

Gold-catalyzed reaction of enynols by a dimerization–fragmentation process: an expeditious assembly of enyne molecular architecture†

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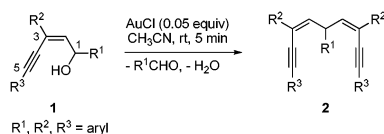
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Intermolecular condensation reaction of 1,3,5-triarylenynols catalyzed by gold as Lewis acid was reported for the first time; the products with unique structures have potential applications in materials chemistry, and tandem reaction product 3n has been used to detect mercury ions as an organic molecular probe.

As multifunctional molecules, enynols have been used as important key building blocks for diversity-oriented organic synthesis. Various oxygen-containing heterocycles such as six-membered lactones,¹ pyrans,² furans and furan derivatives³ have been prepared from 2-en-4-yn-1-ols catalyzed by ruthenium, palladium and silver as transition metals. Recently, organic transformations catalyzed by gold complexes as transition metals and/or Lewis acids have been a focus of attention⁴ and several 2-en-4-yn-1-ols have been used to afford furans and their derivatives catalyzed by gold.⁵ Compared with the usually preferred π -complexation of the alkyne moiety of enynols with Au catalyst as a transition metal, recently we interestingly found an unprecedented Au(I)-catalyzed condensation reaction of 1,3,5-triarylenynols with high stereoselectivity, in which the Au catalyst exhibits its unusual Lewis acidity in enynol chemistry (Scheme 1). Remarkably, this reaction proceeded under very mild conditions (CH₃CN, room temperature, 5 min), and the synthetically interesting dienynes **2** with multiple double and triple bonds could be achieved efficiently from the easily available triarylenynols **1**. The unique structure of these products, which is difficult to obtain directly by other known synthetic methods, features two symmetric conjugated enyne systems linked by a methyne. This condensation reaction may be useful for the expeditious assembly of some structurally complex, highly conjugated functional molecules in materials chemistry. Herein we present our preliminary results on this novel Au(I)-catalyzed cross-coupling.



Scheme 1 Au(I)-Catalyzed condensation reaction of enynols.

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Table 1 Optimization of reaction conditions^a

Entry	Catalyst	Solvent	Time	Yield (%) ^b	
				2a	1aa
1	AuCl	CH ₃ CN	5 min	91	0
2 ^c	Au(PPh ₃)Cl	CH ₂ Cl ₂	—	0	0
3	AuCl ₃	CH ₃ CN	5 min	80	0
4	NaAuCl ₄ ·2H ₂ O	CH ₃ CN	5 min	80	0
5	TiCl ₄	CH ₂ Cl ₂	4 h	0	49
6	Cu(OTf) ₂	CH ₂ Cl ₂	4 h	15	57
7	AlCl ₃	CH ₂ Cl ₂	9 h	5	49
8 ^d	TMSCl	CH ₂ Cl ₂	7 h	Trace ^e	65

^a Reaction conditions: enynol **1a** (0.5 mmol), catalyst (5 mmol%), and solvent (2 mL) at room temperature under Ar atmosphere. ^b Isolated yield. ^c No reaction. ^d 22% of starting material was recovered. ^e Inspected by TLC.

During the course of our studies on the reactivity of 1,3,5-trisubstituted enynols which were prepared readily through the three-component coupling protocol developed by our group,⁶ 1,3,5-triphenyl-enynol **1a** (R¹ = R² = R³ = Ph) was initially taken as a model, and several Au catalysts were screened for their catalytic activity (Table 1, entries 1–4). From this optimization of reaction conditions, it was found that 0.05 equivalent of AuCl in CH₃CN at room temperature gave the best result for the formation of dienynyl **2a**, with both a high yield of 91% and short reaction time of 5 min. While using AuCl₃ or NaAuCl₄·2H₂O as catalyst, a slightly lower yield of **2a** of 80% was found in each case, but Au(PPh₃)Cl was completely ineffective. Employment of non-gold catalyst TiCl₄ resulted in the formation of undesired ether product **1aa** and no expected product was isolated. Cu(OTf)₂ or AlCl₃ gave **1aa** as the major component and afforded **2a** in very low yields. TMSCl in the presence of enynol **1a** bearing a free hydroxyl group was used to generate trace amounts of HCl *in situ*, but none of the expected dienynyl **2a** could be isolated in the current reaction system, in which ether **1aa** could be isolated after 7 h in 65% yield.

To probe the generality of this reaction, a series of enynol substrates were then prepared through the previously reported three-component coupling protocol. Under the optimized reaction conditions above (5 mmol% AuCl in CH₃CN at rt), various enynols bearing different aryl substituents at C-1, C-3

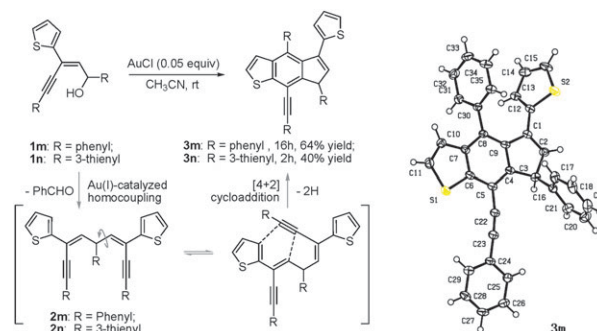
Table 2 Au(I)-Catalyzed condensation of various enynols^a

Entry	1	R ¹ , R ² , R ³	2	Yield (%) ^b
1	1a	R ¹ = R ² = R ³ = Ph	2a	91
2	1b	R ¹ = R ³ = Ph, R ² = 3-C ₆ H ₄ OMe	2b	90
3	1c	R ¹ = R ³ = Ph, R ² = 4-C ₆ H ₄ OMe	2c	82
4	1d	R ¹ = R ³ = Ph, R ² = 3,4,5-C ₆ H ₂ (OMe) ₃	2d	97
5	1e	R ¹ = R ² = Ph, R ³ = 4-C ₆ H ₄ OMe	2e	92
6	1f	R ¹ = R ³ = 2-(6-OMe)-naphthyl, R ² = Ph	2f	92
7	1g	R ¹ = R ³ = Ph, R ² = 4-C ₆ H ₄ F	2g	95
8	1h	R ¹ = R ² = Ph, R ³ = 4-C ₆ H ₄ Cl	2h	95
9	1i	R ¹ = Ph, R ² = 4-C ₆ H ₄ CF ₃ , R ³ = 4-C ₆ H ₄ OMe,	2i	88
10	1j	R ¹ = Ph, R ² = 4-C ₆ H ₄ OMe, R ³ = 4-C ₆ H ₄ CF ₃	2j	84
11	1k	R ¹ = R ³ = 4-C ₆ H ₄ OMe, R ² = 4-C ₆ H ₄ CF ₃	2k	75
12	1l	R ¹ = R ³ = 4-C ₆ H ₄ CF ₃ , R ² = Ph	2l	0 ^c

^a General conditions: enynol **1** (0.5 mmol), AuCl (5 mmol%), and CH₃CN (2 mL) at rt under Ar for 5 min. ^b Isolated yield. ^c Substrate **1l** disappeared under the general conditions, and no desired coupling product was obtained.

and C-5 (**1b–1k**, entries 2–11 of Table 2) were subjected to this condensation reaction. From Table 2, it can be seen that all examples reacted within 5 min in good to high yields (75–97%). It should be noted that the current condensation reaction of enynols was dependent, to some degree, upon the electronic properties of the aryl substituents R¹–R³ in **1**. For example, when substrates bearing electron-donating aryl substituents (entries 2–6) or weakly electron-withdrawing ones (entries 7–8) were employed, this reaction could proceed smoothly to give the expected products in good to high yields. When either of R² or R³ in **1** was an electron-withdrawing group (entries 9–11), the reaction gave slightly lower yields. However, the substrate with two electron-deficient aryls was ineffective in this condensation (entry 12). In addition, only a complex mixture was observed when using substrates **1** where any of the substituents R¹–R³ were aliphatic.

In order to expand the substrate scope, as shown in Scheme 2, the substrate enynol **1m** with a thienyl substituent was designed and prepared from phenylacetylene and 2-thiophenecarboxaldehyde. The condensation reaction proceeded readily under the standard conditions, and the starting material **1m** disappeared after 5 min as before. Surprisingly, however, the expected product **2m** was labile during purification by column chromatography, generating an interesting poly-substituted tricyclic arenof[*h*]indene **3m**.[†] Further investigation disclosed that **3m** could be obtained in 64% yield simply by prolonging the reaction time to 16 h. Moreover, enynol **1n** with three thiophene units prepared from 3-thienylacetylene and 2-thiophenecarboxaldehyde also gave the same type of product **3n** after 4 h in 40% yield (Scheme 2). This protocol provided a straightforward and effective approach to a new type of polysubstituted and polycyclic aromatic compounds. In this case, a novel tandem Au-catalyzed homocoupling–[4 + 2] cycloaddition–dehydrogenation reaction was presented (Scheme 2). To our best knowledge, this kind of intramolecular Diels–Alder reaction of inner–outer-ring dienes with alkynes in an all-carbon skeleton has not been reported.⁷ Clearly, it indicated that the relative configuration

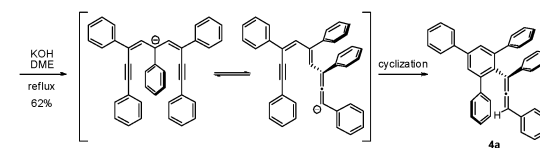
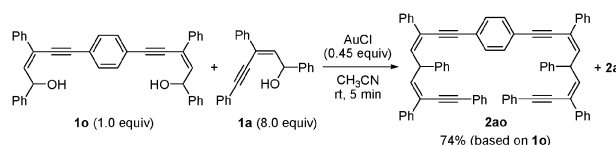
**Scheme 2** Au(I)-Catalyzed tandem condensation–cycloaddition–dehydrogenation reaction of **1m**.

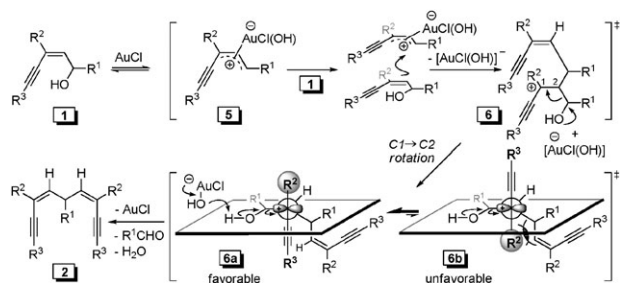
of the olefin moiety in the intermediate **2m** was the same as that of the starting material **1m**, which also provided further support for the stereochemistry of the diyne products **2a–2k** of Table 2.

Intrigued by the tandem reaction mentioned above, we conceived a base-promoted thermocyclization of the diyne **2a** due to the weak bond dissociation energy of the aryl-methylene C–H bond in **2** (Scheme 3). Gratifyingly, the polyaromatic allenic compound **4a** was smoothly afforded in 62% yield through a deprotonation–cyclization process.⁸ This transformation provided a way to further explore the new chemical properties and applications of diynes obtained in the current condensation reaction of enynols.

Furthermore, condensation reaction between **1o** and **1a** was conducted under the present conditions. As shown in Scheme 4, a mixture of **1o** and **1a** was treated with AuCl (0.45 equiv.) in CH₃CN at rt for 5 min, and pleasingly the expected product **2ao** was isolated in 74% yield. This example demonstrated the possibility of the expeditious assembly of polyenyne molecular architecture by combination of different enynol building blocks.

On the basis of the above experimental results, a possible mechanism for our Au(I)-catalyzed condensation reaction was proposed (Scheme 5). Initially, AuCl-promoted dehydroxylation of enynol **1**, which was followed by electrophilic addition of the allylic cation center of **5** to a second molecule of enynol, gave the propargylic carbocation **6**.⁹ Subsequently, **6** underwent a stereoselective Grob fragmentation through the energetically favorable conformation **6a** to furnish the product **2** along

**Scheme 3** Base-promoted thermocyclization of **2a**.**Scheme 4** Condensation of dienynol **1o** with enynol **1a**.



Scheme 5 Mechanism of Au(I)-catalyzed coupling of enynols.

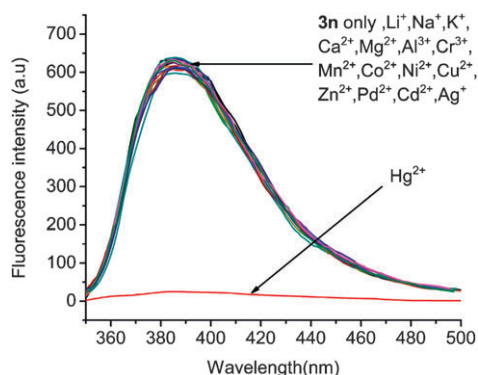


Fig. 1 Fluorescence emission spectra of **3n** in the presence of different metal ions Li^+ , Na^+ , K^+ , Ca^{2+} , Mg^{2+} , Al^{3+} , Cr^{3+} , Mn^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Pd^{2+} , Cd^{2+} , Ag^+ and Hg^{2+} (as their ClO_4^- salts) in CHCl_3 . $\lambda_{\text{ex}} = 335 \text{ nm}$, $[\mathbf{3n}] = 1 \times 10^{-5} \text{ M}$, $[\text{M}^{n+}] = 5 \times 10^{-4} \text{ M}$.

with the elimination of R^1CHO and H_2O as well as the release of AuCl for the next catalytic cycle.^{10,11} Notably, the stability of the carbocations in **5** and **6** of this proposed pathway could be used to rationalize the high efficiency of the condensation reaction when employing substrates **1** with electron-rich substituents at the C-1, C-3 and C-5 positions.

As is well known conjugated molecules have been widely used in the field of organic materials chemistry due to their interesting optical, electrical, photoelectric and magnetic properties.¹² Moreover, small molecule ligands with conjugated systems are attracting strong interest in the detection of chemical species because of their selective optical sensing.¹³ In connection with the highly conjugated molecules obtained by our condensation reaction and tandem reaction, it is assumed that these products may be useful in materials chemistry and a preliminary experiment taking compound **3n** as organic molecular probe (OMP) has been done. As illustrated in Fig. 1, introduction of 50 equiv. of $\text{Hg}(\text{II})$ to a solution of **3n** in CHCl_3 resulted in an almost 96% decrease in emission at 388 nm at room temperature. Moreover, less than 5% fluorescence change occurred following addition of $\text{Li}(\text{I})$, $\text{Na}(\text{I})$, $\text{K}(\text{I})$, $\text{Ca}(\text{II})$, $\text{Mg}(\text{II})$, $\text{Al}(\text{III})$, $\text{Cr}(\text{III})$, $\text{Mn}(\text{II})$, $\text{Co}(\text{II})$, $\text{Ni}(\text{II})$, $\text{Cu}(\text{II})$, $\text{Zn}(\text{II})$, $\text{Pd}(\text{II})$, $\text{Cd}(\text{II})$ and $\text{Ag}(\text{I})$. These experimental results indicated that the easily synthesized compound **3n** can be used as a “turn-off” fluorimetric molecular probe with high selectivity toward mercury ion, which has deleterious effects on environment and human health.¹⁴ The insensitivity of **3n**

to $\text{Cu}(\text{II})$ was notable and modification of **3n** to make it water-soluble would be worthwhile.

In summary, we have discovered a novel intermolecular condensation reaction of 1,3,5-triarylenynols catalyzed by gold as Lewis acid, which involved a dimerization–fragmentation process. This reaction could be developed to give a straightforward method for the effective synthesis of a new kind of structurally unique molecules, which have the highly conjugated dienyne aromatic system. Preliminary experiments showed that the tandem reaction product **3n** can be used as a fluorimetric probe for mercury. Further study of this new kind of potentially useful functional molecules in materials chemistry is ongoing in our group.

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