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

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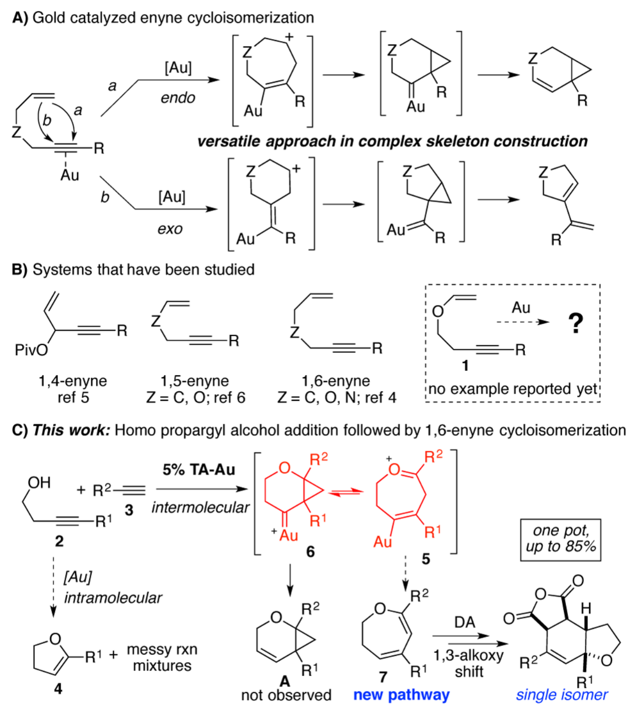
Supporting Information

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 past 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. 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 <50% conversion of **1a**. We charged enyne **1a** with [XPhosAu(TA)]OTf, which gave much slower catalyst decomposition (>80% TA-Au remaining after 24 h).

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 is not straightforward since their synthesis needs almost a stoichiometric amount of $Hg(OAc)_2$ in ethyl vinyl ether (as solvent), giving only 50% yield of product.[11]

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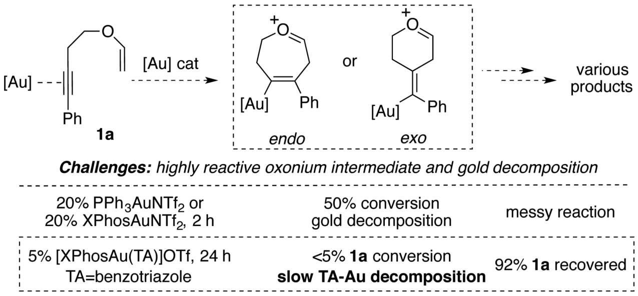
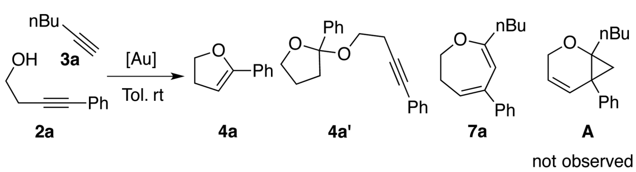


Figure 1. Challenges for vinyl ether reaction: gold decomposition.

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.[12] This design, although is challenging, will deliver an efficient method to synthesize oxygen-containing seve- 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 (h)	convn (%)	4a + 4a′ (%)	7a (%)
1	PPh_3AuNTf_2 (5%)	10	56	46	0
2	$XPhosAuNTf_2$ (5%)	15	90	40	33
3	XPhosAu(TA)OTf (5%)	30	72	16	37
4	**XPhosAu(TA)OTf (5%), $Cu(OTf)_2$ (1%)**	**24**	**100**	**11**	**84**
5	$XPhosAuNTf_2$ (5%), $Cu(OTf)_2$ (1%)	24	100	60	32
6	Other cat: 10% $PtCl_2$, 10% $(COD)_2RhCl$, 10% Cu(OTf); 10% HOTf; 20% AgOTf etc	24	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, a 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) 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.[13] Moreover, Lewis acid can reactivate the poisoned decomposed catalyst.[14] Using $Cu(OTf)_2$ (1%) as co-catalyst, the desired intermolecular condensation product **7a** was observed in 84% NMR yield.

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.[15] 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).

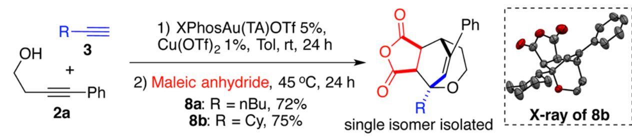
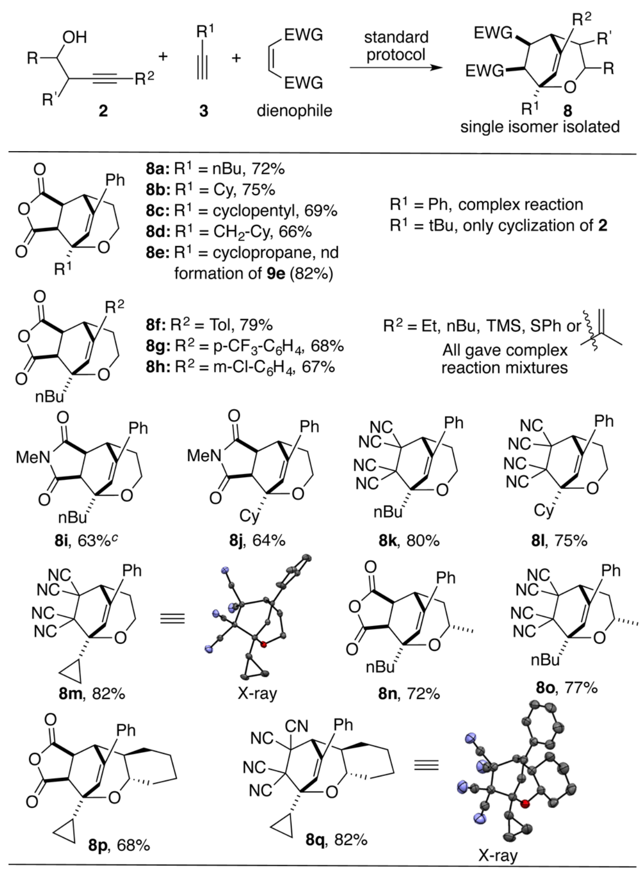


Figure 2. Cascade, one-pot, three-component condensation.

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.

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

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, 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).

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alkyne. Aromatic alkynes gave complex reaction mixtures, suggesting the existence of an 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 in these cases, which caused the undesired side reactions. Other dienophiles were also tested. Both *N*-methylmaleimide and tetra-cyanoethylene worked as efficient as maleic anhydride.

Excellent stereoselectivity was obtained in all cases with only the 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.

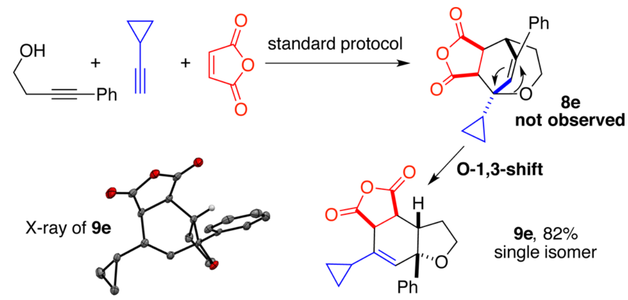
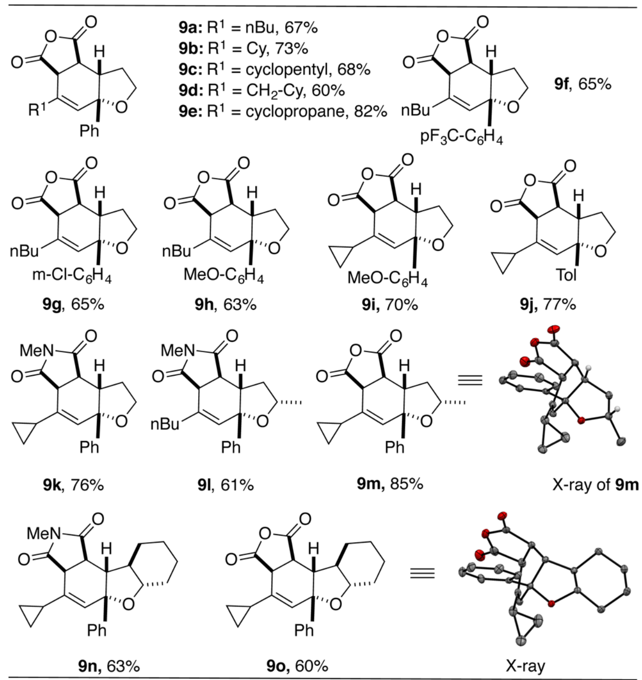


Figure 3. Rapid 1,3-alkoxyl-shift to substituted hydro-benzofuran.

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 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.[16] 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. The result is shown in Table 3.[17]

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 h, no alkoxyl shift was 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.

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, then dienophile (1.3 mmol) added, and the mixture heated on 75 °C for 24 more hours (see details in SI). [b]Isolated yield.

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–9o**). The absolute stereochemistry was again confirmed by X-ray crystallography (**9m** and **9o**). Based on these results, we developed protocol, as shown in Figure 4, to synthesize the single enantiomer of **9m**.

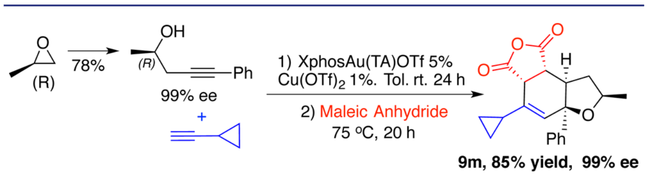


Figure 4. Diasterioselective reaction of nonracemic homopropargyl alcohol with alkyne.

The enantiomeric-enriched homopropargyl alcohol can be readily prepared from alkyne addition to chiral epoxide. Charging the nonracemic 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 is currently ongoing in our group.

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In conclusion, we report herein the first intermolecular homopropargyl alcohol addition to alkyne followed by intramolecular enyne cycloisomerization. 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. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00882.

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Notes

The authors declare no competing financial interest.

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