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A Metal-free Transformation of Alkynes directed by Remote OH Group

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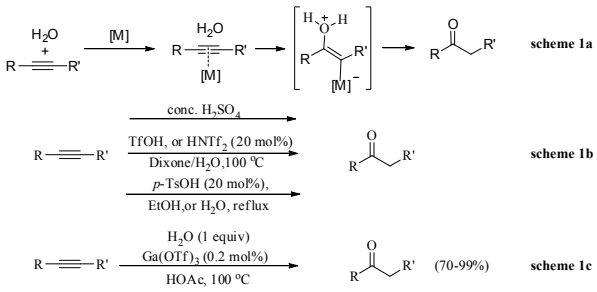
A remote activation and metal-free transformation from alkynes to carbonyl compounds is developed. Just in the solvent of HOAc and EtOH, this reaction artfully converts alkynes to valuable ketones by remote hydroxyl group. Through the comparison and isotope labeling experiments, it is confirmed that the process is a hydration reaction involving acetic acid molecule, instead of water molecule.

The significant research field about how to control the reaction with high selectivity persists as one of the most challenging issues for chemistry. Remote activation represents one of the burgeoning, promising and challenging strategy over the past decades. Currently, Yu and his coworkers using a weak "end-on" interaction between the linear nitrile group and the metal centre, some reports of the U-Shaped nitrile templates to accomplish *meta* C-H bond activation have been reported [1]. Considering the intrinsic weak interaction, the hydroxyl group owns its remarkable hydrogen bond between O, F and N atoms. It will be very valuable to make full use of hydrogen bond in chemical process, owing to the hydroxyl group extensively existing in natural products such as Glucose, Cyclodextrin, etc.

As one of classic research area, the addition of oxygen nucleophiles to carbon-carbon triple bonds has driven many highly useful transformations for organic synthesis. Hydration reaction is the most common transformation from alkynes to carbonyl compounds[2]. Carbonyl compounds, being an important chemical skeleton, can be easily converted to variety of functional groups such as -OH[3a-b], -CN[3c], -NO_2[3d], ester[3e], amide[3f] and amine[3g,] etc. The conversion of alkynes to carbonyl compounds has been developed enormously and used in the design of new organic reactions[4]. Initially, the metal Hg(II)-catalyzed hydration of alkynes has been known for more than a century[5]. Considering the toxicity of Hg, many efforts have been devoted to explore other metal catalysts for the past decades, such as Au[6], Pd[7], Pt[8], Ru[9], Rh[10], Ir[11], Co[12], Fe[13], Cu[7c] and other metal[14]. Most alkynes can be activated by metal aboved, followed bydemetalation then isomerization (scheme 1a)[6j]. The transformation promoted by acids has been rarely reported. Although the concentrated H_2SO_4[15a], TfOH and $HNTf_2$[15b], or *p*-TsOH[15c]-catalyzed alkynes hydrations are known (scheme 1b)[15], the selectivity of reaction and strong acidity limit their synthetic applications. Recently, Hammond and Xu present a Lewis acid $Ga(OTf)_3$-assisted acid catalyzed alkyne hydration with very low catalyst loading (scheme 1c)[15e]. However, two shortages still exist at present. One is that most high regio-selectivity and high-efficiency for hydration come at the cost of environmental pollution and high-cost metal catalysts; the other one is that strong acidity or other additives will be essential.



Scheme 1 Hydration of alkynes.

Homopropargylic alcohols have shown strong potential in constructing useful chemical skeletons, such as CF_3-containing 3-butenal or 3-buten-1-one derivatives[16a], disubstituted isoxazoles[16b] and CF_3S-substituted dihydrofurans[16c]. Primordially, in continuation of our interest in homopropargylic alcohols, we present a metal-free and remote OH activated alkynes transformation without any Lewis acids assisting, just in the unprocessed solvents of HOAc and EtOH.

According to the initial design, we firstly attempt 1,4-diphenylbut-3-1-ol **1a** as the alkyne substrate in presence of acetic acid (Table 1). We fortunately obtain the desired 4-hydroxy-1,4-diphenylbutan-1-one **2a** under O_2 atmosphere at 60 ℃ for 5.5 h, despite of low isolated yield (**entry 1**). We fail to monitor targeted product in EtOH instead of acetic acid (**entry 2**). In search of more effective conditions, reaction conducted with mixed solvents of

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Table 1 Optimization of the reaction conditions[a]

1a 2a

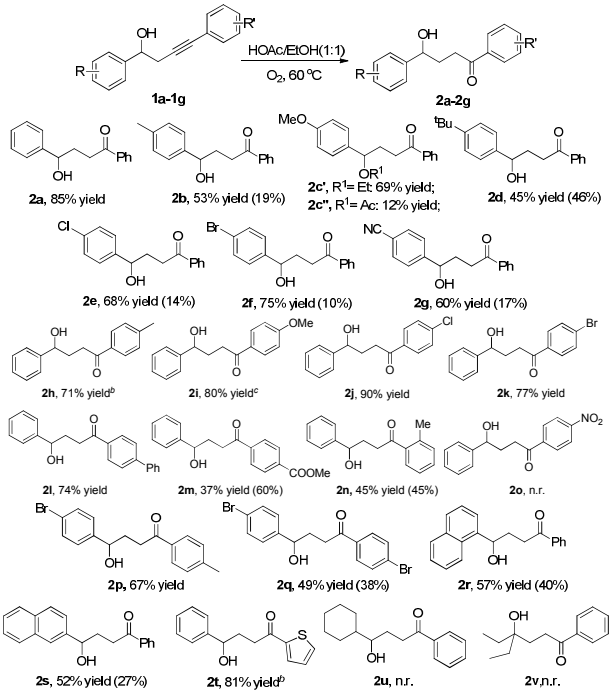
Entry	Sovlent	T(℃)	Atmos.	Yield [%][b]
1	HOAc	60	O_2	35
2	EtOH	60	O_2	0
3	HOAc/EtOH(1:1)	60	O_2	85
4	HOAc/EtOH(1:1)	27	O_2	21(58)
5	HOAc/EtOH(1:2)	60	O_2	28
6	HOAc/EtOH(1:1)	60	Ar	75(13)
7	HOAc/EtOH(1:1)	60	Air	79

[a] Reaction conditions: **1a** (0.2 mmol), solvent (2 mL), volume ratio in parenthesis, 5.5 h. [b] Isolated yield based on **1a**, the amount of recovered starting material in parenthesis.

HOAc/EtOH (V/V=1/1) could lead to high yields, in which we can obtain the highest yield 85% (**entry 3**). However, the yield will slip down to 21% at room temperature (**entry 4**). Attempt to decrease the ratio of HOAc in the solvent failed (**entry 5**). The reaction still obtain high yield under Ar atmosphere, instead of O_2 (**entry 6**), which denies the possibility of O_2 acting as a reaction participant. More surprisingly, despite of a little drop in yield to 79%, the reaction successes under the air as well (**entry 7**), which potentially accords with the benefits of environment and industry. Therefore, the developed method offers a convenient and high-yielding means for the preparation γ-OH ketone, one of important skeletons for medical and natural products[17], as well as the feasibility of this strategy with greener and milder conditions.

Under this optimized conditions, various homopropargylic alcohols analogues are explored as substrates, and the isolated results are summarized in Table 2. Firstly, we change different electron-donating groups, such as -Me, -OMe and -^{t}Bu for **R** on the *para* position. Moderate yields (53%-45%) can be gained for -Me (**1b**) and -^{t}Bu (**1d**) substituted substrates. While more strong electron-donating group -OMe will influence the result, we isolate by-products etherified (**2c'**) and esterified (**2c''**) respectively, in 69% and 12%, which conduces to a better grasp of the mechanism for us. Meanwhile, only trace expected product is monitored. Substrates bearing weak electron-withdrawing substituents such as -Cl, -Br and strong electron-withdrawing substituent -CN on the *para* position are explored (**1e-1g**). The results show good toleration with moderate yield (60-75%). Next, various substrates containing electron-donating substituents (*p*-Me, *p*-OMe, *o*-Me), electron-neutral substituents (*p*-Ph) and electron-withdrawing substituents (*p*-Cl, *p*-Br, *p*-COOMe, *p*-NO_2) for **R'** are tested (**1h-1o**). These reactions perform well and give the expected products in good to excellent yields for substrates **1h, 1i, 1j**, **1k** and **1l**. We obtain moderate yield for substrate containing *p*-COOMe (**1m**) and *o*-Me (**1n**), with substrates recovered. However, the substrate with *p*-NO_2 (**1o**) performs not well, and we cannot monitor product. To substrates with disubstituted groups on the aromatic rings, the transformations occur, furnishing the corresponding products in moderate to good yields (**2p-2q**). The structure of product **2p** is confirmed by X-ray crystal structure analysis[18]. Analogously, substrates bearing fused ring such as 1-naphthyl (**1r**) or 2-naphthyl group (**1s**) are compatible with this transformation in moderate yields. To our delight, substrate containing heteroaromatic thiophene (**1t**) proceeds well in high yield. When we attempt to explore substrates with aliphatic substituents instead of aromatic

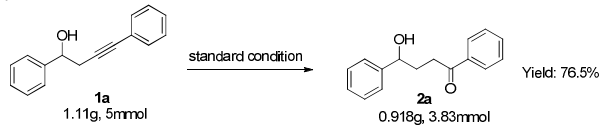
Table 2 Substrate scope[a]



[a] Reaction conditions: **1a** (0.2 mmol), solvent (2 mL), the amount of recovered starting material in parenthesis, 5.5 h, isolated yield. [b] Reaction time: 9 h. [c] Reaction time: 8 h.

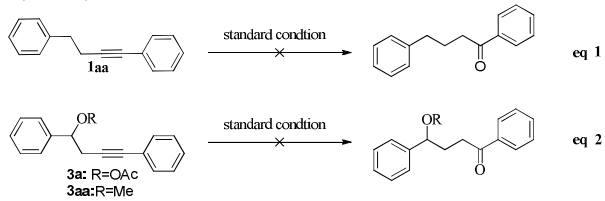
ring (**1u-1v**), this transformation does not complete successfully.

Encouraged by this feasible and environmental strategy, this transformation is subsequently conducted on a gram scale, demonstrating its industrial practicality (Scheme 2). The corresponding product **2a** was isolated in 76.5% yield under the optimal conditions.

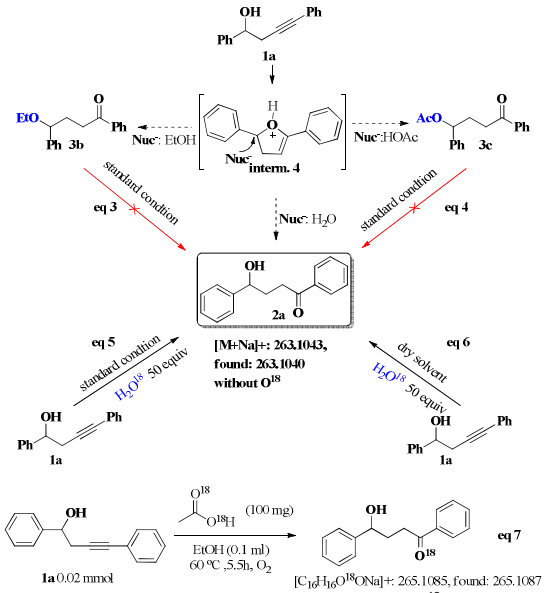


Scheme 2 Synthesis application: scale-up experiments.

In order to gain more details into the reaction mechanism, two control experiments are performed (scheme 3). The reaction of **1aa** without hydroxyl group doesn't obtain the anticipated product under the standard conditions, which indicates that hydroxyl group is crucial for this transformation (eq.1). When esterified substrate **3a** and methylated substrate **3aa** are subjected to the standard conditions, we don't observe the desired products (eq.2). These results reveal that the hydrogen atom of OH group perhaps plays a key role in this reaction.



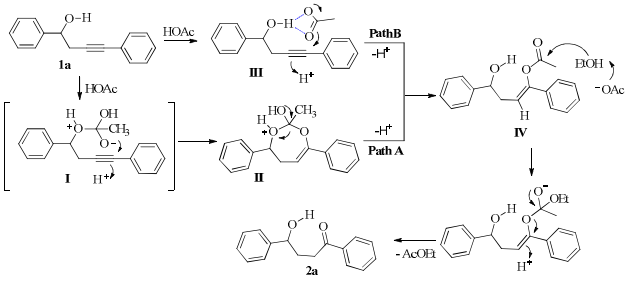
Scheme 3 control experiments.



Scheme 4 Intermediate capturing experiments and O^{18} isotope labeling experiments.

When exploring the scopes of reaction tolerance (Table 2), we obtain the unexpected by-products (**2c'** and **2c''**). We speculate that the reaction may proceed through intermediate **4** (scheme 3), to which nucleophile (EtOH, H_2O and HOAc) attacks giving the corresponding products **3b**, **2a** and **3c** respectively. Additionally, the possibility of by-products **3b** and **3c** converting to **2a** also can be ruled out (eq.3 and eq.4). The intermediate **4** can be ruled out *via* aboved intermediate capturing experiments and isotope labelling studies (eq.5 and eq.6)[19]. Isotope labeling studies are also planned to attain a better understanding of the orgin of the newly introduced O atom. Interestingly, no ^{18}O labeled *γ*-OH ketones are obtained when the standard reactions are performed in the presence of H_2O^{18} (eq.5 and eq.6). Fortunately, we detect ^{18}O labeled product in the presence of ^{18}O labeled acetic acid (95 atom % 18 O) (eq.7). These observations suggest this transformation is a hydration reaction involving acetic acid molecule, instead of water molecule.

On the basis of these results, we propose the mechanism illustrated in Scheme 4. In the first step, homopropargylic OH reacts with the carbonyl of acetic acid and forms (perhaps, transiently) the tetrahedral intermediate **I**. The latter can undergo a 7-*endo-dig* cyclization to give a labile intermediate **II** that can give the ester enolate **IV** (Path A). There is an alternative process (Path B) where HOAc integrates with **1a** through hydrogen bond between H and two O atoms of acetic acid, which is crucial to realize remote activation (about six or eight bonds away). With this pre-transition state **III**, the O atom can be placed nearby the triple bond (Path B), which gives ester enolate **IV** as well. Then the ester enolate **IV** is attacked by EtOH *via* transesterification[20], in which ethyl acetate acts as the leaving molecule, leading to the conformation of **2a**.



Scheme 5 Proposed reaction mechanism.

Conclusions

In summary, we developed a remote activation and metal-free transformation from alkynes to carbonyl compounds. The reaction conditions are also applicable for the gram-scale reaction. Moreover, the value of this reaction firstly is reflected the possibility of activation by hydroxyl group and operational simplicity, covering the shortage of using metal catalysts and strong acidity.

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The authors declare no competing financial interest.

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