accomplished previously by gold catalysis in organic solvents.[7,8,10] We first used the optimized conditions of entry 4 in Table 2 to convert the allenic carbamate **3a** to the pyrroline **4a**, but no reaction took place because the starting material is completely insoluble in pure water. In the presence of 5 vol% of THF, however, full conversion was achieved after 1 hour, giving product **4a** with 82% yield (Table 4, entry 1). Applying the same conditions to the tosylated α-aminoallene **3b** afforded the pyrroline **4b** in 89% yield (Table 4, entry 2). In contrast to these protected substrates, unprotected α-aminoallenes are known to be very unreactive towards gold(III) catalysts in organic solvents;[8] thus, it is not surprising that no conversion took place upon treatment of aminoallene **3c** with $HAuCl_4$ (Table 4, entry 3). In this case, protonation of the amino group by the Brønsted-acidic catalyst may decrease the reactivity even more. The β-hydroxyallenes **5a** and **5b** were also converted smoothly into the corresponding dihydropyrans **6a/b** upon treatment with $HAuCl_4$/LiCl (Table 4, entries 4, 5), whereas the sterically strongly hindered substrate **5c** did not react (Table 4, entry 6). Likewise, the low reactivity of the β-aminoallene **7** (Table 4, entry 7) is in line with previous observations.[10]

The cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans can also be accomplished in the presence of anhydrous acid (*e.g.*, $HCl/CHCl_3$).[7b,12] In order to establish whether the Brønsted acidity of chloroauric acid also contributes to its reactivity towards functionalized allenes, we exposed the α-hydroxyallene **1b**, as well as the α-aminoallene **3b**, to 10 mol% of hydrochloric acid in water. In both cases, no reaction took place, and the unchanged starting materials were recovered after 20 hours at room temperature. In a second control experiment, we treated the hydroxyallenes **1b** and **5a** with an aqueous solution of sodium tetrachloraurate ($NaAuCl_4$; 5 mol%) and observed a smooth conversion to the heterocycles **2b** (75% yield after 45 min) and **6a** (45% yield after 3 h), respectively. These observations clearly indicate that gold catalysis and not acid catalysis is operative in the cyclization of functionalized allenes with $HAuCl_4$.

In conclusion, we have developed a new, more environmentally friendly procedure for the cycloisomerization of various functionalized allenes to five- or six-membered oxygen- or nitrogen-containing heterocycles by using catalytic amounts of chloroauric acid ($HAuCl_4$) in water. All cyclizations take place with full transfer of chirality from the allenic chirality axis to the new stereogenic center. The stability of this catalyst is improved in the presence of lithium chloride. In the case of substrates that are completely insoluble in water, the addition of small amounts of THF or diethyl ether to the reaction mixture strongly accelerates the reaction. Control experiments show that gold catalysis and not acid catalysis is operative in these transformations. A drawback of the $HAuCl_4$/LiCl system is the necessity of using organic solvents for extraction of the products from the aqueous catalyst solution and for chromatographic purification. This is due to the fact that most cyclization products are oily liquids. Moreover, the use of stoichiometric amounts of lithium chloride contributes to the waste produced in the process, and considerable leaching upon extraction of the product prevents recycling of the catalyst. We are actively pursuing remedies to these limitations in order to improve the sustainability of homogeneous gold catalysts.

Experimental

General procedure for the cycloisomerization of α-hydroxyallenes 1

To a mixture of the allene **1** (50 mg) and 9 mL of demineralized water is added LiCl (1 equiv.; 0.2 M stock solution in H_2O) and $HAuCl_4$ (5 mol%; 10.3 mM stock solution in H_2O). The yellow solution is stirred at room temperature until TLC control indicates full conversion. The aqueous solution is extracted three times with diethylether and the organic solvent is removed by evaporation. Purification of the crude product by flash chromatography (silica gel, cyclohexane/ethyl acetate) affords the 2,5-dihydrofurans **2**.

The spectroscopic data of the cyclization products (see ESI)† are identical with those reported previously.[7,8,10]

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