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Communication

Efficient silver-free gold(I)-catalyzed hydration of alkynes at low catalyst loading

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1. Introduction

Gold catalysis has emerged in the past five years as a powerful tool enabling many useful synthetic transformations [1]. Among these organic transformations, gold-catalyzed nucleophilic additions involving heteroatom-containing nucleophiles have been frequently reported [2]. More specifically, the addition of a molecule of water onto triple bonds of molecules such as alkynes [3] or nitriles [4] is one of the simplest intermolecular and atomeconomical reactions performed by gold catalysis. Alkyne hydration permits a simple access to the carbonyl function [5] and has revealed to be a useful tool in total synthesis [6]. Since its first discovery in 1881 by Kucherov [7], this reaction has been widely used especially on industrial scale [8] in spite of the toxicity of the more active catalytic systems, those comprising mercury(II) salts and either Lewis or Brønsted acid [9]. Much effort has been focused on the development of less toxic methods and among them the use of organogold complexes has emerged as an attractive alternative [10]. Tanaka first reported the use of concentrated solutions of strong acids (H₂SO₃, H₃PW₁₂O₄₀, CF₃SO₃H) in association with [(PPh₃)AuMe][3c,d]. Recently, Nolan et al. contributed to the area by developing a method involving [(IPr)AuCl]/AgSbF₆ as catalytic system. This latter showed high efficiency even at part-per-million (ppm) catalyst loadings and proved to be an advantageous alternative to the use of excess strong acid necessary to activate the gold

ABSTRACT

The use of [(IPr)AuOH] as versatile, air- and moisture-stable pre-catalyst permits the *in situ* generation of the cationic gold(I) species [(IPr)Au]X after reaction with a Brønsted acid. This catalytic system presents as a main advantage the lack of use of a silver salt activator or co-catalyst which is often air-, light- and moisture-sensitive. A general gold(I)-catalyzed procedure using this *in situ* activation at very low catalyst loading is reported for the hydration of a broad range of internal and terminal alkynes.

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center [3b]. Nevertheless, a new (NHC)gold(I) (NHC = N-heterocyclic carbene) pre-catalyst [(IPr)AuOH] (1) (IPr = 1,3-bis(2,6-diiso-propylphenyl)imidazol-2-ylidene) [11,12] has recently emerged and this complex has been employed to easily generate the ubiquitous [(IPr)Au]⁺ catalytic active species by protonolysis in the presence of a Brønsted acid (Scheme 1) [13]. The present study focuses on the use of **1** as pre-catalyst in the hydration of various alkynes. The minimum amount of Brønsted acid necessary to activate the gold center in this system is closely examined.

This approach is devoid of any silver additive; the Reader will be reminded that these air-, light- and moisture-sensitive silver salts of type AgX ($X = BF_4$, SbF_6, OTf, PF_6, NTf_2) are usually employed to generate the cationic gold(I) species from [LAuCl] (L = phosphine or NHC). Moreover, this methodology removes any doubt about the role of silver in the mechanism of this specific hydration reaction. A second advantage of this activation type is that water is the only co-product formed which is in any case a reagent or even the reaction solvent in reactions of the type examined here. These initial mechanistic studies into the acid activation of **1** led us to consider a silver-free method for alkyne hydration using low loadings of **1** in association with Brønsted acids as activator of the gold center, providing very environmentally friendly and a very atom-economical method to generate ketones from alkynes.

2. Results and discussion

The investigations started with the determination of the best catalytic system. Keeping in mind the previous work based on the use of silver salts [3b], various Brønsted acids and $HNTf_2$ in aqueous

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Scheme 1. Generation of [(IPr)Au][X] via acid activation of 1.

solutions were used to generate the active gold(I) species in a mixture of MeOH/water (2:1) at 120 °C during 24 h. In order to develop a valuable alternative to silver salts, the amount of catalyst was decreased to 1000 ppm (i.e., 0.1 mol%).

Best results were obtained with HSbF₆ and HNTf₂ with average conversions of 93% (Table 1, entries 1 and 2), whereas the use of HBF₄ led to irreproducible results, with conversions from 0% to 51% under identical reaction conditions (Table 1, entry 3). These experiments are in good agreement with the previously optimized reaction conditions where [(IPr)Au][SbF₆] generated after activation by AgSbF₆ showed the highest activity [3b]. A slight excess of acid is necessary to ensure complete formation of the active species from 1 in the reaction medium. Due to the large amount of water in the reaction medium, the absence of acid or the presence of exactly 1 equivalent can possibly result in an equilibrium involving 1 and [{Au $(IPr)_2(\mu-OH)[X]$ [13,14], which was found slightly less active in alkyne hydration than [LAu]⁺. Noteworthy, alkyne **2a** did not lead to the corresponding ketone 3a in the presence of the Brønsted acid alone; gold is necessary (Table 1, entry 4), proving that the reaction does not proceed via simple acid catalysis. Without any acid and in the presence of a higher catalyst loading of 1 (Table 1, entry 5), the conversion reached was only 12%. This low catalytic activity was already reported in the previous NMR study of Gaillard, Nolan and co-workers revealing the presence of an equilibrium between an analogue of $[{Au(IPr)}_2(\mu-OH)][X]$ and complex **1** when complex **1** is in an aqueous medium [13]. A similar equilibrium with phosphinegold hydroxonium was also proposed based on calculations by Toste and co-workers [15].

Next, in the process of exploring the reaction scope, a divergence between internal and terminal alkynes is observed in terms of the optimum reaction medium. While the hydration of terminal alkynes led to the rapid product formation without observation of any intermediate species in MeOH, the same reaction with

Table 1

Optimization of the reaction conditions^a.



Entry	1 (mol%)	HX (mol%)	GC conversion (%) ^b
1	0.1	HSbF ₆ (0.15)	93
2	0.1	HNTf ₂ (0.15)	93
3	0.1	HBF ₄ (0.15)	31
4	_	HSbF ₆ (0.15)	0
5	2	_	12

 a Reaction conditions: phenylacetylene 2a (2 mmol), complex 1 (solution 10 mg/ mL in MeOH) and Brønsted acid (solution 0.05 M in H_2O) in 2 mL of a 2:1 MeOH/ water mixture.

^b GC conversions are average of at least two runs.

diphenylacetylene proceeds significantly slower and through an intermediate product identified as the vinyl ether, which then converts into the expected ketone. A kinetic profile of the reaction is presented in Fig. 1.

With a higher catalyst loading (4 mol%) (in order to obtain more rapid conversions), diphenylacetylene is completely consumed after 15 min and transformed into the corresponding vinvlether and ketone in a 71:29 ratio. This ratio evolves after 30 min to 46:54. and the proportion of ketone rises continuously to obtain after 2 h a complete conversion of vinylether into ketone. These results fit those obtained by Leyva and Corma [16] concerning the hydration of 1-octyne in alcohol solvents, showing that the attack of MeOH onto the alkyne is faster compared to that of H₂O. Corma postulated that this vinyl ether could react with MeOH to give a diketal that guickly evolves into the ketone in the presence of water. Nevertheless, this diketal could not be observed. These observations have also been recently extended by Sahoo and co-workers to the gold-catalyzed intermolecular hydrophenoxylation of internal alkynes [17]. Fig. 1 clearly suggests that the conversion of vinylether into the desired ketone is the limiting step in the hydration of internal alkynes. While the starting material is consumed within 15 min, the conversion of the intermediate requires 2 h to reach completion. To avoid this vinylether formation and as consequence accelerate the reaction rate, 1,4-dioxane was chosen as solvent when internal alkynes were involved.

Using the optimized conditions with $HSbF_6$ as acid to activate complex **1**, a range of ketones was prepared from both terminal and internal alkynes (Table 2).

The procedure proved to be gratifyingly efficient, since the study of the reaction scope was performed using only 100 ppm of catalyst with all substrates except diphenylacetylene 2j. Terminal alkynes 2a-f were successfully converted in moderate to excellent yields (Table 2, entries 1–6). Besides phenylacetylene 2a, aliphatic alkynes 2b-e were hydrated with high conversions but volatility of compounds **3b** and **3c** led to product isolation in moderate yields after work-up. The α , β -unsaturated ketone **3f** was also efficiently prepared (Table 2, entry 6) demonstrating complete compatibility with conjugated double bonds. Internal alkynes, which have already shown to be less reactive towards hydration, were also hydrated in the same conditions with good yields (Table 2, entries 7-10). Both aromatic and aliphatic alkynes could be converted under the given conditions. Noteworthy, the presence of a hydroxy group was tolerated with the quantitative hydration of 2h in ketone 3h (Table 2, entry 8). As already observed, alkyne 2i led to the two ketones **3i** and **3i**' in, respectively, 15% and 50% yield. The selectivity in this reaction might be improved by lowering the reaction temperature and a concomitant use of a higher catalyst loading. Diphenylacetylene 2j showed the lowest reactivity of all substrates tested (Table 2, entry 9), requiring a higher catalyst loading (1000 ppm) to enable the reaction and obtain product **3***i* with a satisfying yield of 70%. The low reactivity of diphenylacetylene 2i towards hydration has already been observed in other studies [3b-d,16].



Fig. 1. Kinetic follow of the hydration of diphenylacetylene in MeOH.

To further probe the mechanism of the reaction, attempts to isolate a more stable dimethylketal were performed. Michelet, Genêt and co-workers have already shown that cyclic diketals could be prepared from bis-homopropargylic diols in the presence of gold [18]. The reaction was conducted in ethylene glycol as solvent and under anhydrous and acid-free conditions in order to isolate the corresponding cyclic diketal (Scheme 2). The dinuclear complex [{Au(IPr)}₂(μ -OH)][BF₄] (**4**) [14] was used as catalyst in this reaction since no acid activation is required.

As expected and under non-optimized conditions, the ketal **5** is obtained after 72 h at 120 °C in the presence of 1.5 mol% of **4**. This diketal was then reacted with **1** (4 mol%) and HSbF₆ (12 mol%) in a dioxane/water (2:1) mixture and full conversion into the corresponding ketone was observed. These experimental data support the proposed mechanism, which can be written as illustrated in Fig. 2. After activation of the triple bond by the gold center, ketals **I** then **II** are formed, which then react with the other hydroxy function to give the isolated diketal **5**. In the presence of water, this diketal leads to the corresponding ketone **3j**.

In conclusion, a new protocol for the hydration of alkynes involving a Brønsted acid activation of the pre-catalyst [(IPr)AuOH] **1** was developed. This catalytic system proved to be efficient even at low catalyst loadings. Moreover, the use of the air and moisture-stable complex **1** permits to circumvent the use of silver salts and permits the generation *in situ* of the cationic gold(I) species after reaction with strong acids. This system was successfully applied to a range of terminal and internal alkynes variously substituted at a catalyst loading of only 100 ppm for most of substrates and with TON up to 9900.

3. Experimental

All reactions were carried out in air. [(IPr)AuOH] and [{(IPr) Au}₂(μ -OH)][BF₄] were prepared according to literature procedure [11,13]. Phenylacetylene was purified *via* Kugelrohr distillation

before use. Solvents and other reagents were purchased from commercial sources and used without any further purification.

3.1. General procedure for the alkyne hydration at 100 ppm catalyst loading

In a sealed reaction vial equipped with a magnetic stirring bar [(IPr)AuOH] (0.02 μ mol, 12 μ L of a 10 mg/mL solution in MeOH) is added to an aqueous solution of HSbF₆ (0.06 μ mol, 12 μ L of a 0.05 M solution in H₂O) in 2 mL of a 2:1 MeOH/water or 1,4-dioxane/water mixture. The alkyne (2 mmol) is added and the reaction mixture stirred for 24 h at 120 °C. Dichloromethane is then added and the solution dried over MgSO₄, concentrated under reduced pressure and the yield determined by ¹H NMR with 4-nitrobenzaldehyde as internal standard (76 mg, 0.5 mmol).

3.2. 2-Benzyl-2-phenyl-1,3-dioxolane 5

In a sealed reaction vial equipped with a magnetic stirring bar $[{(IPr)Au}_2(\mu-OH)][BF_4]$ (0.03 mmol, 38 mg) is diluted in 2 mL of ethylene glycol. Diphenylacetylene (2 mmol) is added and the reaction mixture stirred for 72 h at 120 °C then allowed to cool at rt and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc/pentane, 2:98) to afford 331 mg of **5** (69%).

¹H NMR (300 MHz, CD₂Cl₂): δ 7.42–7.24 (m, 5H), 7.23–7.06 (m, 5H), 3.86–3.77 (m, 2H), 3.77–3.67 (m, 2H), 3.16 (s, 2H). ¹³C NMR (126 MHz, CD₂Cl₂): δ 143.0, 136.6, 131.2, 128.2, 128.1, 128.0, 126.7, 126.3, 110.3, 65.1, 47.2.

3.3. 1,2-Diphenylethanone 3j

In a sealed reaction vial equipped with a magnetic stirring bar [(IPr)AuOH] (0.08 mmol, 48 mg) is added to a aqueous solution of

Table 2

Alkyne hydration with *in situ* generated cationic gold(I) species^a.

$$R = R' \qquad \begin{array}{c} [(IPr)AuOH] \text{ cat.} \\ HSbF_6 \text{ aq. cat.} \\ \hline MeOH/water (2:1) \\ or \\ 1,4-dioxane/water (2:1) \\ 120^\circ C, 24h \end{array} \qquad \begin{array}{c} O \\ R \\ \hline \textbf{3a-j} \\ \textbf{3a-j} \end{array}$$

Entry	Alkyne	Catalyst loading (ppm)	Product	Yield (%) ^b	TON
1		100	0	81	8100
	2a				
_			38		
2	$\sim //$	100	O L	40	4000
	2b		3b		
3	//,	100	0	41	4100
	\rightarrow		, Č		
	2c				
4	、 、	100	30	00	0000
4		100	$\overset{\circ}{\downarrow}$	50	9000
	2d				
			3d		
5	\bigwedge	100		94	9400
			Ö		
	2e		Зе		
6	//	100	0	76	7600
	2f				
			3f		
7		100	O II	56	5600
	2g		3σ		
8	- OH	100	0	99	9900
			Он		
	2h		3h		
9	~	100	0	15	6500
5		100		15	0500
			()		
	2i		~ <u>3i</u>		
				50	
			3i'		
10		1000	o (70	700
	2i		3ј		
	-J				

^a Reaction conditions: alkyne **2a** (2 mmol), complex **1** (0.02 mmol, 12 μL of a 10 mg/mL solution in MeOH) and acid (0.06 mmol, 12 μL of a 0.05 M solution in water) in 2 mL of a 2:1 MeOH/water or 1,4-dioxane/water mixture at 120 °C during 24 h. ^b NMR yields determined with 4-nitrobenzaldehyde as internal standard.



Fig. 2. Proposed mechanism for the alkyne hydration with ethylene glycol.

 $HSbF_6$ (0.24 mmol, 87.4 mg of a 65% solution in H_2O) in 2 mL of a 2:1 1,4-dioxane/water mixture. The ketal **5** (2 mmol) is added and the reaction mixture stirred for 24 h at 120 °C. Dichloromethane is then added and the solution dried over MgSO₄, concentrated under reduced pressure to afford **3***j*.

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