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[(NHC)Au^I]-Catalyzed Acid-Free Alkyne Hydration at Part-per-Million Catalyst Loadings

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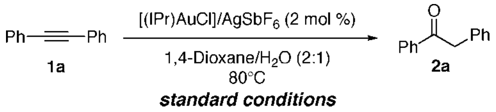
Received October 13, 2008; E-mail: sn17@st-andrews.ac.uk

The alkyne hydration reaction, leading to the formation of carbonyl derivatives, is of prime interest considering the wide availability of alkynyl substrates and the fundamental importance of the carbonyl motif in modern organic synthesis.[1] Advantageously, this reaction, based on the incorporation of a water molecule, can be considered as an outstanding example of both atom economy[2] and environmentally friendly synthetic method. The alkyne hydration reaction possesses a long history, dating back to 1881 and Kucherov's observation[3] that led to the development of a wide variety of metal-based catalytic systems.[4] Among these, gold compounds have gradually taken a prominent place, beneficially replacing toxic mercury(II) salts.[5] Notably, Hayashi and Tanaka reported the use of a [(Ph$_3$P)AuMe]/H$^+$ catalytic system allowing for a high turnover frequency (TOF) in the hydration of 1-octyne.[6] Despite its efficiency, this catalyst suffers from some drawbacks, including the use of concentrated solutions of strong acids (H$_2$SO$_4$, CF$_3$SO$_3$H) and high catalyst loadings.[7]

To palliate these deficiencies, we set out to develop a [(L)Au^I]-based catalytic system allowing alkyne hydration under mild conditions and at very low loadings. Regarding the critical choice of the supporting ligand, we focused on N-heterocyclic carbenes (NHCs)[8] since (1) they have already proven successful in the rapidly developing field of homogeneous gold catalysis[9,10] and (2) they have led, in the context of other organometallic transformations, to the development of highly efficient systems at very low catalyst loadings.[11] Herein, we report a mild and general catalytic system for alkyne hydration, using [(NHC)AuCl]/AgSbF$_6$ in 1,4-dioxane or MeOH, that displays high efficiency at part-per-million (ppm) catalyst loadings.[12]

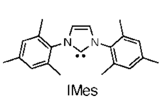
We began the optimization studies on the hydration of diphenylacetylene **1a**, relying on our previous findings that [(NHC)AuCl] complexes promote water addition-type reactions.[13] Several parameters were examined, including temperature, concentration, solvent, water/alkyne ratio, as well as the nature of the silver(I) salt and the NHC ligand; most relevant results are presented in Table 1. The equimolar combination of [(IPr)AuCl] and AgSbF$_6$ was found particularly active (entry 1). Other NHCs led to poor conversion or required extended reaction time (entries 2 and 3). Most silver(I) salts, including AgPF$_6$ (longer reaction time), AgOAc, AgOTs, and AgTFA (no reaction) proved unsatisfactory, whereas AgBF$_4$ and AgClO$_4$ were found as active as AgSbF$_6$. Additionally, only trace conversion to the ketone was observed in the presence of the silver salts alone (i.e., without Au). The composition of the reaction medium was critical, 1,4-dioxane being the best solvent (entries 1, 6−7) when employed in a 2:1 ratio with water (entries 1 and 8). Trials in pure water proved unsuccessful (entry 9).

Table 1. Optimization of the Hydration Conditions

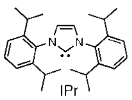


entry	changes from standard conditions	time (h)	GC convn
1	none	1.5	97%
2	IMes instead of IPr	20	NR
3	ItBu instead of IPr	20	93%
4	AgBF$_4$ instead of AgSbF$_6$	1.5	95%
5	AgOAc instead of AgSbF$_6$	20	NR
6	toluene instead of 1,4-dioxane	5	<5%
7	DCE instead of 1,4-dioxane	5	<5%
8	1,4-dioxane/H$_2$O (6:1) instead of (2:1)	1.5	67%
9	neat water instead of 1,4-dioxane/H$_2$O (2:1)	20	NR
10[b]	[Au] (0.1 mol %) instead of (2 mol %)	18	77%

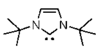
[a] GC conversions are average of at least two runs. NR = no reaction. [b] T = 120 °C.



IMes



IPr



ItBu

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Keeping in mind our initial goal of developing a catalyst efficient at low loadings, the amount of [(IPr)AuCl] used was decreased to 0.1 mol % (i.e., 1000 ppm) for the hydration of **1a** and a promising 77% yield of ketone **2a** (entry 10) was obtained at 120 °C. It should be noted that the hydration of diphenylacetylene **1a** has proven difficult in the past, as for most internal alkynes, and that this result already constitutes a notable improvement.[14]

Finally, during our optimization efforts, the use of alcohol solvents, notably methanol, allowed us to uncover some interesting aspects of the present gold-catalyzed hydration reaction. More precisely, while alkyne **1a** showed slower conversion to ketone **2a** in the presence of MeOH (20 h) when compared to dioxane (1.5 h), this relation was reversed when using phenylacetylene.[15] This dichotomy between internal and terminal alkynes, that was further verified (vide infra), seems to point to two distinct mechanisms in methanol and dioxane. This hypothesis was supported by the observation that in methanol, the alkyne was readily converted to the vinylether corresponding to the addition of methanol across the C≡C bond,[16] which in turn was converted into the ketone.[17] This clearly implies that methanol is not innocent in this reaction and plays an active role in the catalytic cycle.[18]

With a fully optimized set of reaction conditions in hand, the scope of the catalytic system was examined (Scheme 1). The reactivity of several terminal alkynes was investigated. As mentioned above, we observed faster conversions with this type of alkynes when the reactions were performed in methanol instead of 1,4-dioxane.[19] Hence, phenylacetylene could be efficiently converted to acetophenone **2b** with only 50 ppm of the gold catalyst.

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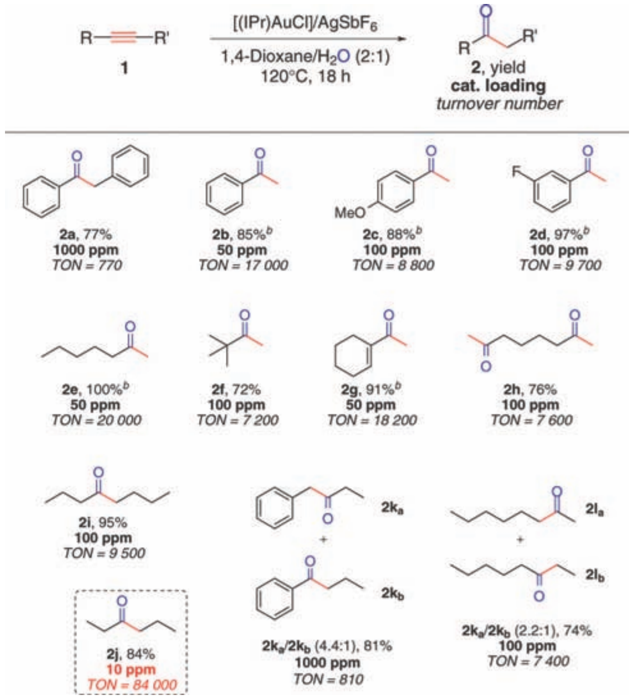
10.1021/ja809403e CCC: $40.75

Scheme 1. Hydration of Alkynes at Low Catalyst Loadings[a]



[a] ^{1}H NMR yields against benzaldehyde as internal standard. Yields are average of at least two runs. [b]Reaction performed with MeOH instead of 1,4-dioxane.

This result corresponds to a decrease in catalyst loading of nearly 2 orders of magnitude from previous studies.[6,12c] Similarly, *p*-OMe- and *m*-F-acetophenones **2c** and **2d** were obtained in high yields, with TONs of 8800 and 9700, respectively.[20] Alkyl-substituted terminal alkynes reacted equally well at 50 ppm (**2e**) and even the very sterically hindered *tert*-butylmethyl ketone **2f** was produced in good yield at low catalyst loading (100 ppm). Remarkably, the presence of an alkene moiety was well tolerated and conjugated enone **2g** was obtained with a high TON of 18200. A double hydration was also efficiently performed at 100 ppm and yielded diketone **2h** in 76%.

Internal alkynes, as observed by Hayashi and Tanaka,[6] are usually more reluctant participants than their terminal counterparts toward hydration. Nevertheless, encouraged by our preliminary results with diphenylacetylene **1a**, we examined the reactivity of both symmetrical and unsymmetrical disubstituted alkynes (Scheme 1). We were then pleased to observe the high yield conversion of 4-octyne into **2i** with a TON of 9500; a reaction that could be scaled up to 20 mmol without loss of activity.[17] Similarly, we obtained 3-hexanone **2j** in high yield. In this case, the reaction could be performed *with only 10 ppm* of [(IPr)AuCl] precatalyst, leading to an unprecedented high TON value of 84000. Finally, two unsymmetrical alkynes were efficiently hydrated, yielding **2k** and **2l**, albeit with moderate selectivity, as previously reported with other catalytic systems.[4] At this point, it should be noted that terminal and internal alkynes possessing any combination of alkyl and aryl substituents (alkyl/H, aryl/H, alkyl/alkyl, alkyl/aryl, and aryl/aryl) were found suitable substrates in the present catalytic system. To the best of our knowledge, this versatility is unprecedented, especially at such low loadings.

In conclusion, we have developed a highly efficient [(NHC)Au^I]-based catalytic system for the hydration of a wide array of alkynes that operates under acid-free conditions and at very low catalyst loadings (typically 50−100 ppm and as low as 10 ppm). Further studies, notably aimed at shedding light onto the mechanism(s) of this reaction, are ongoing in our laboratories.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (Spain), the PRF administered by the ACS, the ICIQ Foundation and the ICREA for financial support. SPN is an ICREA Research Professor. NM (2007FI_A 01466) and RSR (2008FI 01047) thank the AGAUR for predoctoral fellowships. NM thanks Umicore for a Ph.D. award.

Supporting Information Available: Full experimental procedures, analysis of the hydration of diphenylacetylene in MeOH. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Hayashi and Tanaka (see ref 6) reported low catalyst loadings (100 ppm) and low amounts of acid promoter (4 mol %) only for the hydration of 1-octyne. For all other alkynes, catalyst loadings typically range from 0.2 to 1 mol % and acid loadings from 25 to 50 mol %.
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(14) The best result we are aware of was reported by Hayashi and Tanaka (ref 6): 53% with 1 mol % [Au], TON = 53.
(15) For reactions carried out at 65 °C for 18 h, conversion of phenylacetylene into acetophenone: MeOH (100%), 1,4-dioxane (29%).
(16) For a seminal study on the Au-catalyzed alcohol addition to alkyne, see ref 12a.
(17) For details, see the Supporting Information.
(18) We are currently investigating, both experimentally and theoretically, several mechanistic hypotheses that would account for these observations and allow for a more complete understanding of the present reaction.
(19) It should be noted that, unlike in 1,4-dioxane, silver salts alone catalyze the hydration reaction in MeOH, but only to a minor extent.
(20) Of note, the similar behavior of **1c** and **1d** with the present catalytic system contrasts with Hayashi and Tanaka's observation that electron-deficient phenylacetylenes are less reactive than electron-rich ones, see ref 6.

JA809403E