Ligand- and Acid-Free Gold(I) Chloride Catalyzed Hydration of Terminal Alkynes

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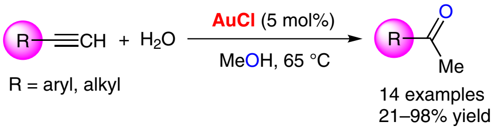

R = aryl, alkyl

14 examples
21–98% yield

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Abstract Our work shows that simple alkynes can be hydrated by the AuCl/MeOH catalyst system to afford the corresponding methyl ketones in moderate to high yields without any additive, ligand, or acid promoter. This methodology is simpler, milder, and operationally easier than those reported before. The reaction media significantly affects the reaction, and methanol is found to be the best solvent. Both aliphatic and aromatic terminal alkynes were able to undergo hydration, affording moderate to excellent yields under the reaction conditions used in the present work, and excellent functional-group tolerance was also observed. A plausible mechanism for the hydration reaction was proposed.

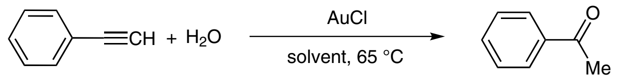
Key words hydration, alkynes, ketones, gold, homogeneous catalysis

Hydration is one of the most useful functionalizations of simple unactivated alkynes.[1] Although acids can mediate the hydration of alkynes, it generally requires a large excess of acidic reagent.[2] In the past, widely employed catalytic systems were made of toxic mercury(II) salts in acidic media.[3] To avoid the use of toxic mercury(II) salts, applications of various transition-metal catalysts containing ruthenium(II),[4] ruthenium(III),[5] rhodium,[5b,6] palladium(II),[7] copper(II)[8] or silver(I),[8] platinum,[9] gold(I),[10] gold(III),[1b,11] and other metal centers were examined. Gold compounds form an important class of catalysts, favorably replacing toxic mercury(II) salts. Gold(I) has attracted attention because it requires mild reaction conditions for product formation.[10] Gold(III)-mediated alkyne hydration has also been reported, with emphasis on terminal alkynes. Gold(III) catalysts facilitating this transformation include salts such as $NaAuCl_4$[1b] and complexes such as $BzPPh_3[Au(NHC_{mes})Cl_3]$[11a] and $[Au(NHC_{IPr})Br_3]$.[11b] Gold(I) catalysts appear to exhibit a broader substrate scope and allow a lower catalyst loading than gold(III). In particular, Hayashi and Tanaka reported the use of $[(PPh_3)AuMe]/H^+$ catalytic system that allows alkyne hydration even at 100 ppm catalyst loading.[10e] Nolan et al. established the $[Au(NHC_{IPr})Cl]/AgSbF_6$ catalytic system,[10c] which can allow hydration under acid-free conditions, using as low as 10 ppm of catalyst loading. Corma et al. reported the use of 0.5–5 mol% $[Au(SPhos)(NTf_2)]$[10d] for the hydration of mostly terminal alkynes at room temperature.

Although the reported hydration of alkynes with either acid-generated or in situ generated gold catalysts via chloride abstraction forming gold(I) cationic complexes was excellent, no study has been conducted so far using AuCl itself as a catalyst. We herein present a method by which a AuCl/MeOH catalyst system can be successfully applied to the hydration of various terminal alkynes to form ketones. This methodology is extremely simple, inexpensive, and environment-friendly; moreover, the hydration of terminal alkynes produces respective Markovnikov ketones, without any acid promoters or additives.

Hydration of phenylacetylene catalyzed by 5 mol% AuCl was chosen as the standard reaction. In a MeOH solution, hydration of phenylacetylene afforded acetophenone as the sole Markovnikov product in 98% yield. The use of 2 mol% AuCl also gave acetophenone in a good yield (Table 1, entry 4). The nature of the reaction medium significantly affected the reaction. The use of other solvents, such as EtOH (88%) and 2-PrOH (72%) resulted in lower yields, and only a trace amount of the product was obtained in both THF and MeCN. However, no product was obtained in CH_2Cl_2.

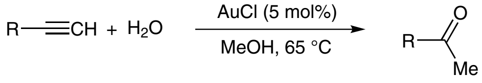
Table 1 Optimization of Reaction Conditions

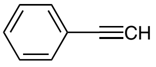
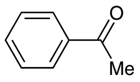
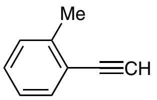
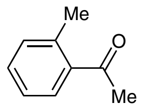
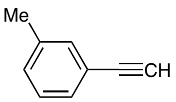
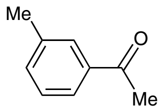
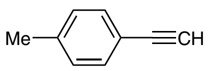
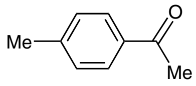
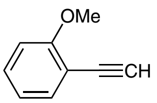
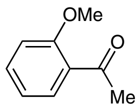
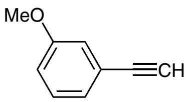
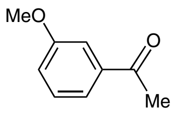
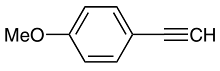
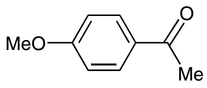
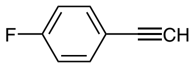
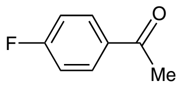
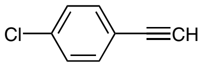
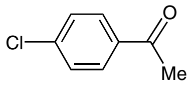
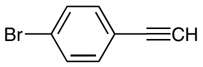
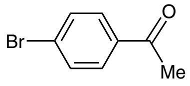
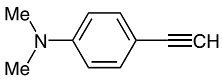
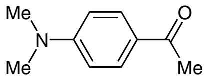
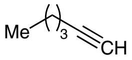
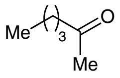
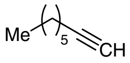
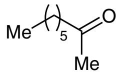
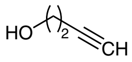
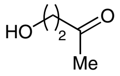


Entry	Catalyst loading (mol%)	Solvent	Time (h)	Water (equiv)	GC yield (%)[a]
1	5	MeOH	3	4	98
2	5	MeOH–CH_2Cl_2	3	4	98
3	5	MeOH–CH_2Cl_2	3	1	93
4	2	MeOH–CH_2Cl_2	3	4	82
5	5	MeOH–H_2O (1:1)	3	excess	0
6	5	EtOH	3	4	88
7	5	2-PrOH	3	4	72
8	5	MeCN	3	4	trace
9	5	THF	3	4	trace
10	5	CH_2Cl_2	3	4	0
11	5	H_2O	3	4	0

[a] GC yields are the average of at least two runs using dodecane as an internal standard.

Table 2 Hydration of Alkynes[12]



Entry	Alkyne	Ketone	Time (h)	Yield (%)[a,b]
1			3	98
2			3	98
3			3	98
4			3	98
5			3	99
6			3	95
7			3	97
8			3 24	81 98
9			24	70
10			24	67
11			3	97
12			3	82
13			3	87
14			24	21

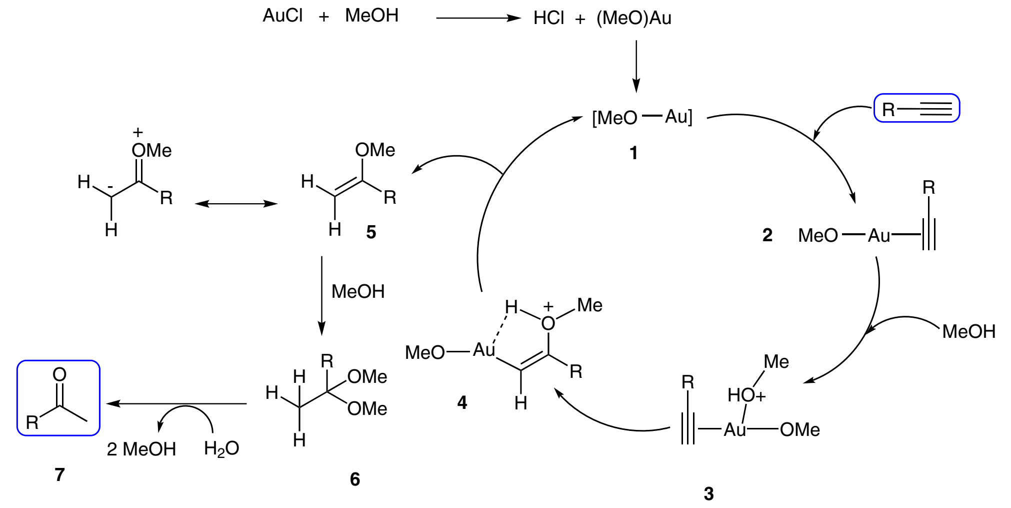
[a] Determined by GC using dodecane as an internal standard.
[b] ^1H NMR yields against 1,3,5-trimethoxybenzene as an internal standard.

The preliminary screening experiments were carried out using a stock solution of phenylacetylene by using dodecane as the internal standard in MeOH–CH_2Cl_2 (9:1). The amount of CH_2Cl_2 was kept low to make the solution homogeneous. However the reaction in only MeOH, afforded a similar yield (Table 1, entry 1). The result indicates that CH_2Cl_2 does not affect the reaction rate in any way. The hydration did not proceed in the presence of a large excess of H_2O (Table 1, entry 5). However, four equivalents of H_2O (vs. phenylacetylene) gave the best result (Table 1, entries 1 and 3).

The applicability of this catalyst system to other types of alkynes is summarized in Table 2. Besides phenylacetylene, other terminal alkynes (both aliphatic and aromatic), including those bearing functional groups such as alkoxy, chloro, bromo, fluoro, hydroxy, and tertiary amine, also underwent hydration, affording moderate to excellent yields. Substituted phenylacetylenes, such as 2-, 3-, and 4-ethynyltoluene, reacted smoothly, forming the corresponding methyl ketones in excellent yields (Table 2, entries 2–4). Similarly, 2-, 3-, and 4-methoxyphenylacetylene gave the corresponding ketones in excellent yields. The above results are in contrast with the results obtained for the [(PPh$_3$)AuMe]/H$^+$-catalyzed hydration of 3- and 4-methoxyphenylacetylene in which 4-methoxyphenylacetylene showed higher reactivity than 3-methoxyphenylacetylene.[10e] The same reaction conditions were applied to halo-substituted phenylacetylenes such as 4-fluoro-, 4-chloro-, and 4-bromophenylacetylene, and moderate to excellent yields were obtained (Table 2, entries 8–10), but longer time was needed to complete the reaction. 4-Ethynyl-*N*,*N*-dimethylaniline showed excellent reactivity, forming the corresponding ketone in 97% yield (Table 2, entry 11). Aliphatic alkynes such as 1-octyne and 1-hexyne gave the corresponding methyl ketones in good yields; when the substituents such as hydroxy groups are attached, the yield is dramatically decreased even after conducting the reaction for 24 hours (Table 2, entry 14).

Different hypotheses for the mechanism of gold(I)-catalyzed hydration of alkynes have been proposed. Tales and co-workers[10f] explained enol ethers and ketals as plausible intermediates in the hydration of alkynes, based on the isolation of these complexes when the reaction was carried out in the absence of water. Hayashi, Tanaka, and co-workers[10e] claimed that the reaction proceeded through the direct attack of water to the alkyne, based on the observation that the reaction occurred in a nonalcoholic medium. However, they cannot completely exclude the formation of dimethyl ketals as intermediates under the conditions they used. In addition, platinum-catalyzed hydration has been reported to work without forming methanol adducts.[9] Laguna and co-workers proposed that the gold(III)-catalyzed hydration of alkynes occurred by the direct attack of water.[11a] Based on theoretical calculations, Lein and coworkers reported the complete mechanism of gold(III)-catalyzed nucleophilic addition of water to an unactivated triple bond, and they claimed that the reaction is not only catalyzed by gold(III) but also catalyzed by water at the same time.[13]

The mechanism of this reaction is presumably similar to that of the reaction that forms with enol ether as a plausible intermediate.[10f] We excluded the possibility of a direct attack by water to the alkyne moiety, because no product was obtained when the reaction was carried out in large excess of water [MeOH–H$_2$O (1:1)] or in pure water (Table 1, entries 5 and 11). Only alcoholic solvents gave the respective ketone whereas no product was obtained in THF, MeCN, or CH$_2$Cl$_2$. Among the alcoholic solvents, MeOH afforded the best result (98%); the yields decreased when EtOH (88%) or 2-PrOH (72%) was used as the solvent medium. We observed that treatment of AuCl with methanol at room temperature for 15 minutes could form an active catalyst, proposed to be a [MeO–Au] species. The observation of a ^{1}H NMR peak (δ = 3.74 ppm) of the gold-coordinated methyl group (methyl group of uncoordinated MeOH showed a peak at δ = 3.37 ppm) in CD$_2$Cl$_2$ supported the formation of the [MeO–Au] complex.[14] We proposed that the [MeO–Au] complex activated the alkyne to form gold–alkyne-π complex **2** (Scheme 1). Complex **2** was then attacked by one molecule of methanol to form intermediate **3** which formed intermediate **4** after immediate rearrangement. A similar rearrangement was observed for the [(Me$_3$PAu)]/H$^+$-catalyzed addition of alcohols to alkynes, where the calculated activation energy for the rearrangement was 43 kJ mol^{-1}, and the overall process was exothermic.[10f] In recent theoretical studies, it is suggested that proton-transfer from **4** to **5** by alcoholic solvents or by water decrease activation energy significantly.[15] Further MeOH addition formed the corresponding dimethyl ketal **6** and subsequent demethoxylation of this intermediate would explain the formation of product **7**.[10d]



Scheme 1 Plausible mechanism for the hydration of alkynes using AuCl as the catalyst

In summary, we have demonstrated the hydration of terminal alkynes using a AuCl/MeOH catalyst system. This methodology is both atom-economical and operationally easier than those reported earlier and works without any additive, ligand, or acid promoter. The catalytic system showed good to excellent activity toward substituted phenylacetylene and excellent functional-group tolerance; however, it failed to hydrate internal alkynes. We proposed that [MeO–Au] is an active catalyst, and the reaction proceeds through the enol ether intermediate pathway.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560573.

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(12) **General Procedure for Alkyne Hydration**
In a 4 mL reaction vial equipped with a magnetic stirring bar, AuCl (5.8 mg, 0.025 mmol, 5 mol%) was added to MeOH (1 mL) under argon atmosphere. The reaction mixture was stirred for 5 min, and then starting material (0.5 mmol, 1.0 equiv) and internal standard dodecane (1.0 equiv) were added, followed by defined amount of distilled H_2O (4.0 equiv). The resulting reaction mixture was heated for 3 h, or for 24 h when needed, at 65 °C. After completion of the reaction, the reaction mixture was diluted and filtered using CH_2Cl_2 and injected in GC for analysis.

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