Isolable Gold(I) Complexes Having One Low-Coordinating Ligand as Catalysts for the Selective Hydration of Substituted Alkynes at Room Temperature without Acidic Promoters

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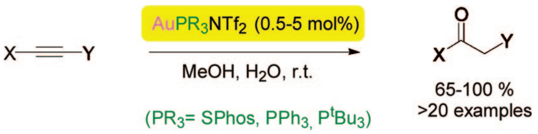
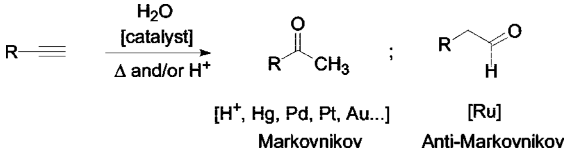


Hydration of a wide range of alkynes to the corresponding ketones has been afforded in high yields at room temperature by using gold(I)−phosphine complexes as catalyst, with no acidic cocatalysts required. Suitable substrates covering alkyl and aryl terminal alkynes, enynes, internal alkynes, and propargylic alcohols, including enantiopure forms, are cleanly transformed to the corresponding ketones in nearly quantitative yields. Acid-labile groups present in the substrates are preserved. The catalytic activity strongly depends on both the nature of the phosphine coordinated to the gold (I) center and the softness of the counteranion, the complex AuSPhosNTf$_2$ showing the better activity. A plausible mechanism for the hydration of alkynes through ketal intermediates is proposed on the basis of kinetic studies. The described catalytic system should provide an efficient alternative to mercury-based methodologies and be useful in synthetic programs.

Introduction

The hydration of alkynes to give the corresponding carbonyl compounds (Scheme 1) represents a model of modern, sustainable transformation in chemistry: waste-free, water as reagent, and catalytic.[1−3] Curiously, although this reaction has been known since the 19th century,[4] its potential in organic synthesis and/or in industrial processes has not been conveniently exploited. The reason for that is the more active catalysts known to date, HgO−H_2SO_4 (Kucherov catalyst)[4,5] and HgO−BF_3 (Hennion−Nieuwland catalyst)[6] are highly toxic mercury salts that, in addition, must be used in combination with either Bronstead or Lewis acids.[7] However, these catalysts were extensively used in high-scale industrial processes[8] until the discovery of the toxicity of mercury salts.

SCHEME 1. Catalytic Hydration of Alkynes



Alternative catalysts for the hydration of alkynes have been searched for over the past 30 years, including Bronsted acids, bases, and metal salts and complexes.[2] However, neither of them has been able to surpass the activity of those systems containing mercury salts. Among them, it is worth mentioning those systems where simple salts, such as $PdCl_2$[9] or Zeise's dimer $[\{PtCl_2(C_2H_4)\}_2]$,[10] were used, along with the recently reported anti-Markornikov hydration of alkynes catalyzed by ruthenium complexes.[3] However, as far as we know, a common characteristic for most of the catalytic systems described until now, including the HgO catalysts, indicates that the use of an additional acid or the heating of the system, or both, are absolutely necessary in order to obtain good results. Very few examples can be found where simple alkynes are hydrated by

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(2) Hintermann, L.; Labonne, A. *Synthesis* **2007**, *8*, 1121.
(3) Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507.
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(6) (a) Hennion, G. F.; Killian, D. B.; Vaughn, T. H.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1934**, *56*, 1130. (b) Nieuwland, J. A.; Vogt, R. R.; Foohey, W. L. *J. Am. Chem. Soc.* **1930**, *52*, 1018.
(7) (a) Killian, D. B.; Hennion, G. F.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1934**, *56*, 1786. (b) Killian, D. B.; Hennion, G. F.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1936**, *58*, 80.
(8) Acetaldehyde. In *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH: Weinheim, 2006.
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10.1021/jo802558e CCC: $40.75

SCHEME 2. Two Ways To Obtain the Cation Gold(I) Triphenylphosphine

$$\mathrm{Ph_3PAuCH_3 + H^+ \longrightarrow \boxed{Ph_3PAu^+} + CH_4\uparrow}$$

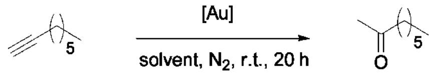
$$\mathrm{Ph_3PAuCl + AgX \longrightarrow \boxed{Ph_3PAu^+}\,X^- + AgCl\downarrow}$$

using a transition metal species at room temperature without help of acidic additives.[11]

Gold chemistry has experienced a great revival in the last years because of the unexpected properties of the supported metal in the nanoparticle size[12,13] and the reactivity of its compounds.[13] In particular, gold shows a high affinity for alkynes as a Lewis acid.[14] The "alkynephilicity" of gold resembles that of mercury, and this behavior has been attributed to the common electronic properties for these two elements in the valence shell, in part due to relativistic effects.[15] Therefore, the use of gold instead of mercury as catalyst for the hydration of alkynes is worthy of study. Thus, Utimoto[16] and Teles[17] applied gold salts and complexes as catalysts for the hydration of alkynes and, more recently, Hayashi and Tanaka,[18] Laguna,[19] and others.[20] They generally reported good yields, especially when gold(I) complexes were combined with strong acids as catalysts under heating. The active catalytic species in these reactions is the cationic gold complex $[(Ph_3P)Au]^+$, generated in situ from $[(Ph_3P)AuCH_3]$ after treatment with a strong acid and release of CH_4[17] (Scheme 2). The excess acid can act as both cocatalyst and stabilizer of the cationic gold (I) species under heating conditions.[19]

Although the results obtained with those acid-generated gold(I) cationic complexes are excellent, the window of application in more elaborated compounds is narrow, since a moderate acidic media under heating is necessary. A more favorable media would be obtained if the gold(I) cation is generated by a well-known procedure[21] (Scheme 2) where the corresponding chloride complexes are treated in situ with a silver salt, thus precipitating AgCl and forming the new complex. A soft, noncoordinating anion such a triflate (OTf) or bis(trifluoromethanesulfonyl)imidate (NTf_2) would make the Au(I) catalytic center sufficiently acidic to perform the reaction without additives. Moreover, this acidity can be modulated by changing both the counteranion and the phosphine present in the complex. These complexes will ultimately be isolated and used directly as stable-bench solids. We report here the results obtained for the hydration of alkynes using isolable gold(I) cationic complexes at room temperature.

TABLE 1. Optimization of the Catalyst, Solvent, and Water Amount for the Hydration of 1-Octyne to 2-Octanone at Room Temperature



entry	solvent	catalyst[a] (mol % of Au)	water (equiv)	ketone[b] (%)
1	DCM	$AuClPPh_3$ + AgOTf (5)		24
2		$AuClPPh_3$ + AgOTf (5)	1.5	7
3		$AuClPPh_3$ + AgOTf (5)	4	<1
4	THF	$AuClPPh_3$ + AgOTf (5)	1	18
5		$[AuPPh_3OTf]$ (5)	1	76
6	CH_3CN	$[AuPPh_3OTf]$ (5)	1	31
7	toluene	$[AuPPh_3OTf]$ (5)	1	5
8	THF	$(PPh_3Au)_3OBF_4$ (5)	1	0
9		$[Au(CF_3C_6H_4)_3POTf]$ (5)	1	30
10		$[AuPEt_3OTf]$ (5)	1	37
11		$[AuP^tBu_3OTf]$ (5)	1	90
12		$AuPPh_3NTf_2$ (5)	1	87
13		$[AuPPh_3OTf]$ (1)	1	0
14		$AuPPh_3NTf_2$ (1)	1	6
15		$AuPPh_3NTf_2$ (1)	4	19
16	MeOH	$AuPPh_3NTf_2$ (1)	4	100
17	EtOH[c]	$AuPPh_3NTf_2$ (1)	4	55
18	^{i}PrOH	$AuPPh_3NTf_2$ (1)	4	22

[a] $AuClPR_3$ + AgX refers to reactions where the AgCl has not been removed by filtration; $[AuPR_3X]$ refers to the filtrated catalyst, and $AuPR_3X$ refers to the pure, isolated compound. [b] GC yield. [c] Denaturalized EtOH containing ppms of thiols gave results similar to those for EtOH-grade HPLC.

Results and Discussion

Study of the Reaction Conditions: Synthesis and Optimization of the Catalysts. The hydration of 1-octyne to 2-octanone catalyzed by different gold(I) cationic complexes was selected as the standard reaction. The results obtained for different catalysts, water amounts, and solvents are shown in Table 1.

As can be seen, the use of in situ generated $AuPPh_3OTf$ in standard nondry dichloromethane solvent gave a surprising 24% of ketone (entry 1). However, addition of more water resulted in a decreased yield, probably due to formation of two phases. THF, a water-miscible solvent, was found to be a suitable solvent under similar conditions, and more importantly, an excellent 76% yield was obtained when the precipaged AgCl was removed from the medium by filtration (compare entries 4 and 5). A systematic study of the catalyst was then accomplished in this solvent. It was found that a bulky donor phosphine such as $^tBu_3P$ was equally suitable when using OTf as counteranion (entry 11). However, an important increase in the yield of ketone was observed when the counteranion was varied from OTf to the softer, less-coordinating NTf_2 (see also Figure 1 below).[22,23] This reflects the cationic nature of the metallic active site, which is free to interact with the alkyne when a less-coordinating anion is present. As expected, the water-miscible solvents are more suitable for the hydration since they admit more equivalents of water in order to accelerate the reaction, with MeOH being the

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(11) (a) Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, *31* (1), 12. In some cases, thermal heating without acidic promoters can be enough to achieve the hydration, see: (b) Chang, H.; Datta, S.; Das, A.; Odedra, A.; Liu, R. *Angew. Chem., Int. Ed.* **2007**, *46* (25), 4744.

(12) (a) Budroni, G.; Corma, A. *Angew. Chem., Int. Ed.* **2006**, *45* (20), 3328. (b) Corma, A.; Serna, P. *Science* **2006**, *313* (5785), 332. (c) Abad, A.; Concepcion, P.; Corma, A.; Garcia, H. *Angew. Chem., Int. Ed.* **2005**, *44* (26), 4066.

(13) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896.

(14) Jimenez-Nuñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333.

(15) Gorin, D. J.; Toste, F. D. **2007**, *446*, 395.

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(17) (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37* (10), 1415. (b) Teles, J. H.; Schulz, M. *Chem. Abstr.* **1997**, *127*, 121–499; BASF AG, WO-A1 9721648, 1997.

(18) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41* (23), 4563.

(19) Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925.

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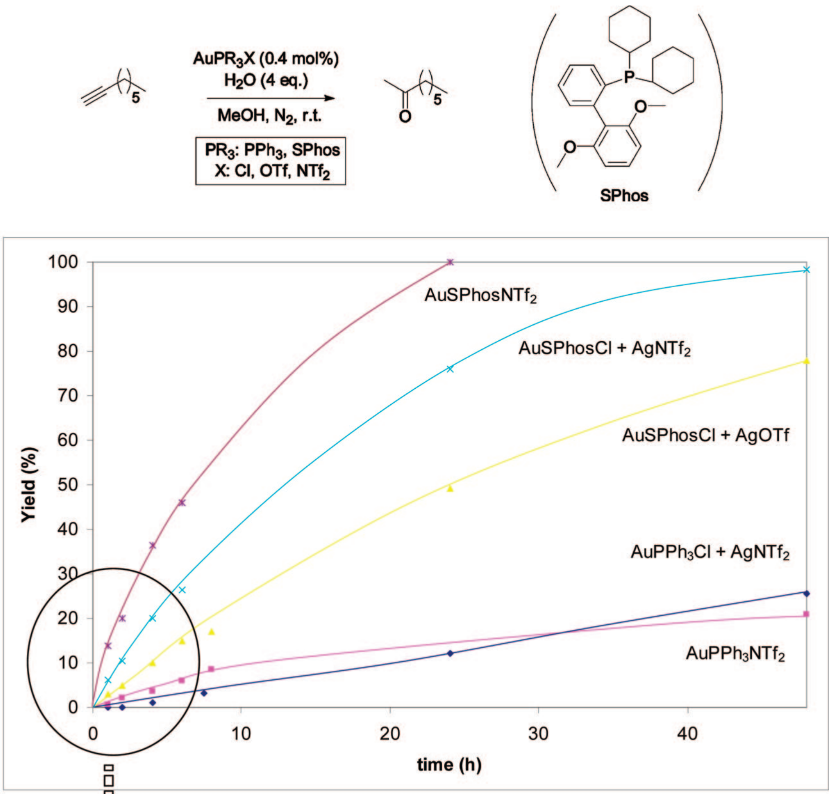
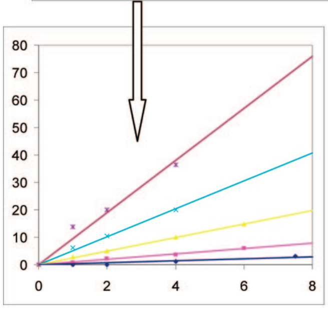
(21) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

(22) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7* (19), 4133. In the present work, the commercially available, dimeric toluene adduct $AuPPh_3NTf_2$ complex (Sigma-Aldrich) is used.

(23) Mathieua, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219.

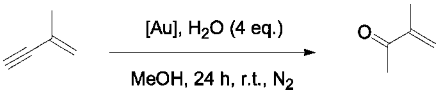




Entry	Catalyst	TOF$_0$ [mmol product / (mmol catalyst x h)]
1	AuSPhosNTf$_2$	23.7
2	AuSPhosCl + AgNTf$_2$	12.7
3	AuSPhosCl + AgOTf	6.2
4	AuPPh$_3$NTf$_2$	2.4
5	AuPPh$_3$Cl + AgNTf$_2$	0.9

FIGURE 1. Kinetic study for different gold catalysts: AuSPhosNTf$_2$ (∗), AuSPhosCl + AgNTf$_2$ (×), AuSPhosCl + AgOTf (▲), AuPPh$_3$Cl + AgNTf$_2$ (■), AuPPh$_3$NTf$_2$ (♦).

TABLE 2. Hydration of 2-Methylbuten-3-yne



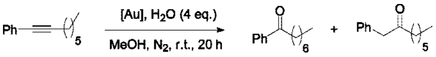
entry	catalyst (mol % of Au)	ketone[a] (%)
1	AuPPh$_3$NTf$_2$ (2)	32
2	AuPPh$_3$NTf$_2$ (5)	73
3	AuSPhosNTf$_2$ (5)	90

[a] GC yield.

solvent of choice (entry 16). However, the use of others alcoholic solvents clearly decreased the reaction rate, which is related to the formation of ketals as intermediates (entries 16−18, see the mechanism study below).

The bis(trifluoromethanesulfonyl)imidate triphenylphosphine gold(I) complex is an easy-to-make air-stable solid recently described by Gagosz and co-workers.[22] By analogy to its procedure, and in order to improve the activity of the catalyst, we synthesized complexes containing this weakly coordinated counteranion and bulkier, better donor phosphines such as ^{t}Bu$_3$P or 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos).

TABLE 3. Hydration of Oct-1-ynylbenzene

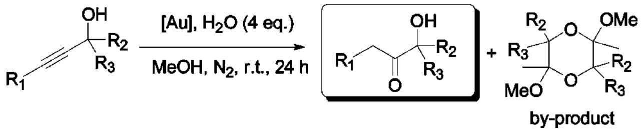


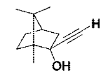
entry	catalyst (mol % of Au)	ketones[a] (%)
1	AuPPh$_3$NTf$_2$ (1)	30 (50:50)
2	AuSPhosOTf (10)	100 (60:40)
3	AuSPhosNTf$_2$ (1)	100 (60:40)

[a] GC yield. Molar ratios are shown in parentheses.

Moreover, we managed to obtain the less stable triflate derivative AuSPhosOTf in pure form as well. Thus, a second study including these isolated catalysts was undertaken under the optimal conditions found in Table 1 (MeOH as solvent, 4 equiv of water). The results obtained are shown in Table S1 (Supporting Information). A similar behavior in the catalytic activity for different gold(I) complexes, depending on the nature of the phosphines and the counteranion, was obtained by using MeOH as solvent instead of THF (compare, for instance, entries 5 and 8 in Table S1, Supporting Information with entries 11 and 9 in Table 1, respectively). Incidentally, the presence of AgCl does not have as a dramatic effect in MeOH as in THF (compare entries 3 and 4, 6 and 7). More importantly, the use of bulky

TABLE 4. Hydration of Different Propargylic Alcohols



Entry	R_1	R_2	R_3	Catalyst (mol Au%)	α-Hydroxyketone (%)[a]
1	H	H	H	$AuPPh_3NTf_2$ (2)	85 (15)[b]
2				$AuSPhosNTf_2$ (0.5)	70 (30)[c]
3	H	pentyl	H	$AuPPh_3NTf_2$ (1)	30
4				$AuSPhosNTf_2$ (1)	>95
5	H	Me	H	$AuSPhos NTf_2$ (1)	84 (11)
6				$AuSPhosNTf_2$ (1)[b,d]	97 (2)
7	H	Me	Me	$AuPPh_3NTf_2$ (2)	<10
8				$AuSPhosNTf_2$ (2)	52
9				$AuSPhosNTf_2$ (5)	43[e]
10				$AuPPh_3NTf_2$ (2, 10, 2 and 60 °C)	<10[f]
11				$AuSPhosNTf_2$ (5)	<10

[a] GC yield. Yields of byproducts are shown in parentheses. [b] After 48 h. [c] When $AuPPh_3NTf_2$ (5 mol %) was used, no solvent was required to obtain a 72% yield. [d] System diluted four times, 16 equiv of water. [e] 53% product recovered after workup, together with a 15% of the Schuster−Meyer rearrangement product formed during workup. [f] Byproduct in some cases.

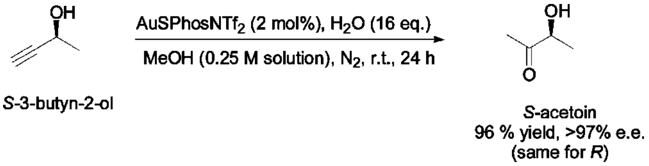
donor phosphines such $^tBu_3P$ or SPhos instead of PPh_3 improved the results again (entries 5, 6, 13, and 14). Similarly, the use of the less-coordinating NTf_2 led to optimal results (entry 14). Unfortunately, the use of a even less-coordinating anion such as $B(C_6F_5)_4$ just inhibited the reaction (entry 15). Since the yield obtained after prolonged reaction times depends not only on the intrinsic activity but also on the stability of the catalyst, a kinetic study was accomplished in order to assess the initial rate and, therefore, the intrinsic activity of the catalysts (Figure 1).

As expected, $AuSPhosNTf_2$ gave the best result in terms of both activity and stability over time, improving in 1 order of magnitude the initial rate obtained with $AuPPh_3NTf_2$ (entry 1 vs 4). The result shows clearly the importance of the phosphine for the catalytic activity of the complex, being even more relevant than the coordination ability of the counteranion (compare NTf_2 vs OTf, entries 2 and 3).

Scope of the Reaction. $AuSPhosNTf_2$ was found to be the best catalyst for all cases studied. This is particularly interesting since this complex is prepared in nearly quantitative yield from the corresponding starting materials (see the Experimental Section) and can be weighed in the open air. Under the optimal experimental conditions found for the hydration of 1-octyne, $AuSPhosNTf_2$ was further compared to $AuPPh_3NTf_2$ for the hydration of a wide range of alkynes, including an enyne (Table 2), an internal alkyne (Table 3), and different propargylic alcohols (Table 4).

The presence of 1 mol % or less of $AuSPhosNTf_2$ in the reaction is sufficient to produce a complete hydration of the alkynes to the corresponding ketones in most of the cases. The same catalytic amounts of $AuPPh_3NTf_2$ gave systematically poorer results. Higher amounts of $AuSPhosNTf_2$ are necessary when sterically demanding alkynes are used (Table 2, entry 3; Table 4, entries 8 and 9). A highly bulky propargylic alcohol such as the camphor derivative in Table 4 (entries 10 and 11) did not react even in the presence of 5 mol % of $AuSPhosNTf_2$.

SCHEME 3. Hydration of the Two Enantiomers of a Chiral Propargylic Alcohol



The results obtained for propargylic alcohols are particularly relevant, since these compounds are prone to give side reactions under acidic or heating conditions, namely the Meyer−Schuster or Rupe rearrangements,[24] or simply polymerize. As mentioned above, the majority of reports for the hydration of alkynes need such conditions, and scarce examples about efficient hydration of propargylic alcohols can be found in the literature except when Kucherov conditions are used.[25] In contrast, the results in Table 4 show that the use of the neutral, mild conditions reported herein avoid side reactions, giving cleanly the corresponding α-hydroxy ketones in high yields. These products are of paramount importance as building blocks for more elaborated molecules, especially those having the hydroxylic carbon as a chiral center. Therefore, the hydration of the chiral propargylic alcohol 3-butyn-2-ol, in the two enantiomerically pure forms *S* and *R*, was tested under the reaction conditions depicted in Scheme 3.

The corresponding *S* and *R* acetoins were cleanly obtained at room temperature; no racemization was found by chiral GC and optical rotation analysis. The same results were obtained with half the catalyst (1 mol %) after 48 h. This simple and practical way to obtain chiral α-hydroxy ketones represents an alternative to current processes such as enzymatic resolution or the enantiomeric hydrogenation of diketones, since the starting materials can be easily prepared by controlled addition of the corresponding alkyne to enantiomerically pure epoxides, which are obtained by Jacobsen's kinetic resolution.

A last comparison study of the two catalysts $AuPPh_3NTf_2$ and $AuSPhosNTf_2$ was performed with molecules containing acid-labile protecting groups. It would be extremely useful in synthesis to have a general protocol for the hydration of triple bonds in the presence of different protecting groups, something lacking in the literature. Thus, alkynes containing different silicon-protected groups as well as a trityl group were prepared and tested under optimized conditions (Table 5). Unfortunately, the TMS group was found to be completely deprotected as either a hydroxyl or an alkynyl protecting group. However, both the more robust TBDPS and the trityl protecting groups showed a good stability under the reaction conditions.

Finally, oncewe determined that $AuSPhosNTf_2$ is the catalyst of choice, different terminal and internal alkynes containing functionalities such as hydroxyl, aryl and alkyl halides, nitro, methyl ester, and ether were hydrated at room temperature. The results obtained are shown in Table 6.

The hydration of the different alkynes is performed in high yields, preserving the functionalities present in the molecules. This means an important improvement compared to previous reports. When the substrates were not soluble solids in the reaction medium at room temperature, such as the trityl-

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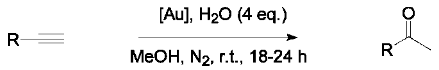
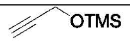
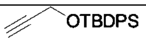
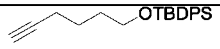
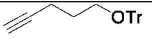
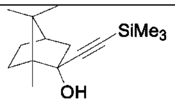
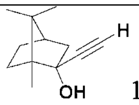
(24) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

(25) (a) Jirkovski, I.; Cayen, M. N. *J. Med. Chem.* **1982**, *25*, 1154. (b) Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045.

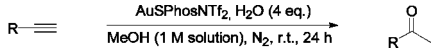
TABLE 5. Hydration of Alkynes Containing Protecting Groups

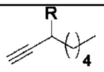
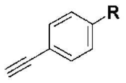
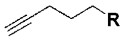
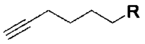
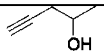


Entry	PG	Catalyst (mol Au%)	ketone (%)[a]
1		$AuPPh_3NTf_2$ (2)	0 (100)
2		$AuSPhosNTf_2$ (0.5)	0 (100)
3		$AuSPhosNTf_2$ (1)	5 (20)
4		$AuSPhosNTf_2$ (1)	85 (15)
5		$AuSPhosNTf_2$ (1)	30 (70)
6		$AuSPhosNTf_2$ (0.3)	70 (25)
7		$AuPPh_3NTf_2$ (2)	 100 %

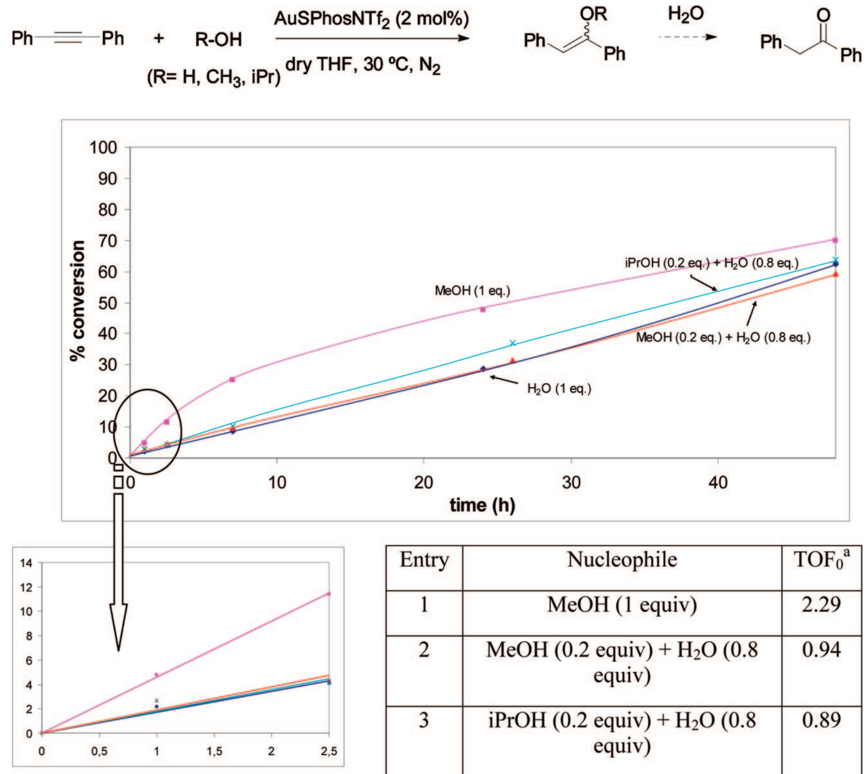
[a] GC yield. Deprotection is shown in parentheses.

TABLE 6. Scope for the Hydration of Alkynes Catalyzed by $AuSPhosNTf_2$



Entry	Alkyne	R	mol Au%	ketone (%)[a]
1		H	1[b]	>99 (93)
2		OH	1	97 (81)
3		H	1	>99[c]
4		Cl	1	>99 (89)[d]
5		OPh	1	>99 (92)
6		OH	0.1	-[e]
7		OTr	0.3	(65)
8		OH	0.5	-[e]
9		OTBDPS	1	80 (75)
10		I	1	91 (79)
11		NO_2	5[f]	>99
12		-	1	95
13	R—≡—R	Ph	2	93[g]
14		CO_2Me	1	100 (83)[h]

[a] GC yield. Isolated yield is shown in parentheses. [b] $AuPPh_3NTf_2$ used as catalyst. When $NaHCO_3$ (aq, 0.14 M, 72 μL, 1 mol %) was used instead of neat water, the hydration did not proceed at all. [c] $AuPPh_3NTf_2$ (1 mol %) gave no complete conversion. [d] Reaction time: 48 h. [e] Isolation gave the corresponding cyclized methyl ketal as major product together with a mixture that could contain the ketone. [f] $AuPPh_3OTf$ as catalyst in wet dichloromethane. [g] H_2O (16 equiv) and THF (3 mL) added to the mixture, reaction time: 48 h. Pure ketone obtained after treatment of the reaction mixture with 0.83 mL of concd aqueous HCl (5 equiv) for 5 h at rt. [h] Mixture of isomers *E*/*Z* (2:1 molar ratio). HCl treatment, as for previous entry, did not return the ketone, the mixture seeming to be stable.

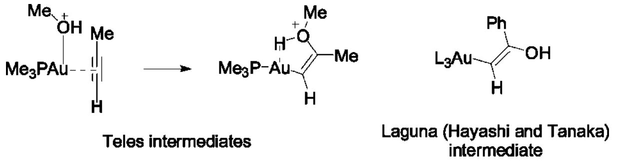


Entry	Nucleophile	TOF$_0$[a]
1	MeOH (1 equiv)	2.29
2	MeOH (0.2 equiv) + H_2O (0.8 equiv)	0.94
3	iPrOH (0.2 equiv) + H_2O (0.8 equiv)	0.89
4	H_2O (1 equiv)	0.85

[a] [mmol products / (mmol catalyst x h)]

FIGURE 2. Kinetic study for different nucleophiles: MeOH (1 equiv, ■); H_2O (1 equiv, ♦); MeOH (0.2 equiv) + H_2O (0.8 equiv, ▲); iPrOH (0.2 equiv) + H_2O (0.8 equiv, ×).

SCHEME 4. Intermediates Claimed for the Hydration of Triple Bonds Catalyzed by Gold(I) or Gold(III) Complexes



protected alkyne (entry 7) or diphenylacetylene (entry 13), the addition of DCM or THF as cosolvents solves the problem and does not hamper the final yield. For highly hydrophobic liquids, the dispersion in the aqueous methanol was good enough to produce the reaction smoothly (entries 1 and 10). The amounts of product recovered after isolation correlate with the yields obtained by GC analyses.

Mechanistic Studies: Ketals as Intermediates. Previous works on the hydration of alkynes catalyzed by gold(I) complexes agree to report methanol as the solvent of choice, but different hypotheses for the reaction mechanism are proposed. On one hand, Teles and co-workers[17] have described enol ethers and ketals as plausible intermediates in the hydration of alkynes, based on the isolation of these compounds when water is not present in the reaction medium (Scheme 4). According to that, coordination of methanol to the previously formed alkyne−cationic gold(I) phosphine would lead to an unstable tricoordinated transition species, which would evolve into the addition of the hydroxyl group to the alkyne to form the enol ether. This crowded transition state would explain the low reactivity of secondary alcohols when compared to primary alcohols, although an outer-sphere pathway would be expected to display the same selectivity. Ab initio calculations from the same authors[17] showed that the relative affinities of the different reagents for a theoretical cationic gold(I) center $[Me_3PAu]^+$ follow the order alkynes > methanol > water. This order correlates with the signals observed in low temperature ^{31}P NMR measurements when methanol and 3-hexyne are sequentially added to in situ formed $[Ph_3PAu]^+[MeSO_3]^-$.[17]

On the other hand, Hayashi, Tanaka, and co-workers[18] claimed that, although they cannot completely exclude dimethyl ketals as intermediates under their reaction conditions (strong acid as cocatalyst, 70 °C), they bank on a direct attack of water to the alkyne since the reaction proceeds in nonalcoholic solvents as well. Besides that, Pt-catalyzed hydration has also been reported to work without any formation of methanol adducts.[10] Finally, Laguna and co-workers[19] propose that the hydration of alkynes when gold(III) complexes are used as catalysts goes through direct attack of water.

To shed light on all these, apparently, contradictory conclusions, we performed a series of kinetic experiments using MeOH, H_2O, or both as nucleophiles. Diphenylacetylene was used as substrate since the corresponding methyl enol ethers are stable enough to be observed at room temperature, using $AuSPhosNTf_2$ as catalyst, in dry THF. The advantage of our methodology over previously reported reaction conditions lies in the absence of any acid promoter, the hydroxyl group interacting freely over the catalyst. The results obtained are shown in Figures 2 and 3.

According to the initial rates obtained, MeOH adds to diphenylacetylene 2.5 times faster than H_2O. A slight increase in the initial rate occurs when 20 mol % of MeOH or iPrOH in

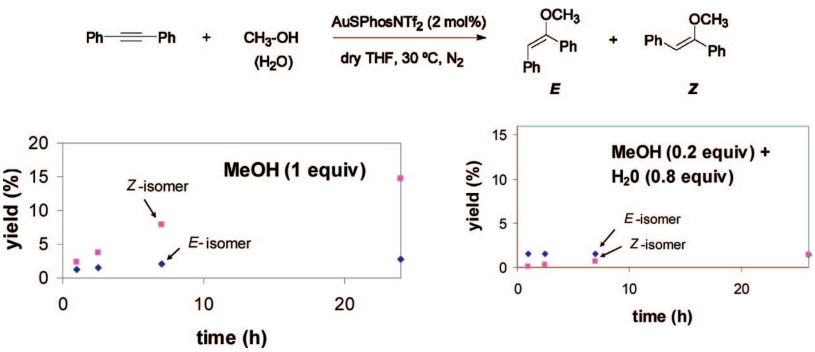
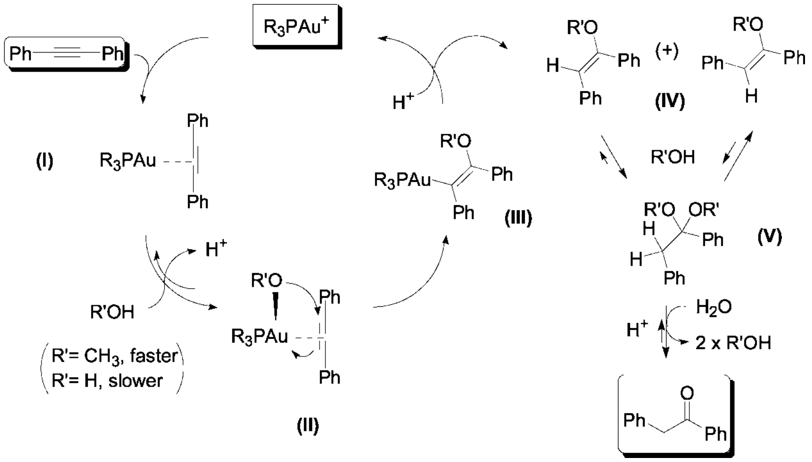


FIGURE 3. Evolution of the *Z* and *E* isomers of the corresponding methyl enol ether when MeOH or H_2O are the major nucleophile.

SCHEME 5. Plausible Mechanism for the Hydration of Alkynes Using $AuPR_3NTf_2$ Compounds as Catalysts



water is used as reagent mixture instead of pure water. These results fit those obtained for the hydration of 1-octyne to 2-octanone in MeOH, EtOH, iPrOH, and THF as solvents (100, 55, 22, and 19%, respectively, see Table 1, entries 15−18), which suggests a possible precoordination of the hydroxyl to the metal center in the transition state.[17] Concerning the formation of *Z* or *E* enol ethers, it is observed that the *Z/E* ratio increases rapidly over the time when MeOH is used as only reagent. In contrast, the *E* isomer is predominant over the *Z* isomer when pure H_2O is used, although the tendency over the time is similarly to increase the *Z/E* ratio. It has to be noted that the *Z* isomer is the more stable thermodynamically in this particular case, and this correlates with the formation of the more stable thermodynamically *E* isomer of dimethylacetylene dicarboxylate[26] as major product (see Table 6, entry 14). With this data in hand, a plausible mechanism for the hydration of alkynes using $AuPR_3NTf_2$ compounds as catalysts at room temperature is depicted in Scheme 5.

The formation of the enolic species (IV) occurs more rapidly when MeOH is used instead of water. Considering than the coordination of MeOH to the alkyne−metal complex (I) is favored over H_2O, and that this could be the controlling step, we cannot conclude which of them, MeOH or H_2O, adds preferentially to the alkyne on the tricoordinated transition state (II), as we suppose that protodeauration in (III) to regenerate the catalyst is much faster. Concerning the regioselectivity, the presence of a constant amount of the less thermodynamically stable *E* isomer over the time, regardless if water is present or not in the medium, seems to point out a *cis*-addition of the alcohol across the triple bond to form *E*-(IV). Clearly, isomerization of this *E* to the *Z* isomer occurs more rapidly over time in the absence of water (see Figure 3, MeOH 1 equiv), in contrast with the direct formation of the ketone in the presence of excess H_2O. Although more data should be compiled to check the following hypothesis, we propose that double addition of MeOH to form the corresponding dimethyl ketal (V) and subsequent demethoxylation of this intermediate would explain the formation of the *Z* from the *E* isomer. This path would be overridden when H_2O is present in the medium, since the corresponding hemiketal of (V) leads to the ketone directly. The gold catalyst could play a role in these last steps as well.

Comparison to Previous Methods. A brief study comparing our methodology to those previously reported[17,18] was carried out. The results obtained are shown in Table 7.

Both methods require similar amounts of gold at room temperature to complete the reaction (compare entries 1−4). However, our method is more selective and preserves acid-labile functional groups in a higher extent.

Conclusions

The high-efficient hydration of a wide range of alkynes to the corresponding ketones by using exclusively gold(I) phosphine complexes has been afforded at room temperature. $AuSPhosNTf_2$, an air-weighable solid, has been synthesized in high yields and proved to be the catalysis of choice in MeOH as solvent. Ketals are intermediates in this transformation since the attack of MeOH to the alkyne is faster compared to H_2O. The absence of acidic promoters allows the use of alkynes containing acid-labile groups. This methodology is milder, more

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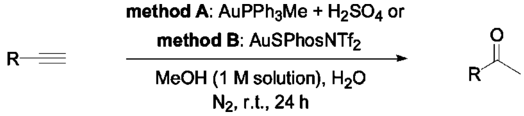
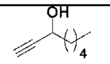
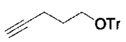
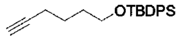
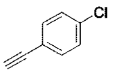
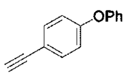
[26] Baag, M. M.; Kar, A.; Argade, N. P. *Tetrahedron* **2003**, *59*, 6489.

TABLE 7. Comparison between Gold-Catalyzed Hydration Methodologies at Room Temperature



Entry	Alkyne	Method	mol Au%	H_2SO_4 (mol%)	ketone (%)[a]
1		A	0.02	1	5
2		A	0.2	10	74
3		A	1	50	90[b]
4		B	1	-	97
5		A	0.06	3	5[c,d]
6		B	0.3	-	70[c,d]
7		A	1	50	0[d]
8		B	1	-	80[d]
9		A	1	50	67
10		B	1	-	76
11		A	1	50	99
12		B	1	-	99

[a] GC yield. [b] Complete conversion; several byproducts were found. [c] 0.5 M solution, DCM used as cosolvent (1:1). [d] The rest of material was deprotected.

selective and operationally easier than those reported before and should be of interest in the synthesis of elaborated molecules.

Experimental Section

Synthesis of $AuSPhosNTf_2$: Following a reported but modified procedure,[27] tetrachloroauric acid trihydrate (394 mg, 1 mmol) was dissolved in distilled water (1 mL) under nitrogen and the solution cooled in ice. Then, 2,2′-thiodiethanol was slowly added over 45 min until disappearance of the color (ca. 300 μL). After that, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 410 mg, 1 mmol) was added followed by 3 mL of ethanol. The mixture was stirred at rt for 3 h. The solid was filtered off and washed with methanol, redissolved in dry dichloromethane, and filtered again. The solution was concentrated to dryness to obtain AuSPhosCl as a white crystalline powder (570 mg, 89%). Following a related procedure,[22] AuSPhosCl (1.33 g, 2.07 mmol) was dissolved in dry dichloromethane (50 mL) and $AgNTf_2$ (820 mg, 2.07 mmol) was added. The mixture was stirred at rt under nitrogen for 30 min and filtered over Celite. The solution was concentrated to dryness to obtain $AuSPhosNTf_2$ as a white solid (1.83 g, quantitative). IR (cm^{-1}): 3444, 2947, 2933, 2862, 2848, 2837, 1599, 1489, 1475, 1390, 1213, 1192, 1130, 1113, 962. ^{1}H NMR (δ, ppm; J, Hz): 7.62 (1H, t, $J = 7.5$), 7.58 (1H, t, $J = 5.9$), 7.51 (1H, dt, $J = 6.0, 1.5$), 7.43 (1H, t, $J = 8.3$), 7.21 (1H, ddd, $J = 7.3, 4.3, 1.1$), 6.71 (2H, d, $J = 8.5$), 3.69 (6H, s), 2.16 (2H, mult), 2.00 (2H, mult), 1.86−1.60 (10H, mult), 1.47−1.18 (12H, mult). ^{13}C NMR (δ, ppm): 157.0 (2C), 142.6, 133.3, 131.7, 131.4, 129.8, 127.2, 125.8, 125.0, 121.5, 117.5, 104.5 (2C), 55.1 (2C), 37.0, 36.6, 30.6, 30.5, 29.5 (2C), 26.7, 26.5 (2C), 26.3, 25.7 (2C). ^{31}P NMR (δ, ppm): 38.6. Anal. Calcd for $C_{28}H_{35}AuF_6NO_6PS_2$: C, 37.89; H, 3.97; N, 1.58; S, 7.22. Found: C, 37.61; H, 3.99; N, 1.57; S, 7.05. FAB$^+$: [M$^+$; calcd for $C_{28}H_{35}AuF_6NO_6PS_2$: 887]: found m/z 887 (M$^+$), 607 (M − $N(SO_2CF_3)_2$). HRMS (ESI): [(M − $N(SO_2CF_3)_2)^+$ calcd for $C_{26}H_{35}AuO_2P$: 607.2040], found m/z 607.2033

Typical Hydration Procedure. $AuSPhosNTf_2$ (17.8 mg, 1 mol %) was placed in a round-bottomed flask under nitrogen. MeOH (2 mL), 1-ethynyl-4-phenoxybenzene (361 μL, 2 mmol), and H_2O (144 μL, 4 equiv) were sequentially added, and the mixture was magnetically stirred at rt for 24 h. Then, a sample was taken for GC analysis, and the mixture was diluted in dichloromethane (20 mL) and extracted with water (10 mL). The water was extracted with dichloromethane (10 mL), and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 1-(4-phenoxyphenyl)ethanone (390 mg, 92%).

Acknowledgment. A.L. thanks CSIC for financial support under the JAE-doctors program.

Supporting Information Available: General methods, experimental procedures including syntheses and characterization of catalysts and substrates, kinetics and reaction procedures, and ^{1}H, ^{13}C, DEPT, and ^{31}P NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802558E

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(27) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.