

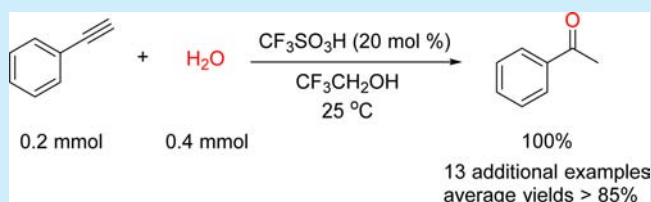
Metal-Free Markovnikov-Type Alkyne Hydration under Mild Conditions

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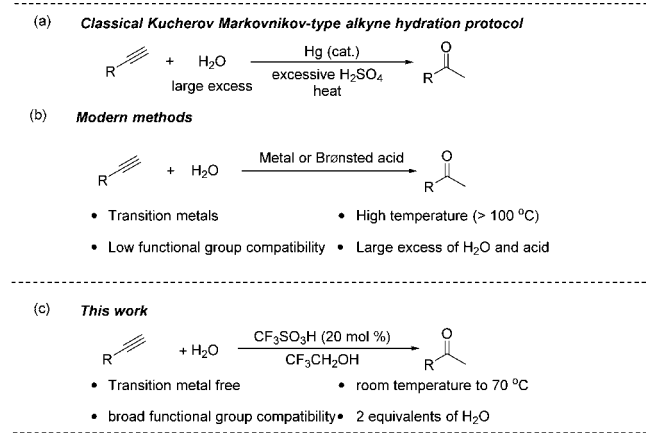
S Supporting Information

ABSTRACT: A Markovnikov-type alkyne hydration protocol is presented using 20% $\text{CF}_3\text{SO}_3\text{H}$ (TfOH) as the catalyst under unprecedented mild conditions applicable to various alkynes, including terminal arylalkynes, terminal nonfunctionalized aliphatic alkynes, and internal alkynes with excellent regioselectivity in good to excellent yields (average yields >85%). The reaction procedure operates under mild conditions (25–70 °C), with broad functional group compatibility, and uses only slightly more than a stoichiometric amount of water in the absence of any transition metal. The success of this protocol hinges upon the utilization of trifluoroethanol as the solvent.



Converting alkynes into carbonyl compounds through hydration, especially Markovnikov-type hydration (Scheme 1a), is a fundamental transformation in organic

Scheme 1. Comparison of Previous Work and This Work



synthesis with 100% atom economy.^{1,2} Classical Kucherov procedures for alkynes' hydration into ketones employ mercuric salt as the catalyst in aqueous sulfuric acid.^{3,4} Due to the toxicity of Hg salts, many other metal-catalyzed alkyne hydration procedures have been developed, including ones catalyzed by Ru,⁵ Rh,⁶ Pd,⁷ Pt,^{8,9} Sn–W,¹⁰ Au,^{11–17} Fe,^{18,19} Ir,^{20,21} Co,²² Ag,^{23,24} etc. Besides various metal catalysts, Brønsted-acid-catalyzed hydration reactions also exist in the literature.^{25,26} However, most of the reactions reported so far have suffered from at least one drawback: (1) high temperature (>100 °C); (2) expensive noble metals (Ru, Rh, Pd, Pt, Au, Ir, Ag, etc.); (3) narrow functional group compatibility; (4) large excess of water and acidic additive besides the metal catalysts if any

(Scheme 1b). Therefore, a method that could operate under mild conditions (i.e., room temperature) with broad functional group tolerance at the cost of close to a stoichiometric amount of water and a catalytic amount of acid in the absence of any transitional metal²⁷ would be highly desirable. In this paper, we describe such a protocol that fulfills all of these requirements (Scheme 1c).

Our work was inspired by the facts that (1) vinyl (phenyl) carbocation can be strongly stabilized in $\text{CF}_3\text{CH}_2\text{OH}$ (TFE) as the solvent and (2) TFE cannot react with the carbocation due to its low nucleophilicity.^{28–30} Given that alkyne's hydration is generally via a vinyl carbocation intermediate,^{31–34} we hypothesized that TFE's ability to stabilize a vinyl carbocation could decrease the transition state energy to form the carbocation intermediate, which may cause the hydration reaction to proceed under conditions milder than those of reactions occurring in other solvents. Besides, low Lewis basicity of TFE would not compete with the triple bond to be activated by the acid catalysts (including metal and Brønsted catalysts). To quantitatively compare the difference between TFE and other solvents, we conducted DFT calculation on the protonation step in different solvents (Figure 1). TFE and ethanol were selected as the solvents to conduct the DFT analysis comparison because these two solvents bear nearly identical steric hindrance. As expected, the energy of intermediate in TFE is 10.4 kcal/mol lower than that in ethanol,³⁵ which suggests that the low Lewis basicity of the oxygen in TFE would be much more favorable to this reaction compared to ethanol.

To begin testing our hypothesis, phenylacetylene was selected as the model substrate with TFE as the solvent. We

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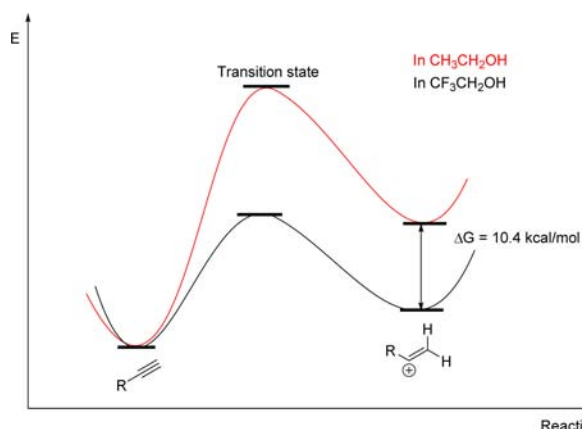


Figure 1. DFT calculation comparison on the protonation step of alkyne in TFE and ethanol.

rapidly found that the acidity of the Brønsted acid catalyst is crucial to the reaction efficiency after briefly screening common organic acids. With TFE as the solvent, 20 mol % of $\text{CH}_3\text{CO}_2\text{H}$ as the catalyst cannot produce any product (entry 1 in Table 1),

Table 1. Optimization of the Model Reaction

entry ^a	solvent	acid catalyst	yield (%) ^b
1	$\text{CF}_3\text{CH}_2\text{OH}$	$\text{CH}_3\text{CO}_2\text{H}$	0
2	$\text{CF}_3\text{CH}_2\text{OH}$	$\text{CF}_3\text{CO}_2\text{H}$	3
3	$\text{CF}_3\text{CH}_2\text{OH}$	$\text{CF}_3\text{SO}_3\text{H}$	100
4	cyclohexane	$\text{CF}_3\text{SO}_3\text{H}$	3
5	PhCl	$\text{CF}_3\text{SO}_3\text{H}$	trace
6	DMF	$\text{CF}_3\text{SO}_3\text{H}$	0
7	DMSO	$\text{CF}_3\text{SO}_3\text{H}$	0
8	MeOH	$\text{CF}_3\text{SO}_3\text{H}$	0
9	THF	$\text{CF}_3\text{SO}_3\text{H}$	0
10	DCE	$\text{CF}_3\text{SO}_3\text{H}$	0
11	1,4-dioxane	$\text{CF}_3\text{SO}_3\text{H}$	trace
12	DCM	$\text{CF}_3\text{SO}_3\text{H}$	5
13	CHCl_3	$\text{CF}_3\text{SO}_3\text{H}$	3
14	H_2O	$\text{CF}_3\text{SO}_3\text{H}$	0
15	HFIP	$\text{CF}_3\text{SO}_3\text{H}$	96
16	CH_3CN	$\text{CF}_3\text{SO}_3\text{H}$	0
17	$\text{CH}_3\text{CH}_2\text{OH}$	$\text{CF}_3\text{SO}_3\text{H}$	0
18	$\text{CH}_3\text{CO}_2\text{H}$	$\text{CF}_3\text{SO}_3\text{H}$	trace

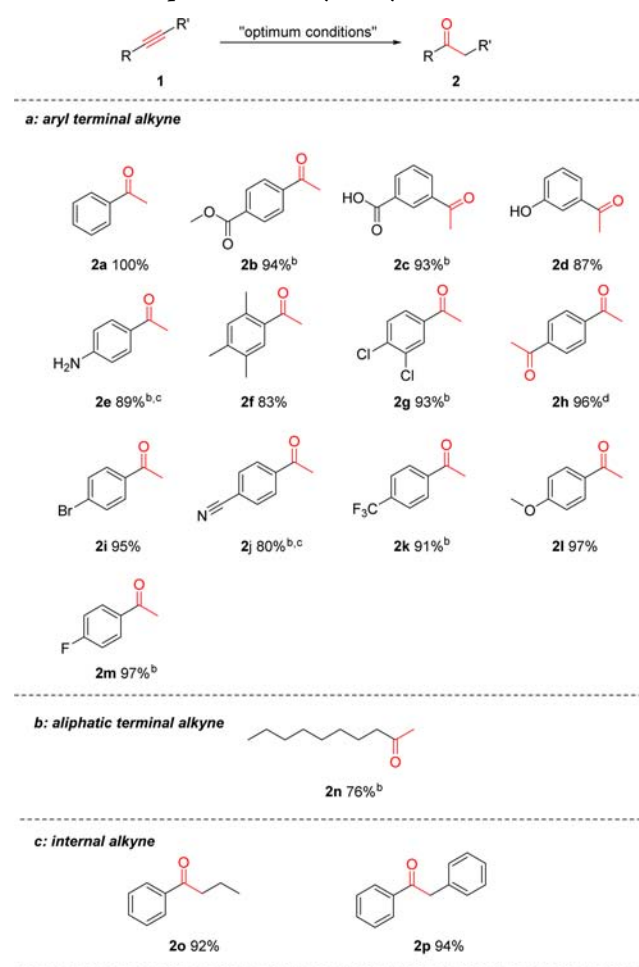
^aReaction conditions: phenylacetylene (22 μL , 0.2 mmol), H_2O (8 μL , 0.4 mmol, 2 equiv), acid (0.04 mmol, 0.2 equiv), solvent (1 mL), 25 $^\circ\text{C}$, 45 h. ^bYield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.

whereas $\text{CF}_3\text{CO}_2\text{H}$ could only deliver the product in 3% yield (entry 2). By choosing a stronger acid as the catalyst, we were pleased to find that $\text{CF}_3\text{SO}_3\text{H}$ (20 mol %) could give the desired product with a quantitative yield (entry 3). To further confirm the power of TFE in this reaction, we conducted control experiments using other common solvents, including protic organic solvents, aprotic polar solvents, aprotic nonpolar solvents, and water. Most solvents could not produce any hydration product (entries 6–10, 14, 16, and 17), and some

could only generate the product in very low yields (<5%) if any (entries 4, 5, 11–13, and 18). Not unexpectedly, as the twin of TFE, hexafluoro-2-propanol (HFIP) could also generate the product in excellent yield (96%), as efficiently as TFE (entry 15). However, considering the price difference of these two fluoro-containing solvents, we decided to employ TFE as the solvent to execute further investigations. Therefore, the “standard conditions” were set as alkyne (1 equiv), H_2O (2 equiv), $\text{CF}_3\text{SO}_3\text{H}$ (0.2 equiv), and $\text{CF}_3\text{CH}_2\text{OH}$ (1 mL) at 25 $^\circ\text{C}$.

After confirming our hypothesis, we then examined the functional group compatibility by utilizing various arylalkynes **1** with different functional groups. Arylalkynes without strong electron-withdrawing groups (EWG) (**2a**, **2d**, **2f**, **2h**, **2i**, **2l**) could generate the hydration products in excellent yields under the standard conditions (Scheme 2). With EWGs attached to the aromatic rings, a higher temperature (i.e., 70 $^\circ\text{C}$) was required (**2b**, **2c**, **2g**, **2j**, **2k**, **2m**) to generate the desired hydration products with excellent yields. In contrast, a previously reported TfOH-catalyzed alkyne hydration protocol in THF only produced 4% GC yield after 78 h at 100 $^\circ\text{C}$ when

Scheme 2. Scope of This Alkyne Hydration Reaction^a



^aPlease refer to the supporting information for the reaction details including reaction time for each substrate. All the yields are isolated ones. ^bReaction conducted at 70 $^\circ\text{C}$. ^cAcid (1.2 equiv) was added in the reaction system. ^d1,4-Diethynylbenzene (0.2 mmol, 26 mg), H_2O (0.8 mmol, 16 μL), $\text{CF}_3\text{SO}_3\text{H}$ (0.08 mmol, 8 μL), $\text{CF}_3\text{CH}_2\text{OH}$ (1 mL), 25 $^\circ\text{C}$.

4-trifluoromethylphenylacetylene was used as the substrate.²⁵ With basic reaction sites (such as $-\text{NH}_2$ and $-\text{CN}$) in the substrates (**2e**, **2j**), apart from the 20% acid catalyst, another equivalent of acid was necessary to quench the basicity. Most organic functional groups, including ester (**2b**), $-\text{CO}_2\text{H}$ (**2c**), $-\text{OH}$ (**2d**), $-\text{NH}_2$ (**2e**), alkyl group (**2f**), $-\text{Cl}$ (**2g**), $-\text{Br}$ (**2i**), $-\text{CN}$ (**2j**), $-\text{CF}_3$ (**2k**), $-\text{OMe}$ (**2l**), and $-\text{F}$ (**2m**), could survive the reaction conditions, and they all delivered the products in excellent yields (80–100%). This broad functional group compatibility and mild conditions would provide enormous potential to further functionalize the hydration products, especially in complex natural product synthesis. Besides aryl alkynes, aliphatic alkyne can also deliver the Markovnikov-type hydration product with good yield (76%), although a higher temperature (70 °C) was necessary (**2n**). Unfortunately, the protocol is not applicable to the functionalized aliphatic alkynes including propargylic alcohol and methyl propiolate. However, our reaction procedure is applicable to the internal arylalkynes (**2o**, **2p**) by using the standard conditions.

To further examine the synthetic potential of our protocol, we also conducted a gram scale reaction by choosing phenylacetylene (1.4 g, 14 mmol) as the substrate (Scheme 3). Under our standard conditions, the desired hydration product acetophenone could be isolated at a 91% yield, which confirms its suitability for large-scale reactions.

Scheme 3. Gram Scale Reaction under Our Standard Conditions



In summary, we have developed an extremely mild protocol to accomplish alkyne hydration. Our reaction operates at low temperature with broad functional group compatibility, is applicable to various alkynes, and only requires slightly more than a stoichiometric amount of water in the absence of any transition metals. Moreover, the reaction conditions are also applicable for the large-scale reaction. The success of our reaction lies in the use of TFE as the solvent. Exploration of other nucleophiles to attack the vinyl carbocation is underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00801.

Experimental section, spectroscopic data, and ^1H , ^{13}C , and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(35) We tried to optimize the transition state structure for this protonation step. Unfortunately, the transition state optimization could not produce any converged structure. Nevertheless, we were able to obtain the converged structure for the vinyl carbocation intermediate in both solvents. Based on Hammond's postulate, we envisioned that the transition state information could be reflected by the intermediate. Therefore, we concluded that comparing energy differences between the intermediates in both solvents still revealed useful information.

■ **NOTE ADDED AFTER ASAP PUBLICATION**

Reference 2Sb was added on April 20, 2016.