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Mutual Cooperation in the Formal Allyl Alcohol Nucleophilic Substitution and Hydration of Alkynes for the Construction of γ-Substituted Ketones

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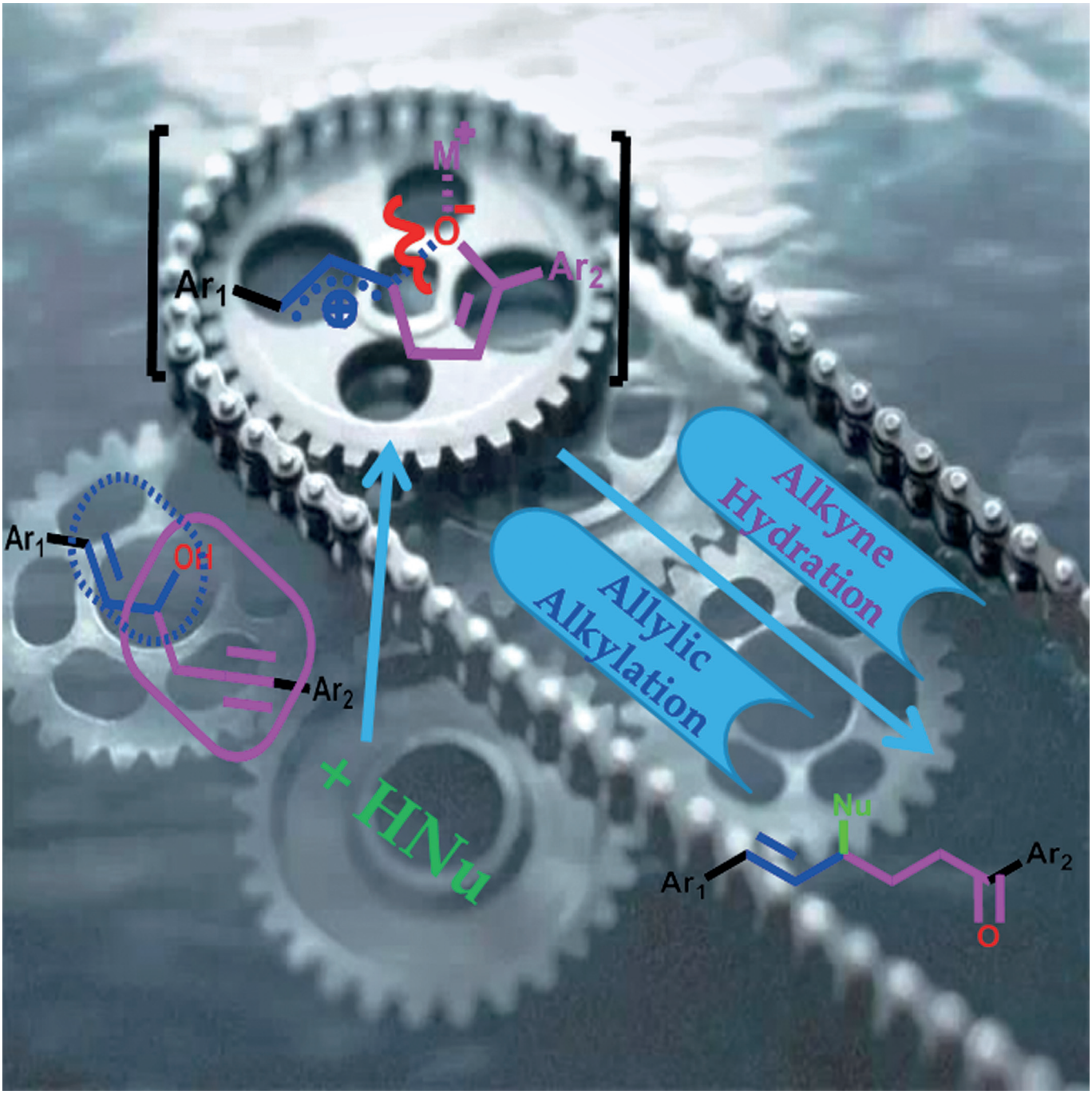

Abstract: Mutual cooperation in the formal allyl alcohol nucleophilic substitution reaction and hydration of an alkyne has been utilized in the presence of a gold catalyst to give a series of γ-functionalized ketones with high to excellent yields. This reaction actually involved an intramolecular O–H insertion cyclization of an alkyne to form the dihydrofuran intermediate, which was followed by the nucleophilic addition ring-opening of a dihydrofuran to give the target compound.

Transition-metal-catalyzed allyl substitution of unactivated allyl alcohol substrates has attracted increasing interest due to the possibility of forming new C–X (X = O, N, C) bonds;[1] this reaction has broad application prospects for the synthesis of natural products or pharmaceutical intermediates.[1,2] From the atom/step economic and environmental perspective, the direct use of readily available allyl alcohol instead of its derivatives as substrates undoubtedly represents an improved process as water is the sole generated byproduct. However, due to the poor leaving capability of the hydroxyl group, the direct nucleophilic substitution of allyl alcohol is disfavored and challenging, and thus the hydroxyl groups are usually changed to better leaving groups, such as halides, carboxylates, or sulfonates.[3] A variety of catalytic systems, such as Brønsted acids,[1c,4] Lewis acids, transition-metal complexes, Pd, Pt, Mo, Bi, Ru, Ir, and Au[1,2] or iodine, have been developed to achieve this transformation.[5] Recently, there are also some reports on the direct nucleophilic substitution of allyl alcohol; however, either a high reaction temperature is required or a promoter must be added to enhance the leaving ability of the hydroxy group.[1a,b,e]

On the other hand, the addition of an oxygen nucleophile (water or alcohol) to the alkyne group, known as hydration or hydroalkoxylation of alkynes, is a well-developed powerful tool to convert alkynes into carbonyl or acetal compounds. Various metal catalysts, such as Pd, Rh, Ru, and Pt, as well as other metals have been developed for this transformation to avoid using the toxic Hg salt, which has been known for more than a century in the hydration of alkynes.[6] More recently, the gold-catalyzed hydration or hydroalkoxylation of alkynes with high efficiency has attracted the increasing attention of chemists.[7] Despite of these great achievements, developing a highly efficient catalytic system is desirable and challenging, especially with regards to regioselective hydration and hydroalkoxylation of internal alkynes.[8] Directing-group strategies have been employed to control hydration of both alkyl- and aryl-substituted alkynes.[8a,d] For example, Hammond and co-workers developed an Au^{III}-catalyzed hydration of 3-alkynoates to provide γ-ketoesters in high yields with high regioselectivity.[8d] They proposed that the regioselectivity was dependent on the initial intramolecular attack of the ester group to the neighboring alkyne group, which is a favored 5-*endo-dig* cyclization rather than the alternative 4-*exo-dig* process. Hydrolysis of the resulting oxonium ion and protodeuration would then form the desired γ-ketoesters. In a similar fashion, another example showed that the aldehyde or ketone carbonyl group can act as the directing group for the hydration of an internal alkyne to generate dicarbonyl products with high regioselectivity.[9] Moreover, no reaction occurred when using the substrate bearing no directing group. Additionally, the nucleophile was limited to water in these reports.[8d,9] For the tethered alcohol nucleophile,[1g,7e,8a,10] Genet and co-workers have reported the gold-catalyzed intramolecular hydroalkoxylation of terminal alkynes by utilizing bis(homopropargylic) diols substrates, opening a door to an interesting family of strained acetals.[10b] Krause and co-workers reported that the pendent alcohol group is an excellent directing group for the intramolecular hydroalkoxylation of internal alkynes, which furnished a five-membered acetal in the presence of an external nucleophile and Brønsted acid catalyst.[10f]

Considering the above and as a continuation of our ongoing work, (Scheme 1 a),[11] we herein chose the unprotected 1,5-enynol **2** as a substrate, which includes three functional groups, such as a double bond, triple bond, and a hydroxy group. As a result, an unexpected γ-functionalized ketone **3** was mainly obtained in high yields by the addition of external nucleophiles. Herein, a new C–O, C–N, or C–C bond is simultaneously formed besides the hydration of the alkyne. Obviously, this new ketone product was generated from an initial formal 5-*endo-dig* cyclization of the homopropargyl alcohol activated by the gold catalyst, and subsequently formal nucleophilic addition ring-opening of the vinyl dihydrofuran (Scheme 1 b). To the best of our knowledge, this type of ring-opening of vinyl dihydrofuran was unprecedented and it was the first time that the mutual cooperation of hydration of alkyne and formal nucleophilic substitution of allyl alcohol were successfully achieved in one pot. This interesting result intrigued us to further investigate this cascade reaction.

In our initial study, we used (*E*)-1,6-diphenylhex-1-en-5-yn-3-ol as a model substrate. In a DCM/MeOH (10:1) mixture,[12] a new compound **3a** was generated almost quantitatively in the presence of a cationic gold(I) complex of $[(Ph_3P)AuCl]/AgNTf_2$ (Table 1, entry 1).[13] Other catalysts and reaction parameters were further screened. It was found that whether using Au^{I} (entries 1, 2, 5) or Au^{III} (entry 6), the reaction could smoothly proceed and afford the corresponding product **3a** in high to excellent yield. But to our surprise, when using only $[(Ph_3P)AuCl]$, no catalytic activity was observed, whereas when using only $AgNTf_2$ the reaction gave a moderate yield of γ-methoxy ketone **3a** with part of the starting material recovered over a long reaction time (entry 3 vs. 4). Both platinum(II) chlo-

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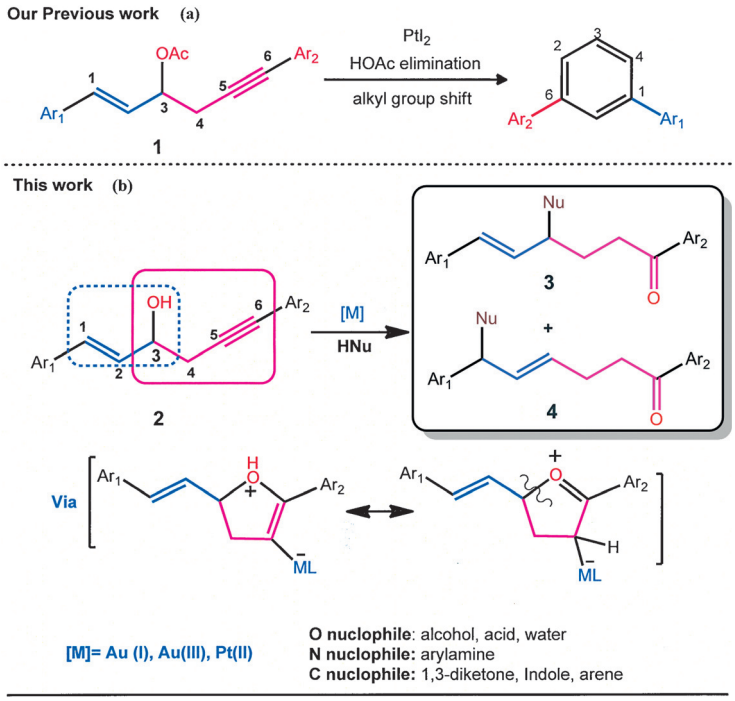
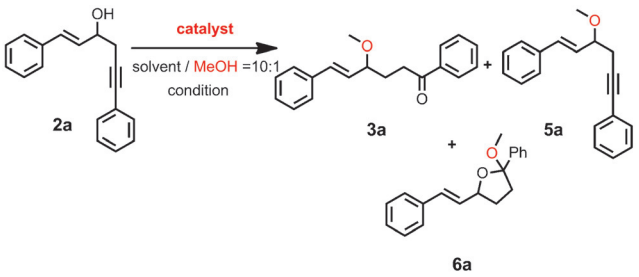


Scheme 1. Cascade reactions of 1,5-enyne alcohols.

Table 1. Optimization studies of the nucleophilic substitution of **2a**.[a]



Entry	Catalyst (mol%)	Conditions	Yield [%][b]
1	**[(PPh_3)AuCl] (5), $AgNTf_2$ (5)**	**DCM, rt, 2 h**	**99**
2	[(X-phos)AuCl] (5), $AgNTf_2$ (5)	DCM, rt, 2 h	90
3	[(PPh_3)AuCl] (5)	DCM, rt, 48 h	–
4	$AgNTf_2$ (5)	DCM, rt, 48 h	50
5	AuCl (5)	DCM, rt, 30 min	80
6	**$AuCl_3$ (5)**	**DCM, rt, 30 min**	**91**
7	$PtCl_2$ (20)	toluene, 80 °C,1.5 h	73
8	$PdCl_2$ (30)	toluene, 80 °C, 2 h	87
9	[$Pd(PPh_3)_4$] (20)	$CHCl_3$, 60 °C, 24 h	–
10	$SnCl_2$ (30)	$CHCl_3$, 60 °C, 24 h	–
11	$SnCl_2$ (30)	toluene, 80 °C, 2 h	trace (**5a**)
12	PtI_2 (5) *N*-phenylmaleimide (50)	toluene, 45 °C, 4 h	89 (**6a**)
13	[Ir(cod)Cl]$_2$ (5)	MeOH, rt, 24 h	14 (**3a**)+21 (**6a**)

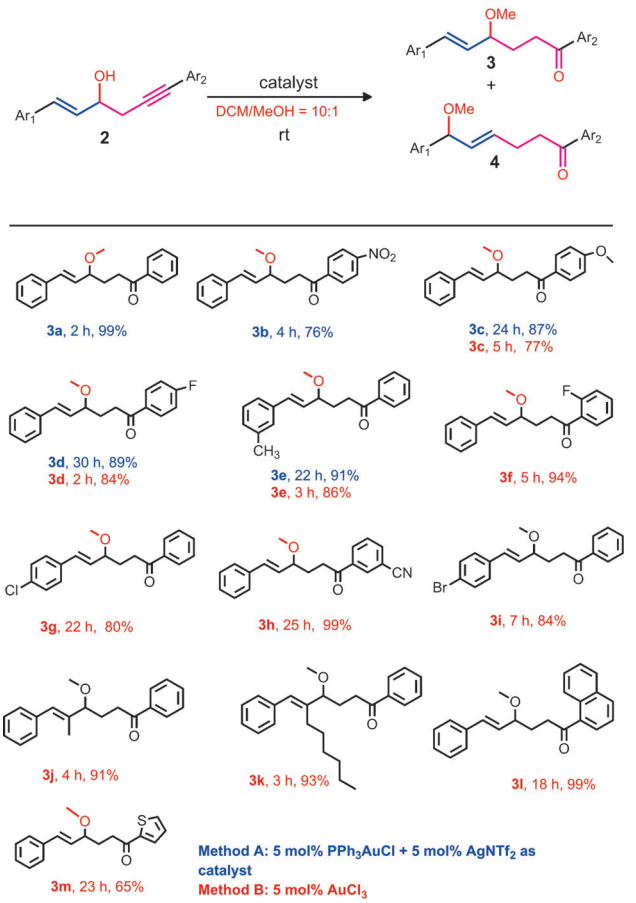
[a] Standard procedure: under an N_2 atmosphere, catalyst and solvent (2 mL) were added into the Schlenk tube, [(PPh_3)Au]NTf_2 (5% mol) was prepared in situ by stirring a mixture of [(PPh_3)AuCl] (5 mol%), $AgNTf_2$ (5 mo%l) in dry (2 mL) solvent for 20 min. After the addition of MeOH (0.2 mL) and the substrate (0.1 mmol), the reaction was carried out under the given reaction conditions and the products were subsequently detected by TLC. [b] Isolated yield.

ride and palladium(II) chloride could also effectively promote this reaction in toluene at a high temperature (entries 7 and 8). However, no desired product was obtained in $CHCl_3$ solvent when using [$Pd(PPh_3)_4$] or $SnCl_2$ even when prolonging the reaction time for 24 h (entries 9 and 10). However, a trace of allyl alcohol etherification product **5a** was obtained in the presence of $SnCl_2$ in toluene/methanol at 80 °C (entry 11). Interestingly, upon changing $PtCl_2$ to PtI_2, the reaction afforded the vinyl tetrahydrofuranyl ether **6a** in 89% isolated yield with a d.r. value of 52:48 in toluene at 45 °C (entry 12).[10b,14] Krause and co-workers have reported that an analogue of **6a** could be generated with the necessity of TsOH except when using gold catalyst. Moreover, **6a** could be slowly converted herein to the desired product **3a** under the same reaction conditions by prolonging the reaction time. When using 5 mmol% [Ir(cod)Cl]$_2$ (cod = 1,5-cyclooctadiene), the substrate **2a** gave the product **3a** and **6a** in 14 and 21% isolated yield, respectively, after 24 h (entry 13).[10e] In summary, the combination of 5 mol% [(PPh_3)AuCl] with $AgNTf_2$ was the best catalytic system and gave the highest yield, whereas using $AuCl_3$ (5 mol%) as the catalyst consumed the shortest reaction time.

Under the optimized reaction conditions, we next examined various aryl-substituted 3-hydroxy-1-en-5-ynes **2** with methanol as an external nucleophile. As shown in Table 2, two methods A (shown in blue) and B (shown in red) were applied to 3-hydroxy-1-en-5-ynes with various aryl groups at the terminal of the alkene and alkyne, respectively. It was found that all reactions could afford the corresponding γ-methoxylation ketones isomers **3** in high or excellent yields (**3**/**4** > 20:1), and method A was generally suitable for the substrates with various aryl groups at the terminal of the alkyne (**3a**–**e**), whereas method B was more efficient for those substrates with various substituted aryl or alkyl groups at the double bond (**3f**–**k**). Nevertheless, in the case of 1,5-enynols with a heteroaromatic group thiophenyl or steric hindrance naphthyl on the terminal of alkyne, only method B was applicable. Namely, these two reactants were successfully transformed to γ-methoxyketones by using 5 mol% $AuCl_3$ salt (**3l** and **3m**). In addition, for the substrates with *p*-MeO and *p*-F-substituted aryls at the terminal of the alkyne as well as the reactant with *m*-Me-substituted phenyl on the double bond, two methods were both effective (**3c**–**e**). In comparison, the [(Ph_3P)AuCl]/$AgNTf_2$ (5 mol%) catalytic system needed a longer reaction time than $AuCl_3$ in these three cases (Table 2, **3c**–**e**).

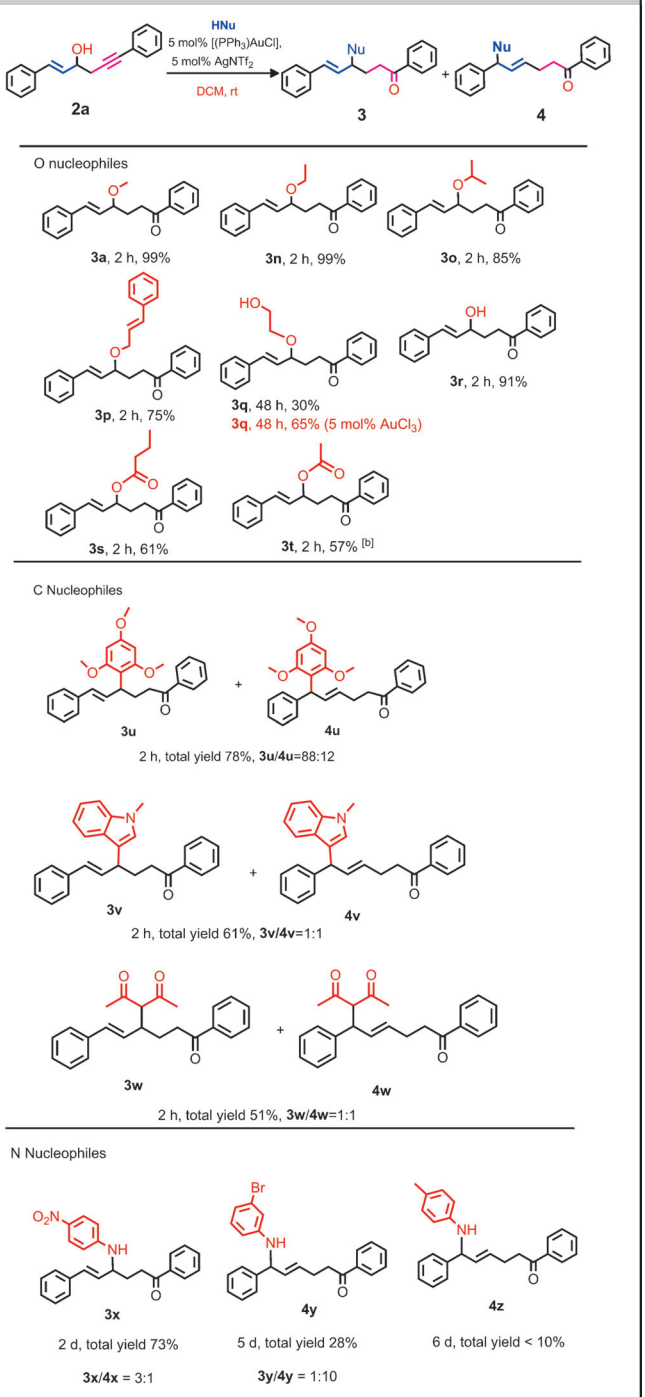
Meanwhile, we also attempted to apply this methodology to other nucleophiles (Table 3). For example, various O-, C-, and N-nucleophiles were all investigated with 1,5-enynol **2a** by using 5 mol% [(Ph_3P)AuCl]/$AgNTf_2$ in DCM (2 mL) at room temperature. Apparently, all kinds of O-nucleophiles, including all kinds of alcohols, acid, and water, could react with 1,5-enynol **2a** to

Table 2. The allyl methoxylation of various aryl-substituted 1,5-enynols.[a]



[a] Standard procedure: Under a N_2 atmosphere, the reactions were conducted with substrate on a 0.1 mmol scale in the presence of [(Ph_3P)AuCl] (5 mol%) and $AgNTf_2$ (5 mol%) or $AuCl_3$ in dry DCM/MeOH = 10:1 (2 mL) at room temperature, and the products were subsequently detected by TLC.

Table 3. The scope of nucleophilic reagents attacking the 1,5-enynols.[a]

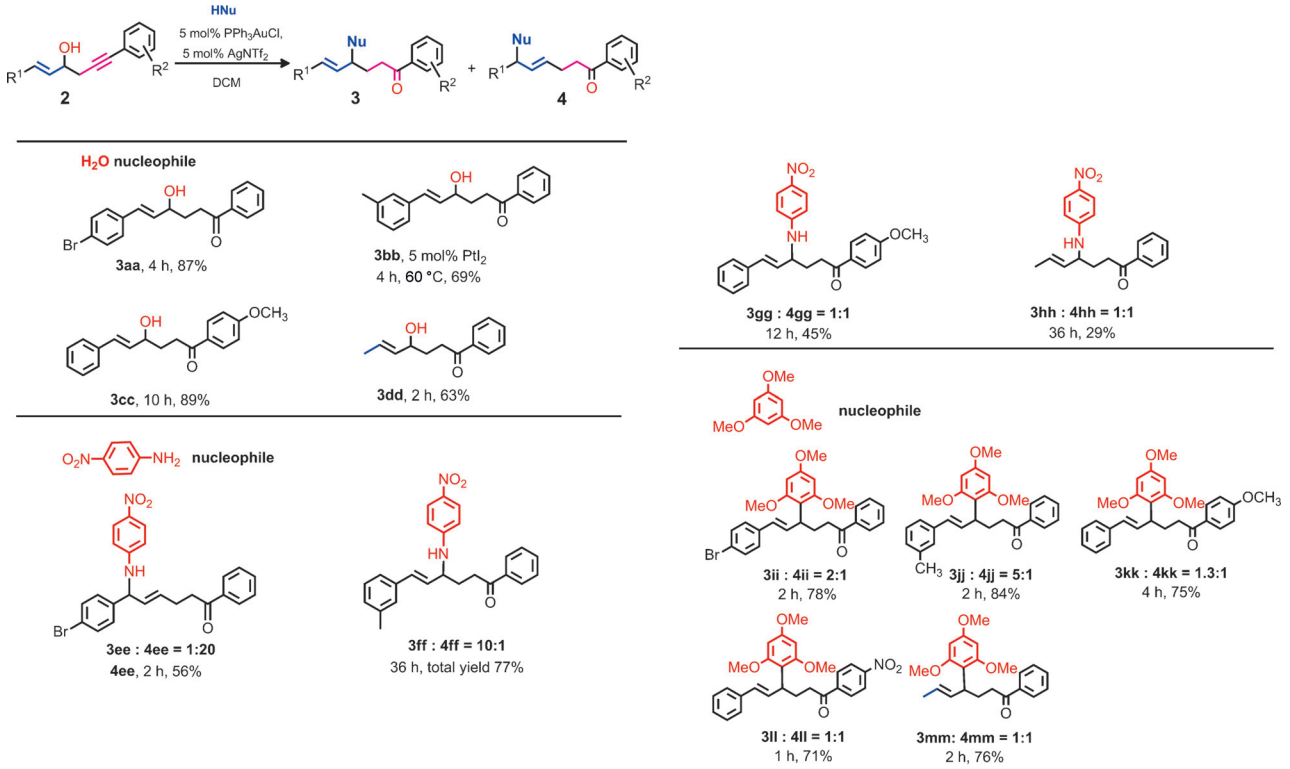


[a] Standard procedure: Under a N_2 atmosphere, [(PPh_3)Au]NTf_2(5 mol%) was prepared in situ by stirring the mixture of [(PPh_3)AuCl] (5 mol%) and $AgNTf_2$ (5 mol%) in dry DCM (2 mL) for 20 min. Then the nucleophile and substrate (0.1 mmol) were added into the above catalyst system. The reaction mixture was stirred at room temperature, and the products were subsequently detected by TLC. The amount of N- and C-nucleophile, *n*-butyric acid and acetic anhydride is 3 equiv of the substrate, while 0.2 mL O-nucleophilic reagent such as alcohols or water was utilized in these transformations. [b] Acetic anhydride (3 equiv of **2a**) as a nucleophile.

give the corresponding γ-alkoxy, carboxylic and hydroxyl ketones (**3a**, **3n**–**t**) as major products in good to high yields, respectively. Among them, for the glycol, $AuCl_3$ displayed higher catalytic activity than [(Ph_3P)AuCl]/$AgNTf_2$, resulting in γ-alkoxyketone in 65% yield (**3q**). The reactions of carboxylic acids with **2a** gave lower yields of γ-functionalized ketones than that of alcohols and water. In the examples of C-nucleophiles, we chose three types of compounds, 1,3,5-trimethoxybenzene, 1-methyl-1*H*-indole, and 2,4-pentanedione. As a result, two regioselective products, γ- and ε-functionalized ketones were obtained at the same time in good yields (**3u**–**w**, **4u**–**w**). Apart from that, the *p*-nitroaniline and *m*-bromoaniline could also react with1,5-enyol **2a** and give the corresponding γ-arylamino ketone or ε-arylaminoketone with a prolonged reaction time (**4x** and **4y**). Notably, the regioselectivity of N-nucleophiles was completely different from the O- and C-nucleophiles. The reason remained unclear at present, and this reaction was very sluggish when using *p*-methylaniline (**4z**).

In order to demonstrate the efficiency of this protocol, we investigated different nucleophiles, including water, *p*-nitroaniline, 1,3,5-trimethoxybenzene, and various substituted aryls-1,5-enynols (Table 4). A closer inspection of the results shown

Table 4. The scope of the allylic substitution of various aryl-substituted 1,5-enynols.[a]



[a] Standard procedure: Under a N_2 atmosphere, [(PPh_3)Au]NTf_2 (5 mol%) was prepared in situ by stirring the mixture of [(PPh_3)AuCl] (5 mol%) and $AgNTf_2$ (5 mol%) in dry DCM (2 mL) for 20 min. After the addition of nucleophile and the substrate (0.1 mmol), the reaction was carried out under the given reaction conditions and the products were subsequently detected by TLC. NuH = H_2O, 0.2 mL; when NuH is the N- or C-nucleophile, the ratio of nucleophile to enynol is 3:1.

in Table 4 revealed that the reaction worked well with several typical substituted 1,5-enynols, affording good to high yields of the desired products. In a general method, the H_2O nucleophile afforded the respective γ-hydroxyketone (**3aa**–**dd**) in good yields. Herein, the substrate with a 3-methylaryl group at the terminal alkene resulted in the corresponding product **3bb** with 69% isolated yield in the presence of 5 mol% PtI_2, whilst suffering decomposition using Au catalyst. Notably, the alkyl substituent (methyl) instead of a phenyl group on the terminal of alkene was also competent (**3dd**). As far as *p*-nitroaniline was concerned, only the 1,5-enynols with nonsubstituted or electron-withdrawing-substituted arenes on the double bond and electron-donating-substituted arenes on the triple bond were efficient in this cascade reaction (**4x**–**z** of Table 3, **4ee**, **3ff**–**hh** in Table 4), and the ε-arylaminoketones were mainly obtained for the enynol with an electron-withdrawing aryl on the terminal of alkene (**4ee**). Additionally, when using 1,3,5-trimethoxy-benzene as the C-nucleophile, the reaction could proceed smoothly and give a mixture of γ-substituted ketones and ε-substituted ketones in a short time, respectively (**3ii**–**mm** and **4ii**–**mm**). In short, all kinds of nucleophiles and aryl- or alkyl-substituted 1,5-enynols were competent in this cascade reaction.

Next, we investigated the possible mechanism for this cascade formal allyl substitution and hydration of alkyne. As entry 12 (Table 1) shows, the vinyl tetrahydrofuranyl ether **6a** was isolated with 89% yield. Moreover, TLC analysis and the following NMR spectroscopic experiments disclosed that the final product, γ-methoxyketone **3a**, was formed by this vinyl tetrahydrofuranyl ether intermediate **6a** in the presence of Au^I, Au^{III}, or Pt^{II} catalyst (Figure 1). The substrate **2a** was almost quantitatively converted into the intermediate **6a** after 8 min. Then the Au^I salt as the Lewis acid promoted the allylic position C–O bond cleavage and the formation of the allyl cation; MeOH as a nucleophile attacked the allyl cation by S_N or S_N' allyl alkoxylation,[1c,1g] thus rendering a mixture of compounds γ-methoxylketone **3a** and ε-isomer **3a′**. Interestingly, the characteristic peaks of ε-methoxylketone **3a′** began to disappear slowly as the reaction time was prolonged, and the signals of **3a** were correspondingly strengthened. This demonstrated that ε-methoxylketone **3a′** was isomerized to **3a** by a gold-mediated allylic substitution of allylic ether moieties and provided the only thermodynamically stable γ-methoxyl ketone.[15] Simultaneously, high regioselective hydration of internal alkynes was achieved through this strategy, although the unsymmetrical disubstituted internal alkyne remains a challenge for the regioselective hydration.

Based on this, we proposed a possible mechanism for this cascade reaction (Scheme 2). The initial 5-*endo*-*dig* cyclization through the hydroxyl group O–H insertion into the carbon–

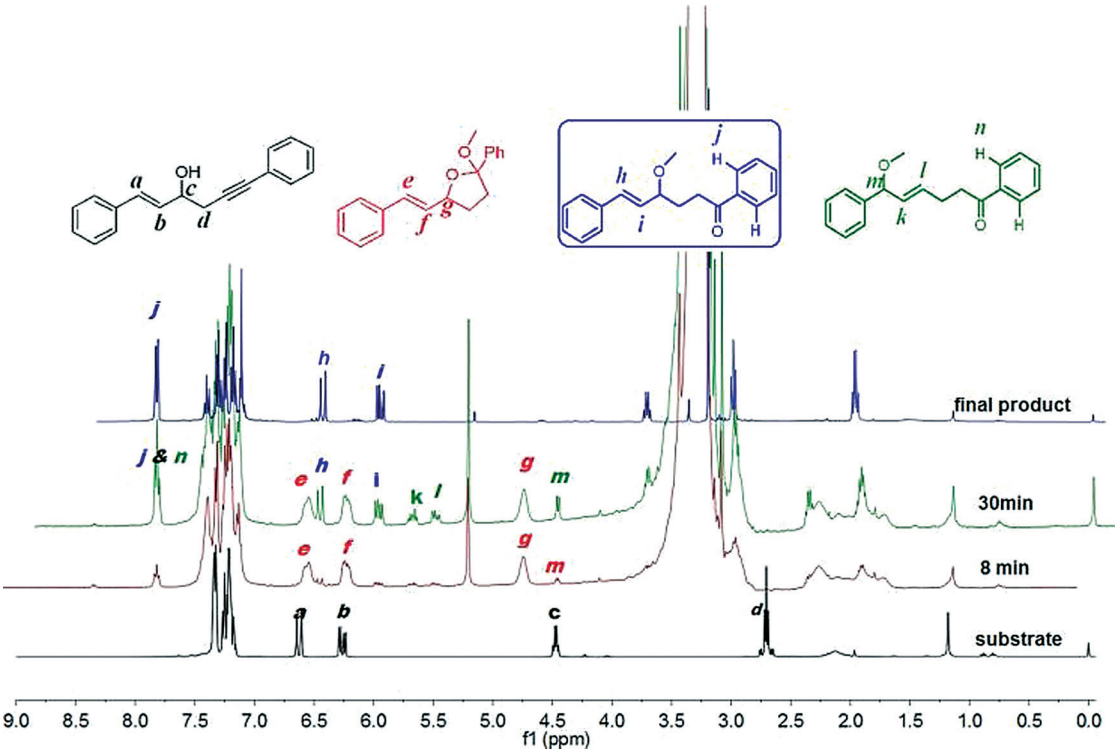
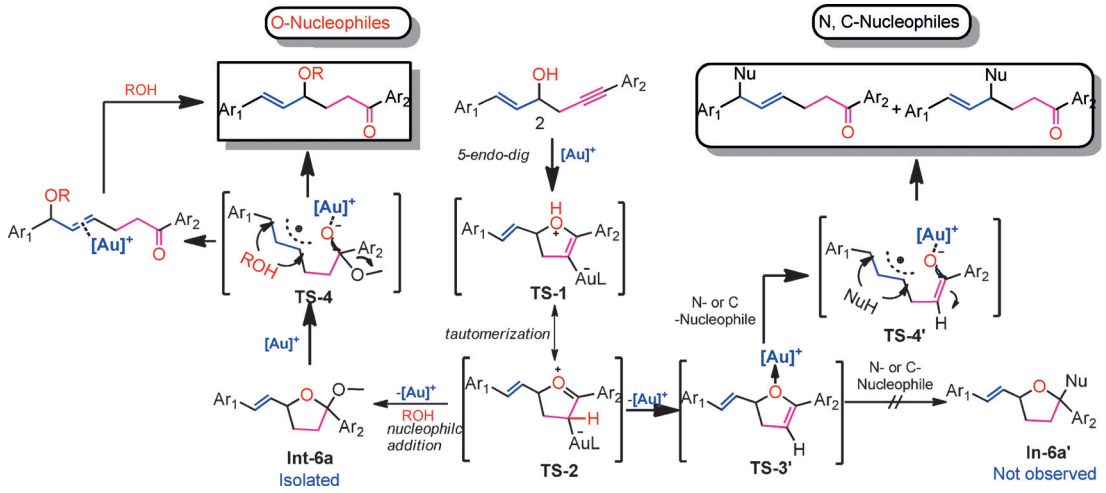


Figure 1. ^{1}H NMR trace of the reaction between homopropargylic alcohol **2a** and MeOH.

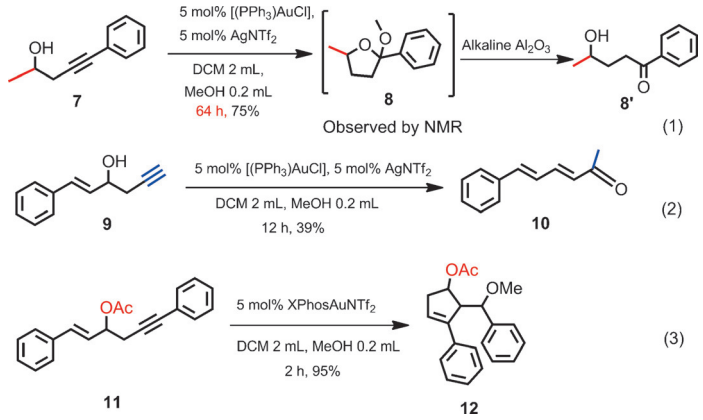


Scheme 2. Proposed possible mechanism for O-, N- and C-nucleophiles.

carbon triple bond activated by Au provided the dihydrofuran metal intermediate **TS-1**, which can be tautomerized to **TS-2**, followed by intermolecular hydroalkoxylation to give the five-membered acetal product **Int-6a**.[10,14a,b] With the assistance of Lewis acid Au^{I} or Au^{III} salt, the C–O bond at the allylic position is cleaved, and simultaneously the ring-opening of **Int-6a** occurred and gave the allyl cation intermediate **TS-4**. To the best of our knowledge, this type of ring-opening of the vinyl tetrahydrofuran was unprecedented.[15,16] The external alcohol as a nucleophile attacked the allyl cation to complete the S_N1 allylic alkoxylation and resulted in the only thermodynamically stable γ-methoxylketone. Herein, the gold catalyst acts as both π-acid to accelerate the O–H insertion into the triple bond and Lewis acid to mediate allylic ether C–O bond cleavage. For the external N-, C-nucleophiles, the first step is similar with the proposed path of O-nucleophiles, the pendent hydroxyl group directed 5-*endo-dig* cyclization to give **TS-1**, which was isomerized to **TS-2**. However, subsequent steps are different from O-nucleophiles. No signal was observed of the corresponding N- or C-nucleophilic addition to the cyclized vinyl metal intermediate **TS-3′** to form the possible vinyl tetrahydrofuran product **In-6a′**.[14a,b] Instead, **TS-3′** was activated to form the allylic

cation **TS-4′** in the presence of gold catalyst. At the end of the catalytic cycle, the external N- or C-nucleophile attacks the allylic cation to deliver the final γ-substituted products and ε-functionalized isomer.[14a]

To further ascertain the above mutual cooperation process, we performed several additional control experiments



Scheme 3. Controlled experiments of various functional substrates.

(Scheme 3). In the case of simple homopropargyl alcohol **7** without a double bond, no γ-methoxylketone was detected even after stirring for 64 h with only furanylmethylether **8** generated in 75% ^{1}H NMR spectroscopic yield. Compound **8** was then transformed to γ-hydroxyl ketone **8′** through alkaline Al_2O_3 column chromatography (Scheme 3, Eq. (1)). When using the terminal 1,5-enynol **9**, a conjugated dienone **10** was generated in 39% isolated yield under the optimized conditions (Scheme 3, Eq. (2)). For the protected 1,5-enynol **11**, another cycloisomerization product **12** was rendered by 5-*endo* and alkoxycyclization of 1,5-enyne (Scheme 3, Eq. (3)). All these results demonstrated that the structures of the internal alkyne and allyl alcohol were necessary for this novel cascade reaction. The regioselective hydration of internal alkyne and formal nucleophilic substitution of an allyl alcohol involve mutual cooperation. In this sense, the existence of the vinyl group that could stabilize the allyl cation formed is the driving force for the subsequent possible ring-opening reaction and allyl-substitution reaction.

In conclusion, a cooperated formal allyl alcohol nucleophilic substitution reaction and hydration of alkyne was developed in the presence of gold catalyst in one pot. This transformation occurs under very mild conditions using readily available 1,5-enynols (based on homopropargyl alcohols), and a series of γ-functionalized ketones can be obtained in high to excellent yields. O-, N- and C-based nucleophiles are all competent in this cascade reaction. Importantly, this reaction actually involved an intramolecular O–H insertion cyclization of alkyne to form a vinyl dihydrofuran intermediate, which was followed by nucleophilic addition ring-opening to give the highly regioselective γ-functionalized ketone. The ring-opening mode of vinyl dihydrofuran involved was unprecedented. Despite of the challenging regioselective hydration of the internal alkyne and the nucleophilic substitution of allyl alcohol, our substrates structural properties endow them self-selectivity and self-activation functions to achieve this cascade reaction. This corresponding γ-substituted ketone is a prevalent subunit in several classes of biologically relevant molecules, and the reactivity of the vinyl dihydrofuran functional group was explored. Future plans include establishing the chiral γ-substituted ketone that may be achieved by this method with an additional chiral ligand, understanding the factors governing the ring-opening of this vinyl dihydrofuran intermediate, and pursuing synthetic applications.

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Keywords: 1,5-enynols · cyclization · gold catalysis · hydration · nucleophilic substitution · ring-opening reactions

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