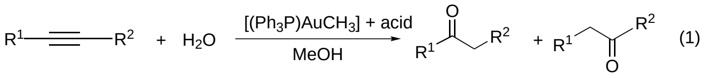
Highly Efficient Au^I-Catalyzed Hydration of Alkynes**

Eiichiro Mizushima, Kazuhiko Sato,
Teruyuki Hayashi,* and Masato Tanaka*

Hydration of unsaturated carbon compounds is one of the most straightforward and environmentally benign methods to form the carbon–oxygen bond. Synthesis of carbonyl compounds by the hydration of alkynes is an important variation in this category, which has been extensively studied.[1] Acid-catalyzed hydration of alkynes is long known.[2,3] However, only electron-rich acetylene compounds, such as alkynyl ethers, alkynyl thioethers and ynamines react satisfactorily.[1d,4] The reaction of simple alkynes is usually sluggish and needs cocatalysts, typically toxic mercury(II) salts, to enhance the reactivity.[5] More recent interest lies in the use of transition-metal-complex catalysts containing Ru^{II},[6] Ru^{III},[7] Rh,[8] Pt,[9] Au^{III},[10] and other metal centers.[11] However, the process catalyzed by these complexes is not efficient either. The highest turnover frequency (TOF) is 550 h^{-1} claimed as the initial TOF for the hydration of 3-pentyn-1-ol catalyzed by [*cis*-$PtCl_2(tppts)_2$] (tppts = $P(m\text{-}C_6H_4SO_3Na)_3$), but its overall TOF is no more than approximately 100 h^{-1}.[9c] Recently Teles and co-workers reported the addition of methanol to alkynes catalyzed by Au^I species in conjunction with acidic cocatalysts.[12] Hydration of propargyl alcohol was also briefly mentioned in their patent application,[13] although the yield was quite low.[14] Herein we report that the Au^I–acid systems in aqueous methanol serve as powerful catalysts,[15] which promote the hydration of alkynes [Eq. (1)] and have turnover frequencies of at least two orders of magnitude higher than [*cis*-$PtCl_2(tppts)_2$].



In a preliminary experiment, a mixture of 1-octyne (1 mmol), [$(Ph_3P)AuCH_3$] (0.01 mmol, 1 mol%) and concentrated sulfuric acid (0.5 mmol, 50 mol%) in aqueous methanol (1.5 mL, methanol:H_2O = 2:1 v/v) was heated for 1 h at 70 °C affording the corresponding Markovnikov hydration product, 2-octanone, in 95% yield without anti-Markovnikov hydration, or possible methanol addition.[12] The reaction did not proceed in the absence of either the Au catalyst or sulfuric acid.

The following aspects about the catalytic system are worth noting. First, the nature of the reaction medium significantly affects the reaction. The reaction run without using solvent (in otherwise the same conditions as the preliminary experiment) did not furnish 2-octanone. On the other hand, the use of 2-propanol (71%), dioxane (56%), acetonitrile (53%), or THF (11%) resulted in a low yield, and the yield obtained with dichloromethane, DMF, or toluene was even lower. Thus methanol was the solvent of choice for this particular transformation.[16]

Second, the efficiency of the catalyst was significantly enhanced by addition of appropriate ligands, which enabled the quantity of the precious catalyst used to be minimized. For instance, the control experiment run without ligand addition under the conditions shown in Table 1 (only 0.01 mol% catalyst) gave 2-octanone in only 35% yield (TOF = 3500 h^{-1}, entry 1), while the yield dramatically increased to 99% when the reaction was carried out under an atmosphere of carbon monoxide (TOF = 9900 h^{-1}, entry 2). Addition of triphenyl phosphite (2 equiv relative to Au) also boosted the yield, to 90% (TOF = 9000 h^{-1}, entry 3). The reaction of phenylacetylene under the standard conditions of Table 1 gave a 14% yield of acetophenone (TOF = 1400 h^{-1}), while the same reaction carried out under an atmosphere of carbon monoxide resulted in a 33% yield (TOF = 3300 h^{-1}). Although the provenance of the ligand effect is ambiguous at this time, it is envisaged to be associated with the stability of the catalyst. The reactions without the addition of ligand occasionally proceeded with catalyst deterioration, which could be observed as metallic particle precipitation. However, when these reactions were run in the presence of CO, phosphites, or ethyl diphenylphosphinite, particle formation was not evident. On the other hand, addition of triphenylphosphane resulted in a total loss of catalytic activity.

Table 1. Hydration of 1-octyne in methanol.[a]

Entry	Acid	Additive	Yield[b]
1	H_2SO_4	–	35%
2	H_2SO_4	CO (1 atm)	99%
3	H_2SO_4	$(PhO)_3P$ (0.004 mmol)	90%
4	CF_3SO_3H	–	99%
5	CH_3SO_3H	–	77%
6	$H_3PW_{12}O_{40}$	–	80%

[a] Reaction conditions: [$(Ph_3P)AuCH_3$] 0.002 mmol, acid 0.5 mmol, 1-octyne 20 mmol, water 1 mL, methanol 10 mL, 70 °C, 1 h. [b] GC yield of 2-octanone.

Third, other acid catalysts, such as CF_3SO_3H, CH_3SO_3H, and $H_3PW_{12}O_{40}$ (entries 4–6) also gave extremely high yields even in the absence of the coordinative additives. The reaction of 1-octyne in the presence of CF_3SO_3H using only 0.005 mol% of the gold catalyst under otherwise the same conditions as those in entry 4 gave a 70% yield (TOF = 14000 h^{-1}). Since the activity was already high, the effect of carbon monoxide was only marginal, but a distinct increase in the yield to 78% (TOF = 15600 h^{-1}) was obtained when the reaction was run under an atmospheric pressure of carbon monoxide. The turnover frequency reported herein is the highest recorded.

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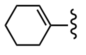
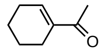
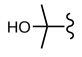
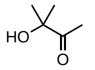
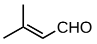
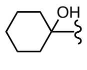
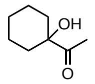
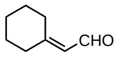
[*] Dr. T. Hayashi, Prof. Dr. M. Tanaka, Dr. E. Mizushima, Dr. K. Sato
National Institute of Advanced Industrial Science and Technology
Tsukuba Central 5, Tsukuba, Ibaraki 305-8565 (Japan)
Fax: (+81) 298-61-4511
E-mail: t.hayashi@aist.go.jp
m.tanaka@res.titech.ac.jp
Prof. Dr. M. Tanaka
Chemical Resources Laboratory
Tokyo Institute of Technology
4259 Nagatsuta, Midori-ku, Yokohama 226-8503 (Japan)
Fax: (+81) 45-924-5244

[**] E.M. thanks the NEDO for a postdoctoral fellowship.

0044-8249/02/4123-4563 $ 20.00+.50/0

Table 2. Gold(I)-catalyzed hydration of alkynes, see Equation (1).[a]

Entry	Alkynes R¹	 R²	Adducts	Cat. mol %	Time	Yield[b]	
1[c]	n-C_6H_{13}	H	n-$C_6H_{13}C(O)CH_3$	0.1	1 h	80 %	
2[d]	n-C_4H_9	H	n-$C_4H_9C(O)CH_3$	0.2	2 h	99 %	
3		H		1.0	1 h	90 %	
4	$NC(CH_2)_3$	H	$NC(CH_2)_3C(O)CH_3$	0.2	1 h	83 %	
5[e]	$Cl(CH_2)_3$	H	$Cl(CH_2)_3C(O)CH_3$	1.0	4 h	72 %	
6		H	 	1.0	2 h	44 %[f]	20 %[g]
7[h]		H	 	1.0	2 h	45 %[f]	17 %[g]
8[i]	C_6H_5	H	$C_6H_5C(O)CH_3$	0.2	1 h	98 %	
9	o-$CH_3OC_6H_4$	H	o-$CH_3OC_6H_4C(O)CH_3$	0.2	1 h	95 %	
10	m-$CH_3OC_6H_4$	H	m-$CH_3OC_6H_4C(O)CH_3$	1.0	1 h	77 %	
11	p-$CH_3OC_6H_4$	H	p-$CH_3OC_6H_4C(O)CH_3$	0.2	1 h	93 %	
12[i]	p-$CH_3C_6H_4$	H	p-$CH_3C_6H_4C(O)CH_3$	0.2	1 h	96 %	
13	o-ClC_6H_4	H	o-$ClC_6H_4C(O)CH_3$	0.2	1 h	66 %	
14	p-ClC_6H_4	H	p-$ClC_6H_4C(O)CH_3$	1.0	1 h	54 %	
15	n-C_3H_7	n-C_3H_7	n-$C_4H_9C(O)(n$-$C_3H_7)$	0.2	5 h	92 %	
16	C_6H_5	C_6H_5	$C_6H_5CH_2C(O)C_6H_5$	1.0	5 h	53 %	
17[d]	n-C_3H_7	CH_3	n-$C_4H_9C(O)CH_3$ n-$C_3H_7C(O)C_2H_5$	0.2	5 h	42 %	34 %

[a] Reaction conditions: $[(Ph_3P)AuCH_3]$, H_2SO_4 50 mol %, alkyne 1 mmol, water 0.5 mL, methanol 1–3 mL, 70 °C. [b] GC yield. [c] H_2SO_4 25 mol %, alkyne 2 mmol. [d] 60 °C. [e] Run under CO (1 atm). [f] Yield of ketone. [g] Yield of aldehyde. [h] $H_3PW_{12}O_{40}$ was used as acid in place of H_2SO_4. [i] CF_3SO_3H was used as acid in place of H_2SO_4.

The new procedure was applied to various alkynes as summarized in Table 2. Besides 1-octynes, other terminal alkynes, both aliphatic and aromatic, including those bearing functional groups such as alkoxy, cyano, chloro, and olefinic groups were all able to undergo hydration under similar reaction conditions. However, the reactivity significantly depended on the nature of the substituent, and ligand addition was occasionally required to obtain acceptable yields.

Ethynylcyclohexene and hexynonitrile reacted smoothly (entries 3 and 4) leading to the formation of the corresponding methyl ketones in good yields. Interestingly, the olefinic and cyano functional groups remained intact although these functional groups could be potentially hydrated or hydrolyzed. Conversely, the reactions of 5-chloropentyne and 5-hexyn-1-ol did not give satisfactory yields (11 and ~1 % yields in 1 h, respectively) even when 1 mol % catalyst was used (otherwise identical conditions).[17] Since metallic particle precipitation was evident in these reactions, the low activity was a result of the deterioration of the catalyst. When the reaction with 5-chloropentyne was carried out under an atmospheric pressure of carbon monoxide for 4 h, the corresponding methyl ketone was obtained with a 72 % yield (entry 5). The yield of the 5-hexyn-1-ol reaction was also improved in the presence of carbon monoxide or triphenyl phosphite, resulting in 33 and 31 % yields, respectively, over 3 h.

Propargylic alcohols, which are totally inert in the Au^{III}-catalyzed hydration,[10a] also reacted smoothly in the new procedure (entries 6 and 7). However, they afforded mixtures of methyl ketones (Markovnikov addition) and α,β-unsaturated aldehydes (anti-Markovnikov addition[6] followed by dehydration[18]), although all the other terminal alkynes examined formed only Markovnikov adducts.

Phenylacetylene derivatives having electron-donating groups (entries 8, 9, 11, and 12), reacted smoothly. However, as the results of *o*- and *p*-chlorophenylacetylenes and *m*-methoxyphenylacetylene show, electronegative groups bound to the aromatic ring appear to weaken the reactivity towards hydration, which suggest that the hydration (entries 10, 13, and 14) mechanism has an electrophilic nature.

Finally, internal alkynes displayed a low reactivity, presumably because of steric hindrance. Diphenylacetylene being less reactive (entry 16) than more electron-rich 4-octyne (entry 15) is in agreement with the forgoing statement on the nature of the hydration.

In summary, the $[(Ph_3P)AuCH_3]$ and acid catalyst systems are highly efficient in the hydration of a wide range of alkynes in aqueous methanol. The new procedure offers a valuable alternative to the Wacker oxidation, especially in the field of total synthesis.

Experimental Section

Typical procedure (entry 4, Table 1): A mixture of $[(PPh_3)AuMe]$ (1.0 mg, 0.002 mmol), CF_3SO_3H (75 mg, 0.5 mmol), water (1 mL), 1-octyne (2.2 g, 20 mmol) dissolved in methanol (10 mL) was stirred at 70 °C for 1 h. Analysis of the resulting mixture by gas chromatography showed the formation of 2-octanone in 99 % yield.

Received: July 3, 2002 [Z19655]

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[1] a) P. F. Hudrlik, A. M. Hudrlik in *The Chemistry of the Carbon-Carbon Triple Bond, Part 1* (Ed.: S. Patai), Wiley, New York, **1978**, p. 199; b) G. H. Schmid in *The Chemistry of the Carbon-Carbon Triple Bond, Part 1* (Ed.: S. Patai), Wiley, New York, **1978**, p. 275; c) R. C. Larock, W. W. Leong in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford,

1991, p. 269; d) J. March, *Advanced Organic Chemistry*, Wiley, New York, **1992**, p. 762.

[2] a) A. Schrohe, *Chem. Ber.* **1875**, *8*, 367; b) A. Baeyer, *Ber.* **1882**, *15*, 2705; c) W. H. Perkin, Jr., *J. Chem. Soc.* **1884**, *45*, 170.

[3] a) T. Tsuchimoto, T. Joya, E. Shirakawa, Y. Kawakami, *Synlett* **2000**, *12*, 1777; b) Y. Izumi, *Catal. Today* **1997**, *33*, 371; c) I. V. Kozhevnikov, *Chem. Rev.* **1998**, *98*, 171.

[4] a) W. Drenth, H. Hogeveen, *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 1002; b) A. D. Allen, Y. Chiang, A. J. Kresge, T. T. Tidwell, *J. Org. Chem.* **1982**, *47*, 775, and references therein.

[5] a) V. Jäger, H. G. Viehe in *Methoden Org. Chem. (Houben-Weyl) 4th ed. 1952–, Vol. 5/2a* **1977**, p. 726; b) M. Kutscheroff, *Chem. Ber.* **1884**, *17*, 13; c) R. J. Thomas, K. N. Campbell, G. F. Hennion, *J. Am. Chem. Soc.* **1938**, *60*, 718; d) G. W. Stacy, R. A. Mikulec in *Organic Syntheses, Coll. Vol. 4* (Ed.: N. Rabjohn), Wiley, New York, **1963**, p. 13; e) G. A. Olah, D. Meider, *Synthesis* **1978**, 671.

[6] a) M. Tokunaga, Y. Wakatsuki, *Angew. Chem.* **1998**, *110*, 3024; *Angew. Chem. Int. Ed.* **1998**, *37*, 2867; b) T. Suzuki, M. Tokunaga, Y. Wakatsuki, *Org. Lett.* **2001**, *3*, 735; c) M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi, Y. Wakatsuki, *J. Am. Chem. Soc.* **2001**, *123*, 11917; d) D. B. Grotjahn, C. D. Incarvito, A. L. Rheingold, *Angew. Chem.* **2001**, *113*, 4002; *Angew. Chem. Int. Ed.* **2001**, *40*, 3884.

[7] a) J. Harpern, B. R. James, A. L. W. Kemp, *J. Am. Chem. Soc.* **1961**, *83*, 4097; b) J. Harpern, B. R. James, A. L. W. Kemp, *J. Am. Chem. Soc.* **1966**, *88*, 5142; c) T. Khan, S. B. Halligudi, S. Shukla, *J. Mol. Catal.* **1990**, *58*, 299.

[8] a) B. R. James, G. L. Rempel, *J. Am. Chem. Soc.* **1969**, *91*, 863; b) J. Blum, H. Huminer, H. Alper, *J. Mol. Catal.* **1992**, *75*, 153.

[9] a) W. Hiscox, P. W. Jennings, *Organometallics* **1990**, *9*, 1997; b) W. Baidossi, M. Lahav, J. Blum, *J. Org. Chem.* **1997**, *62*, 669; c) L. W. Francisco, D. A. Moreno, J. D. Atwood, *Organometallics* **2001**, *20*, 4237.

[10] a) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729; b) Y. Fukuda, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013.

[11] a) K. Imi, K. Imai, K. Utimoto, *Tetrahedron Lett.* **1987**, *28*, 3127; b) I. K. Meier, J. A. Marsella, *J. Mol. Catal.* **1993**, *78*, 31.

[12] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.

[13] J. H. Teles, M. Schulz BASF AG, WO-A1 9721648 **1997** [*Chem. Abstr.* **1997**, *127*, 121499].

[14] The authors reported 200–400 turnovers for propynol and but-1-yn-3-ol, however, the product yield was no more than approximately 2 and 6%, respectively.

[15] a) For catalysis by gold species, see: G. Dyker, *Angew. Chem.* **2000**, *112*, 4407; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237; b) A special issue on gold catalysis has appeared: *Catal. Today* **2002**, *72*, whole issue.

[16] One reviewer pointed out a possible mechanism that involves methanol addition forming a dimethyl acetal as a transient intermediate, which is rapidly hydrolyzed under the acidic conditions to give the final ketone product. Although we are unable to rigorously exclude this possibility when the reaction is run in methanol, the following points strongly support the theory that the reaction involves the direct attack of water. First, the hydration reaction reported herein proceeds in non-alcoholic solvents. Second, the regiochemistry of the hydration reaction is not in full agreement with the methanol addition reaction. In addition, the [*cis*-$PtCl_2(tppts)_2$]-catalyzed reaction of alkynes in aqueous methanol showed that hydration proceeds preferentially, without forming the methanol adduct.[9a] Note that this platinum-catalyzed hydration was run in the absence of acid promoters.

[17] The reaction of 5-hexyn-1-ol did not form any other product and the substrate could be recovered nearly quantitatively.

[18] Acid-catalyzed Rupe-type rearrangement of the starting propargylic alcohols appeared to be another possibility leading to the formation of the α,β-unasturated aldehydes. However, the following control experiments exclude this possibility. A reaction similar to entry 7, Table 2 run using only $H_3PW_{12}O_{40}$ in the absence of the gold complex did not furnish the α,β-unsaturated aldehyde and the 1-ethynyl-1-cyclohexanol was recovered quantitatively. Another control experiment using $H_3PW_{12}O_{40}$ and PPh_3 (1 mol% relative to 1-ethynyl-1-cyclohexanol) in the absence of the gold complex did not form the α,β-unsaturated aldehyde either. In general, Rupe rearrangement of tertiary α-acetylenic alcohols gives α,β-unsaturated ketones as the major product, which is not consistent with our observation. See: S. Swaminathan, K. V. Narayanan, *Chem. Rev.* **1971**, *71*, 429.