Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b00882 • Publication Date (Web): 09 Mar 2016

Intermolecular Homopropargyl Alcohol Addition to Alkyne and a Sequential 1,6-Enyne Cycloisomerization with Triazole-Gold Catalyst

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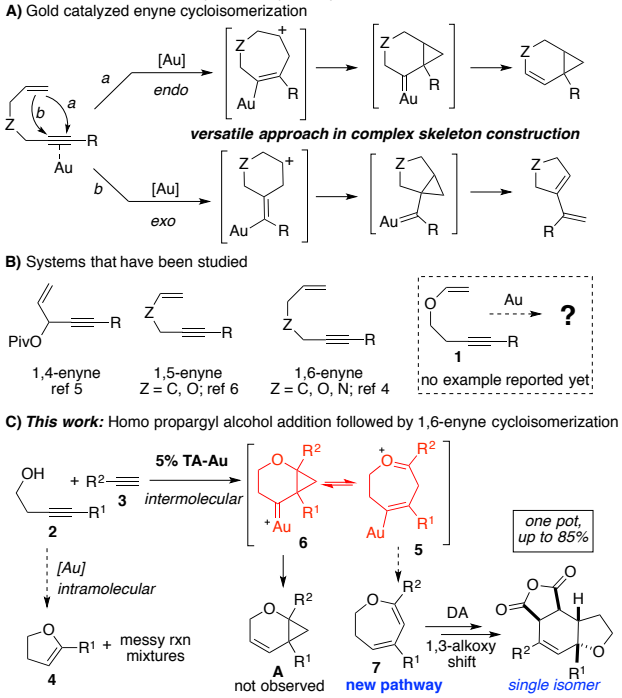
Supporting Information Placeholder

ABSTRACT: While gold-catalyzed homopropargyl alcohol cyclization is a known process, a triazole-gold catalyst prevented the intramolecular cyclization in the presence of terminal alkynes. As a result, an intermolecular addition to an alkyne was achieved. A sequential 1,6-enyne cycloisomerization gave the unusual 2,3-dihydrooxepine, which revealed another new reaction path. Diels-Alder reaction of oxepine followed by a 1,3-alkoxyl shift gave hydrobezofuran derivatives in high yields. Diasterioselective reaction of homopropargyl alcohol to final product enabled one-step formation of five stereogenic centers with excellent enantiomeric selectivity.

Gold-catalyzed reactions developed very fast during the last decade.[1] The enyne cycloisomerization is a fundamentally important process in chemistry research due to its ability to open access to complex architectures through simple steps[2] and its mechanisms that often reveal new chemistry insights.[3] Homogeneous gold(I) catalysts have been employed in promoting enyne cycloisomerization with pioneering works reported by Echavarren,[4] Fürstner,[5] Toste[6] and others.[7] Implementation of enyne cycloisomerization for synthesizing complex building blocks and its mechanistic insight is advancing rapidly.[8] In most of the gold-catalyzed enyne cycloisomerization examples, formation of gold carbene intermediates was proposed.[9] As shown in **Scheme 1A**, depending on the *endo* or *exo* cyclization paths, various functional cyclic skeletons can be synthesized.

Our interest in enyne cycoisomerization was initiated from our recent success in synthesizing vinyl ethers through triazole gold-catalyzed intermolecular alcohol addition to alkyne.[10] As shown in **Scheme 1B**, cycloisomerization of 1,6-enyne bearing vinyl ether moiety has not been reported in the past. The attractive synthetic utility and mechanistic novelty ensured urgency and significance of investigating cycloisomerization of this special type of 1,6-enyne. Compared with other reported 1,6-enyne substrates, the vinyl ether substrate **1** will give the oxonium intermediate instead of simple carbocation. Hence, thermodynamic stability of the oxonium cation **5** versus gold carbene **6** will play an important role in this equilibrium. Thus, different reactivity is expected. Hypothetically, protodeauration of intermediate **5** could lead to seven-membered diene intermediate of 1,6-enyne cyclization, which was never trapped before (**Scheme 1C**). Herein, we report the first successful example of homopropargyl vinyl ether cyclization in forming dihydrooxepine as unprecedented product. The cycloaddition/isomerization of the dihydrooxepine (with the presence of dienophile) gave highly functional tricyclic skeletons with excellent stereoselectivity (**Scheme 1C**).

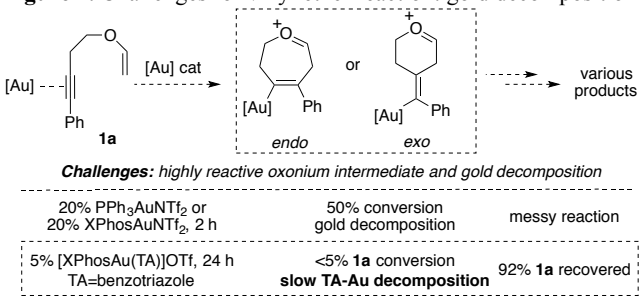
Scheme 1. Gold-catalyzed enyne cycloisomerizations



We began our study with homopropargyl vinyl ether **1a**. In fact, reaction of **1a** with typical $[L\text{-}Au]^+$ catalysts gave rapid gold decomposition associated with the formation of very complex mixtures (**Figure 1**). Even, loading 20% $XPhosAuNTf_2$ gave only less than 50% conversion of **1a**. During the last several years, our group has been working on developing new transition metal catalysts using 1,2,3-triazole as ligand.[11] Those efforts led to the discovery of triazole-gold (TA-Au) with significantly improved catalyst stability.[12] We charged enyne **1a** with [XPhosAu(TA)]OTf, which gave much slower catalyst decomposition (>80% TA-Au remaining after 24h).

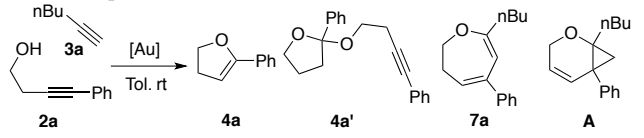
Although TA-Au alone could not activate **1a**, it offered a potential solution to promote enyne cycloisomerization with balanced catalyst reactivity-stability (developing more reactive TA-Au). Additionally, synthesis of vinyl ethers are not straightforward since their synthesis needs almost stoichiometric amount of $Hg(OAc)_2$ in ethyl vinyl ether (as solvent), giving only 50% yield of product.[13]

Figure 1. Challenges for vinyl ether reaction: gold decomposition



With all these concerns, we proposed the intermolecular reaction between homopropargyl alcohol and terminal alkyne to form vinyl ether **1** (1,6-enyne) in situ.[14] This design, although is challenging, will deliver an efficient method to synthesize oxygen containing seven membered rings **7** (oxepane derivatives), which can be further used as a building block in complex cyclic structure synthesis. To evaluate this hypothesis, various gold catalysts were applied to react with homopropargyl alkyne **2a** and terminal alkyne **3a**. The results are summarized in **Table 1**.

Table 1. Optimization of the reaction condition[a,b]



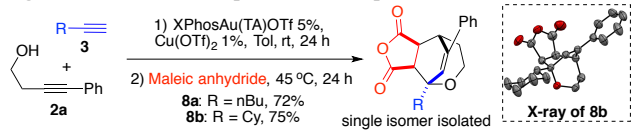
Entry	cat	Time	convn (%)	4a+4a' (%)	7a (%)
1	PPh_3AuNTf_2 (5%)	10 h	56	46	0
2	$XPhosAuNTf_2$ (5%)	15 h	90	40	33
3	XPhosAu(TA)OTf (5%)	30 h	72	16	37
4	**XPhosAu(TA)OTf (5%), $Cu(OTf)_2$ (1%)**	**24 h**	**100**	**11**	**84**
5	$XPhosAuNTf_2$ (5%), $Cu(OTf)_2$ (1%)	24 h	100	60	32
6	Other cat: 10% $PtCl_2$, 10% $(COD)_2RhCl$, 10% Cu(OTf); 10% HOTf; 20% AgOTf etc	24 h	up to 100	<20	<5

[a] Conditions: **2a** (1 mmol), **3a** (3 mmol), gold cat. (5 mol %), copper (1 mol %), solvent (10 mL). [b] ^{1}H-NMR yields using 1,3,5-trimethoxybenzene as internal standard.

Using PPh_3AuNTf_2 catalyst, significant amount of intramolecular cyclization product **4a** and its derivative **4a'** was obtained, along with rapid catalyst decomposition. Interestingly, with 5% $XPhosAuNTf_2$, diene **7a** was observed by crude NMR, though in low yield. Notably, clear gold decomposition was observed over long reaction time. Switching $XPhosAuNTf_2$ to XPhosAu(TA)OTf (TA-Au) not only helped preventing gold catalyst decomposition, but also significantly reduced the formation of **4a**. As reported in our previous works, application of Lewis acid as co-catalyst with TA-Au will help triazole dissociation of gold, giving more reactive catalyst while maintaining good stability.[15] Moreover, Lewis acid can reactivate the poisoned decomposed catalyst.[16] Using $Cu(OTf)_2$ (1%) as co-catalyst, the desired intermolecular condensation product **7a** was observed in 84% NMR yield. Other Lewis acid co-catalysts have also been evaluated (see detailed screening in SI) and $Cu(OTf)_2$ gave the best result. Notably, product **A** was not observed in this new transformation. Other typical catalysts, including Pt, Rh, Ag and HOTf, have also been evaluated. The product **7a** was not observed in all other tested cases, which greatly highlighted the unique reactivity of TA-Au catalyst for this cascade transformation.

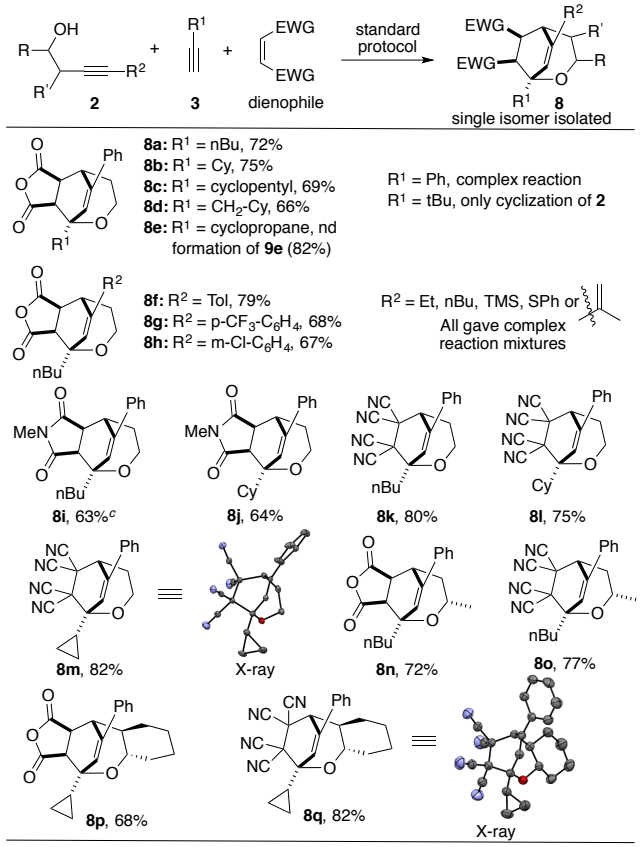
Although, **7a** was clearly observed according to the crude NMR and MS, its purification using column chromatography and concentration on roto-vap was problematic due to the gradual decomposition. Theoretically, **7a** as a highly reactive electron rich diene, which makes it a good choice for Diels-Alder reaction.[17] Maleic anhydride was applied to the reaction mixture of **7a** (one-pot). As expected, the desired product **8** was observed in excellent yields (**Figure 2**).

Figure 2. Cascade, one-pot, three-component condensation



Excellent stereoselectivity was achieved for this cascade reaction with only *endo*-product obtained. The structure was confirmed by X-ray crystallography (**8b**). To evaluate the reaction scope, various homopropargyl alcohols, alkynes and dienophiles were tested as shown in **Table 2**.

Table 2. Reaction scope for synthesis of Diels-Alder product[a,b]

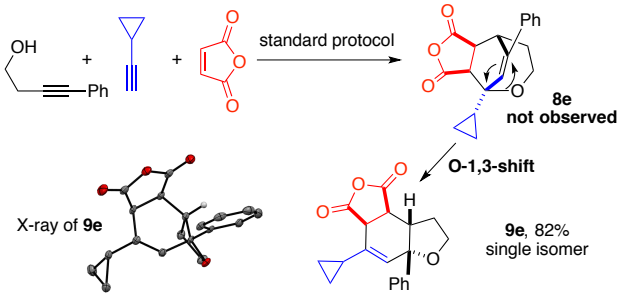


[a] General reaction conditions: a solution of **2** (1 mmol), **3** (3 mmol), gold cat. (5 mol%), copper (1 mol%) and toluene (10 mL) stirred at rt. The mixture passed through a short silica pad and then dienophile (1.3 mmol) added and the mixture heated on 45 °C for 24 more hours. (See details on SI). [b] Isolated yield. [c] NMR yield (due to the substrate decomposition during purification).

For terminal alkyne **3**, aliphatic R^1 groups, such as *n*Bu (linear) and cyclohexyl (cyclic) alkynes work well, except *tert*-butylacetylene and trimethylsilylacetylene. This is likely due to the steric effect, which caused slow alcohol addition to terminal alkyne. Aromatic alkynes gave complex reaction mixtures, suggesting the existence of alternative reaction path due to the formation of benzylic carbocation intermediate. In contrast, the homopropargyl alcohol bearing aromatic alkynes gave good results (**8f–8h**). Complex reaction mixtures were obtained with aliphatic group at R^2 positions. Potentially, 6-exo cyclization can occur on those cases, which caused the undesired side reactions. Other dienophiles were also tested. Both N-methylmaleimide and tetra-cyanoethylene worked as efficient as maleic anhydride. Mono-EWG activated alkene, including α,β-unsaturated ester and nitroalkene, could not give good yield of the desired product under optimal conditions due to their lower reactivity.

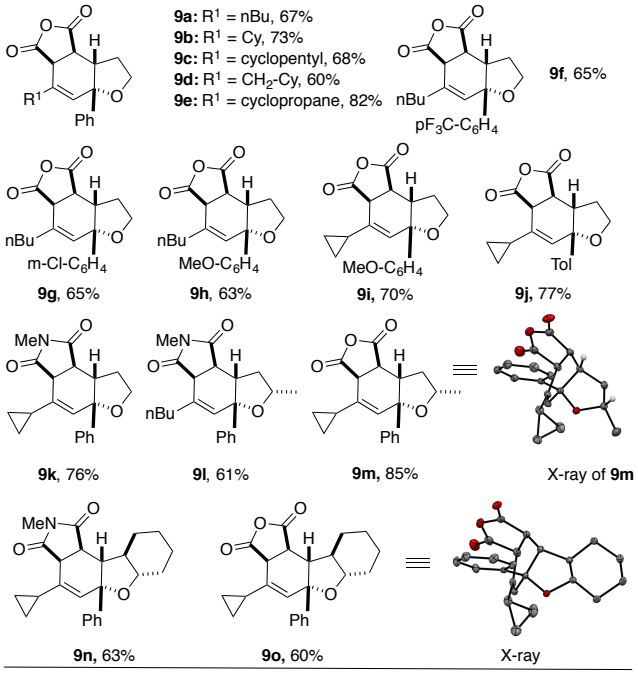
Excellent stereoselectivity was obtained in all cases with only endo product observed. Moreover, with substituted homopropargyl alcohol (R≠H), single isomer was isolated (**8n–8q**). This result highlighted the great advantage of this new method in constructing complicated multicyclic structures with high diasteroselectivity. One interesting observation was the reaction of cyclopropylacetylene, which under the standard conditions, Diels-Alder product **8e** was not observed. Instead, a tricyclic compound **9e** was obtained as a single isomer with 82% isolated yield (**Figure 3**). But for the case of **8p**, the Diels-Alder product formed.

Figure 3. Rapid 1,3-Alkoxyl-shift to substituted hydrobenzofuran



The relative configuration of each stereogenic center of **9e** was confirmed by X-ray crystallography. Based on the structure, **9e** was evolved from **8e** through an unusual (unprecedented) alkoxyl 1,3-rearrangement. Notably, no cyclopropane ring opening products were observed, suggesting the concerted mechanism over stepwise carbocation pathway approach. There are few examples reported in literature for concerted 1,3-O-suprafacial rearrangements, unlike hydrogen or alkyl 1,3-shift.[18] It is possible that the shape of cyclopropyl group forced the structure of **8e** to adopt a conformation that allowed the orbital rearrangement at relatively mild condition (45 °C). Whereas, compound **8a** (R^1 = *n*Bu) needed elevated temperature in order for oxygen shift to take place. Conducting this reaction in a one-pot fashion (directly from **1a** and performing second step at 75 °C, the desired substituted hydrobenzofuran **9a** was obtained in 67% isolated yield (combining three steps). This result is exciting since it not only revealed an interesting 1,3-O sigmatropic rearrangement, but also provided a new strategy to prepare complex hydrobezofuran derivatives from simple starting materials with excellent overall yield and stereoselectivity. Various homopropargyl alcohols and terminal alkynes were used to evaluate the reaction scope. The result is shown in **Table 3**.[19]

Table 3. Reaction scope for synthesis of the tricyclic structures[a,b]

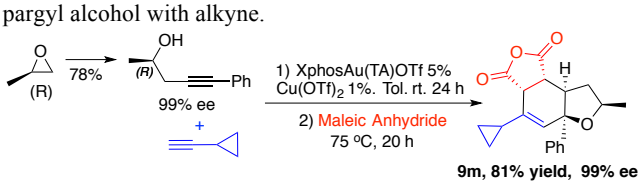


[a] General reaction conditions: a solution of **2** (1 mmol), **3** (3 mmol), gold cat. (5 mol%), copper (1 mol%) and toluene (10 mL) stirred at rt. The mixture passed through a short silica pad and then dienophile (1.3 mmol) added and the mixture heated on 75 °C for 24 more hours. (See details on SI). [b] Isolated yield.

As shown in **Table 3**, this 1,3-alkoxy rearangement works for compounds **8** derivatives from either maleic anhydride or N-methylmaleimide. Surprisingly, the tetracyano substituted products (**8k-8m, 8o** and **8q**) demonstrated much higher stability toward alkoxyl shift even with cyclopropyl group at R^1 position. Even upon heating compound **8m** at 100 °C for 48 hours, no alkoxyl shift observed (>95% **8m** recovered). Analyzing the crystal structures of **8b** and **8m** revealed almost identical geometry of the core [3. 2. 2] structure between the two compounds. Considering the significantly different reactivity between **8b** and **8m**, it is likely that the electronic effect is very influential for this 1,3-O-shift. Investigations on the mechanism are currently undergoing.

Excellent stereoselectivity was achieved with one dominating stereoisomer isolated in all cases. Additionally, using chiral homo propargyl alcohol as the starting materials, the desired benzofurans were obtained as a single isomer (**9l–9p**). The absolute stereochemistry was again confirmed by X-ray crystallography (**9m** and **9p**). Based on these results, we developed protocol as shown in **Figure 4** to synthesize single enantiomer of 9m.

Figure 4. Diasterioselective reaction of non-racemic homopropargyl alcohol with alkyne.



The enantiomeric enriched homopropargyl alcohol can be readily prepared from alkyne addition to chiral epoxide. Charging the non-racemic homopropargyl alcohol with terminal alkyne

under the standard protocol, the chiral hydrobenzofuran **9m** was observed in 81% isolated yields with more than 99% ee. Overall, five stereogenic centers were successfully set up through two simple steps. Application of this strategy toward some challenging natural product synthesis are currently undergoing in our group.

In conclusion, we report herein the first intermolecular homopropargyl alcohol addition to alkyne followed by intramolecular enyne cycloisomerization. Using triazole-gold catalyst, we effectively prevented both the homopropargyl alcohol intramolecular cyclization and gold decomposition caused by the vinyl ether intermediate. The success in trapping diene **7** through Diels-Alder cycloaddition and observation of unusual 1,3-O-shift highlighted the advantages of this new strategy for the preparation of complex organic molecules with high efficiency and excellent stereoselectivity.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank the NSF (CHE-1362057) and NSFC (21228204) for financial support. We are thankful to Sri Krishna Nimmagadda and Professor Jon Antilla in helping us performing chiral HPLCs.

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