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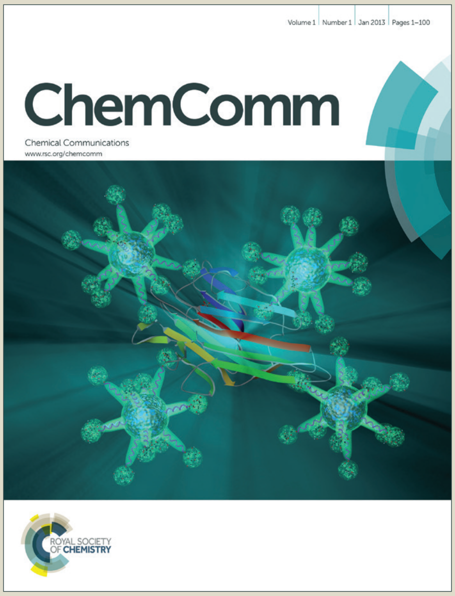

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# Efficient Hydration of Alkynes through Acid-Assisted Brønsted Acid Catalysis

Shengzong Liang, Gerald B. Hammond,* Bo Xu*

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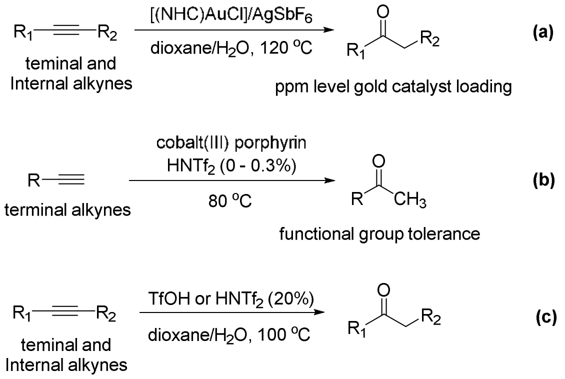
**The combined acid catalyzed hydration of alkynes is an efficient one-step synthesis of carbonyl compounds. This atom-economical method is effective with a wide range of substrates, and the products are obtained in very good yields with low catalyst loading (0.2%). Furthermore, solid acids like Nafion were also efficient and could be easily recycled multiple times without loss of reactivity.**

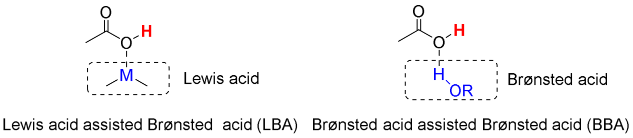
The hydration of alkynes is a straightforward and atom economical method for the preparation of carbonyl compounds.[1, 2] Indeed, the mercury (II)-catalyzed hydration of alkynes has been known for more than a century.[3, 4] To avoid the use of toxic mercury(II) salts, many metal catalysts, such as Fe,[5-7] Ru,[8-11] Pd,[12-15] Ir,[16] Pt,[17-20] Ag,[21, 22] Au[23-27] as well as other metals[28-34] have been developed. Notable examples include the [(NHC)Au$^I$] catalyzed alkyne hydration at ppm gold catalyst loadings by Nolan and coworkers (Scheme 1a)[23] and the cobalt porphyrin complex catalyzed alkyne hydration by Naka and coworkers, which exhibited good functional group tolerance (Scheme 1b).[35]

Compared to metal Lewis acid catalysts, the Brønsted acid catalysts are generally inexpensive, and, in some cases, environmentally friendly. Not surprisingly, the metal-free Brønsted acid (e.g. TfOH, $HNTf_2$) catalyzed alkyne hydrations are known (Scheme 1c),[36-38] but most of them need very high Brønsted acid loading (e.g. 20%), long reaction times and high temperatures. These disadvantages hinder them for wide synthetic applications. Herein, we are glad to report an acid-assisted Brønsted acid catalyzed alkyne hydration with very low catalyst loading (Scheme 2).



**Scheme 1** Notable examples of alkyne hydration.

The concept of combined acid catalysis was first proposed by Yamamoto and coworkers, which included Brønsted acid-assisted Brønsted acid (BBA) catalysis and Lewis acid-assisted Brønsted acid (LBA) catalysis.[39] Based on this concept, we proposed that the acidity of a weak Brønsted acid like acetic acid can be enhanced significantly by combining it with a Brønsted acid or Lewis acid (Scheme 2). This enhanced acidity may speed up the hydration of alkynes. What's more, there are many readily available Brønsted acids and Lewis acids to choose from and each of them has different acid strength and counterions, so we can fine tune the reactivity of the combined acid system to achieve the best efficiency.



**Scheme 2** Concept of combined acid catalysis.

We used the hydration of phenyl acetylene **1a** as our model reaction (Table 1). As expected, the weak Brønsted acid acetic

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*Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, USA E-mail: bo.xu@louisville.edu and gb.hammond@louisville.edu, Fax: (+) 1-502-852-5998*

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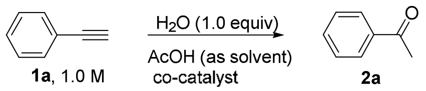
acid itself did not promote the hydration of **1a** (Table 1, entry 1) even at 120°C, but the combination of acetic acid with only a very mild Lewis acid (KCl) gave a 16% conversion under the same conditions (Table 1, entry 2). The combination of acetic acid with a slightly stronger Lewis acid ($LiNTf_2$) gave a good yield of the hydration product **2a** (Table 1, entry 3). We also tried to lower the loading of the acid co-catalyst and reduce the temperature: the combination of AcOH with a strong Brønsted acid TfOH (0.5%) was very efficient at 100 °C (Table 1, entry 4). TsOH, $HBF_4{\cdot}Et_2O$, and $Tf_2NH$ were less efficient (Table 1, entries 5-7). Super acid $Tf_3CH$[40] also gave a very good yield of product (Table 1, entry 8). These results indicated that a Brønsted acid-assisted Brønsted acid (BBA) combination was able to catalyze the hydration of **1a** at low catalyst loadings (0.5 mol %). Then, we explored the viability of using a Lewis acid-assisted Brønsted acid (LBA) system because there are more choices of available Lewis acids. Most of the AcOH/Lewis acid combinations tested were effective (Table 1, entries 9-12). Among them, $Ga(OTf)_3$ (Table 1, entry 12) gave the best reactivity. We could further lower the catalyst loading down to 0.2% by increasing the concentration of **1a** (Table 1, entry 13). The combination of AcOH and $Ga(OTf)_3$ is important; without AcOH $Ga(OTf)_3$ is not a good catalyst for the hydration reaction (Table 1, entry 14).

**Table 1** Screening for the best conditions of alkyne hydration.

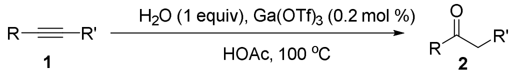


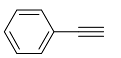
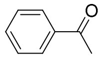
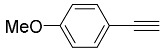
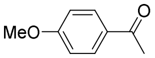
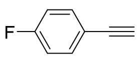
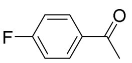
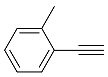
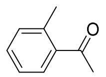
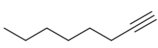
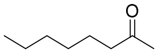
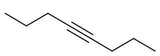
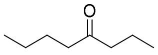
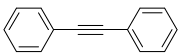
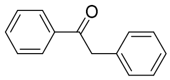
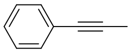
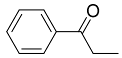
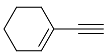
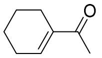
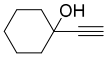
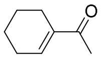
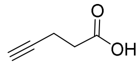
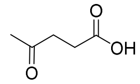
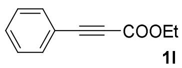
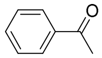
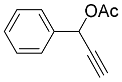
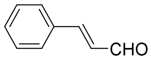
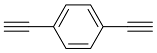
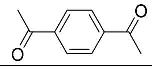
| entry | co-catalyst (mol %) | condition | Yield[b] (%) |
|---|---|---|---|
| 1 | - | Mw,[a] 120 °C, 1 h | trace |
| 2 | KCl (4%) | Mw,[a] 120 °C, 1 h | 16 |
| 3 | $LiNTf_2$ (4%) | Mw,[a] 120 °C, 1 h | 93 |
| 4 | TfOH (0.5%) | 100 °C, 10 h | 99 |
| 5 | TsOH (0.5%) | 100 °C, 24 h | Trace |
| 6 | $HBF_4{\cdot}Et_2O$ (0.5%) | 100 °C, 24 h | 4 |
| 7 | $Tf_2NH$ (0.5%) | 100 °C, 24 h | 56 |
| 8 | $Tf_3CH$ (0.5%) | 100 °C, 10 h | 99 |
| 9 | $Yb(OTf)_3$ (0.5%) | 100 °C, 14 h | 99 |
| 10 | $Sc(OTf)_3$ (0.5%) | 100 °C, 12 h | 99 |
| 11 | $In(OTf)_3$ (0.5%) | 100 °C, 10 h | 99 |
| 12 | $Ga(OTf)_3$ (0.5%) | 100 °C, 8 h | 99 |
| 13[c] | $Ga(OTf)_3$ (0.2%) | 100 °C, 6 h | 99 |
| 14[d] | $Ga(OTf)_3$ (0.5%) | 120 °C, 1 h | trace |

[a] Mw = Microwave. [b] $^1$H NMR Yield. [c] [1a] = 2.5 M. [d] The reaction was conducted in dioxane.

With the optimized conditions in hand (AcOH/TfOH or AcOH/$Ga(OTf)_3$), we explored the substrate scope of this new methodology (Table 2). Substituted phenyl acetylenes with either electron-donating or electron–withdrawing groups all gave close to quantitative yields of hydration products **2** (Table 2, entries 2-4). Terminal aliphatic alkyne also worked well (Table 2, entry 5). The hydration of internal alkynes was slower than that of terminal alkynes, and a slightly higher catalyst loading (1 mol %) was needed to achieve good yields (Table 2, entries 6-8). Alkenes and carboxylic acids were well tolerated (Table 2, entries 9 and 11), but the -OH group in 1-ethynylcyclohexanol (**1j**) did not survive the hydration condition (Table 2, entry 10). Hydration of ethyl phenylpropiolate (**1l**) gave the decarboxylation product **2a** in 70% yield (Table 2, entry 12). An anti-Markovnikov product cinnamaldehyde (**2m**) was

**Table 2** Scope of the LBA alkyne hydration



| entry | 1 | | 2 | | time (h) | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1[b] |  | 1a |  | 2a | 6 | 99 |
| 2[b] |  | 1b |  | 2b | 3 | 96 |
| 3[b] |  | 1c |  | 2c | 5 | 99 |
| 4[b] |  | 1d |  | 2d | 2 | 99 |
| 5[e] |  | 1e |  | 2e | 3 | 91 |
| 6[c] |  | 1f |  | 2f | 1 | 92 |
| 7[c] |  | 1g |  | 2g | 1 | 99 |
| 8[d] |  | 1h |  | 2h | 12 | 85 |
| 9[b] |  | 1i |  | 2i | 2 | 99 |
| 10[b] |  | 1j |  | 2i | 20 | 97 |
| 11[b] |  | 1k |  | 2k | 20 | 99 |
| 12[c] |  | 1l |  | 2a | 1 | 70 |
| 13[d] |  | 1m |  | 2m | 12 | 96 |
| 14[f] |  | 1n |  | 2n | 1 | 78 |

[a] Yields were determined by $^1$H NMR. [b] Condition A: [**1**] = 2.5 M in HOAc, $H_2O$ (1 equiv), $Ga(OTf)_3$ (0.2 mol %), 100 °C using oil bath. [c] Condition B: [**1**] = 2.5 M in HOAc, $H_2O$ (1 equiv), $Ga(OTf)_3$ (1 mol %), 100 °C using microwave. [d] Condition A with $Ga(OTf)_3$ (1 mol %). [e] Condition B with $Ga(OTf)_3$ (1 mol %) at 90°C. [f] Condition A with $H_2O$ (2 equiv) and a microwave was used.

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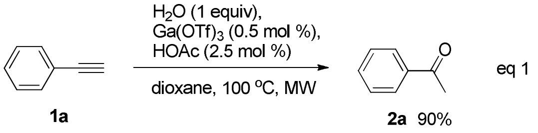
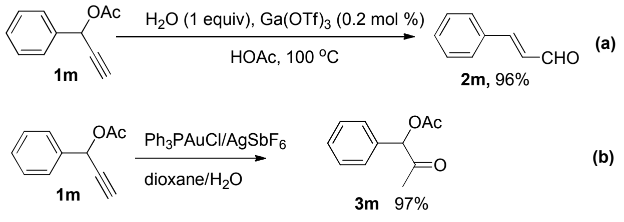
formed in the hydration of propargyl acetate (**1m**) (Table 2, entry 13). Finally, hydration of diyne (**1n**) also gave the expected di-hydration product **2n** in good yield (Table 2, entry 14).

Considering the use of relative inconvenient solvent (HOAc), we furthermore tested the hydration reaction in dioxane in the presence of catalytic amount of combined acid (eq 1). It turned out that 90% of the hydrolysis product was obtained with 10% of unreacted **1a** left after 70 minutes in a microwave. Therefore, compared to two control experiments (Table 1, entries 1 and 14), this result clearly showed that the LBA system is very efficient for hydration of alkyne.

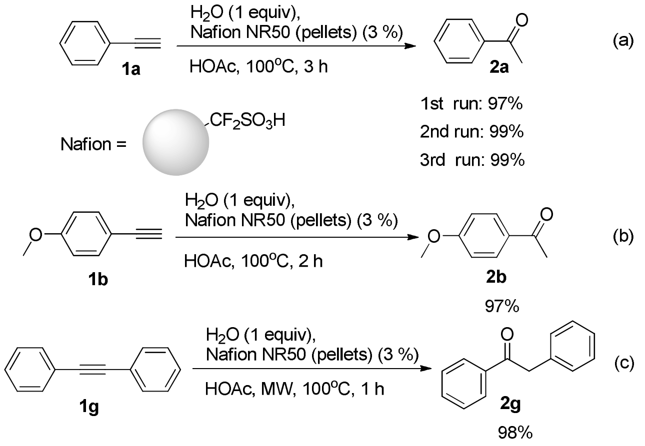


It should be noted that our combined acid catalysis sometimes had higher or different regioselectivities compared to transition metals (e.g., Au) catalyzed counterparts due to different reaction mechanisms. For example, the hydration of phenyl substituted internal alkyne **1h** (Table 2, entry 8) produced the aryl ketone isomer (**2h**), but the gold catalyzed hydration of **1h** gave a mixture of two isomers.[23] In a more extreme case, the gold catalyzed hydration of propargyl acetate gave the Markovnikov product **3m** (Scheme 3b).[41, 42] However, our system furnished the anti-Markovnikov product **2m** exclusively (Scheme 3a). The regioselectivity of our system can be rationalized by relative stability of the corresponding carbocation intermediates.



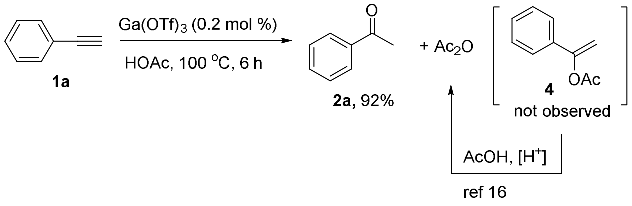
**Scheme 3** Regioselectivity for hydration of **1m**.

We also examined the feasibility of using solid acids in our LBA or BBA strategy for alkyne hydration because heterogeneous solid acids can be easily recycled and are less corrosive than acids in solution phase. We investigated common solid acids catalysts such as Zeolite (ZSM-5) and Nafion. ZSM-5 showed relatively slow reaction on the hydration of phenylacetylene **1a** (71% after 24 hours). Nafion gave a much better result, it could be easily reused and did not lose its reactivity after 3 reaction cycles (Scheme 4a). We also tested two other alkyne substrates **1b** and **1g**, both of which gave similar results as those obtained with $Ga(OTf)_3$ (Scheme 4b and 4c). Nafion is a tetrafluoroethylene-based copolymer with perfluroalkanesulfonic acid functionality; its excellent performance could be due to its higher acidity (compared to Zeolite).



**Scheme 4** Examples of BBA alkyne hydration using Nafion NR50.

The possible reaction pathway of this transformation was also investigated. Although acetic acid is a weak nucleophile compared to water, due to its high concentration (as solvent) it is possible that hydroacetoxylation reaction takes place first followed by hydrolysis of the enol acetate intermediate to give ketone product **2**. In this process, the acidity of either $Ga(OTf)_3$ or HOAc was not strong enough to activate the triple bond of alkyne, but the combined system of them (LBA) provided much stronger acidity than when one of them was used. To capture the possible enol acetate intermediate we conducted the hydration of **1a** under anhydrous condition. We found that even in the absence of water we can still obtain hydration product **2a** in 92% yield along with acetic acid anhydride (Scheme 5), but no enol acetate was observed. It has been reported that acid can catalyze the acetoxylysis of enol acetate to give corresponding ketone and acid anhydride (Scheme 5).[43] So one plausible explanation for formation of acid anhydride is that the reaction went through our proposed enol acetate intermediate **4**.



**Scheme 5** Hydration of **1a** using anhydrous acetic acid.

In summary, we have developed a highly efficient acid-assisted Brønsted acid catalysis system for alkyne hydration. This methodology worked well for various alkyne substrates using very low catalyst loading. Furthermore, solid acids like Nafion were also efficient and could be recycled easily multiple times without loss of reactivity.

## Acknowledgements

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