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Gold-Catalyzed Cascade Friedel−Crafts/Furan−Alkyne Cycloisomerizations for the Highly Efficient Synthesis of Arylated (*Z*)-Enones or -Enals

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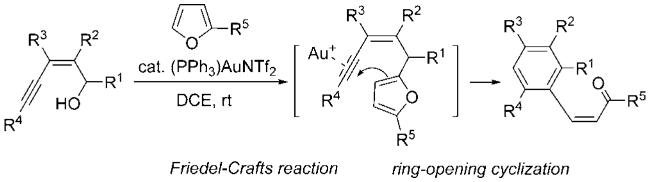
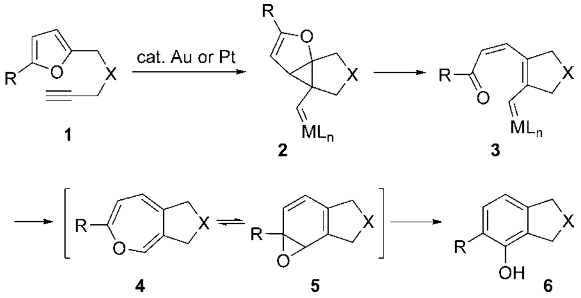
ABSTRACT



An efficient domino approach for the synthesis of arylated (*Z*)-enones or -enals through gold(I)-catalyzed reactions of enynols with furans was developed. PPh_3AuNTf_2 was found to be an excellent catalyst to catalyze both of the Friedel−Crafts and furan/alkyne cyclization reactions in the same vessel. This method offers several advantages such as high stereoselectivities, mild reaction conditions, and easily accessible starting materials.

The transition-metal-catalyzed cycloisomerization of alkynes bearing proximate C, O, N nucleophiles has proven to be a powerful synthetic route to a wide variety of carbo- and/or heterocycles.[1] Especially in recent years, gold catalysts have been found to be efficient alkynophilic Lewis acids to activate the π- systems toward nucleophilic attack, rendering them attractive reagents in organic synthesis.[2] For example, Hashmi et al. reported that an intramolecular alkyne/furan cyclization could be catalyzed by gold to afford phenols **6** (Scheme 1).[3] Other transition metals with a d^8 configuration such as $PtCl_2$, palladium(II), iridium(I), and rhodium(I) also catalyze this transformation;[3b,4] however, gold catalysts were found to be most active. One of the drawbacks of these

Scheme 1



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(1) For reviews, see: (a) Makamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2258, and references therein.

(2) For recent reviews on gold-catalyzed reactions, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Lipshutz, B. H.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 2793. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (f) Jimeńez-Nuíñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (h) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

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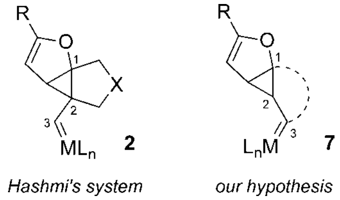
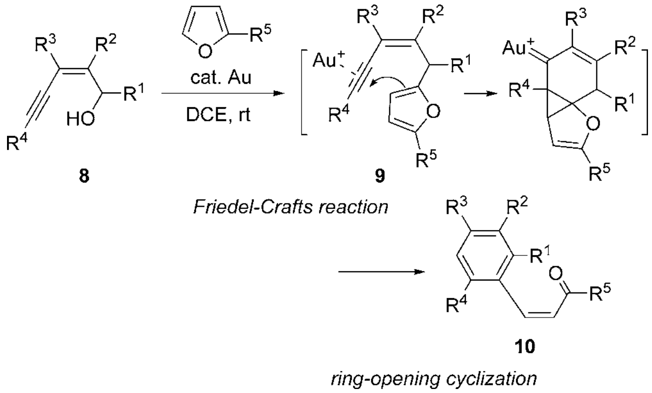
reactions is that only terminal alkynes can be used in most cases. A series of mechanistic investigations revealed that the reactions proceed through the first formation of cyclopropyl carbenoid **2**, which undergoes ring-opening to provide the conjugated carbenoid **3**, cyclization of **3** to the oxepine **4** and arene oxide **5**, followed by ring-opening leading to phenol **6**.[3o] We envisioned that if a gold−carbenoid intermediate with a 1,3-linked structure like **7** derived from an endocyclization is formed (Figure 1), the transformation to the arene oxide **5** could be avoided, which may provide different products such as enones other than phenols. However, such reactions have rarely been found in the literature.[5] Recently, we have developed gold-catalyzed cycloisomerizations of (Z)-enynols[6a,b] and the straightforward synthesis of allylic amines from allylic alcohols through direct amination reactions, etc.[6c] Inspired by these methods, we could further develop new domino processes for the efficient construction of pyrroles[6d] and indole-fused carbocycles[6e] directly from enynols. In this paper, we describe our discovery and investigations of the gold-catalyzed tendem reactions involving Friedel−Crafts reactions of furans with enynols followed by the furan/alkyne cyclizations in a one-pot procedure, which affords arylated (*Z*)-enones or -enals in a highly stereoselective manner. The furan cyclization step may involve an intermediate of type **7**; furthermore, in our reactions, internal alkynes could also be used (Scheme 2).



Hashmi's system *our hypothesis*

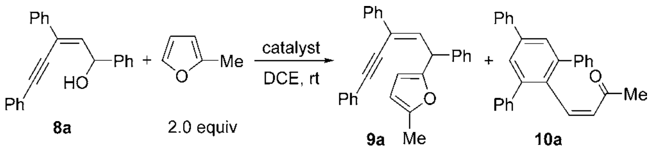
Figure 1. Comparison of the key intermediates.

Scheme 2



The requisite enynols were easily prepared by the Sonogashira coupling reactions of iodinated allylic alcohols with terminal alkynes. The iodide precursors were conveniently synthesized from the corresponding propargylic alcohols by their reaction with Red-Al followed by iodination of the organoaluminum intermediate.[6b,d,e,7] To probe the feasibility of the proposed transformations, we initially investigated the reactions of (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-ol **8a** with 2-methylfuran (Table 1). It was found that the use of AuCl$_3$ or AgOTf only afforded the arylated product **9a** in good yields. However, treatment of **8a** and 2-methylfuran in DCE

Table 1. Optimization Studies for the Formation of (*Z*)-Enones



entry	catalyst (5 mol %)	time	yield (%) of **9a**[a]	yield (%) of **10a**[a]
1	AuCl$_3$	30 min	86	
2	AgOTf	1 h	87	
3	Ph$_3$PAuNTf$_2$	1 h		87
4	Ph$_3$PAuCl/AgOTf	2 h	16	57

[a] Isolated yields.

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(5) There is only one example of such type of reaction, in which a seven-membered dihydrooxepine was observed in low yield (7%) in the formation of isochromanes; see ref 3m.

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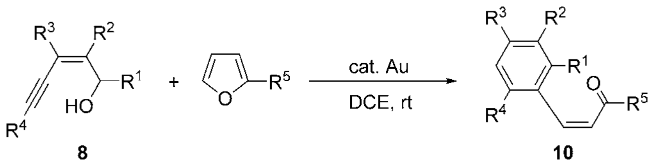
Table 2. One-Pot Synthesis of (*Z*)-Enones or -Enals through the Reactions of Enynols with Furans



entry	enynol	R^1	R^2	R^3	R^4	R^5	time(h)	product	yield(%)[a]
1	**8a**	Ph	H	Ph	Ph	Me	1	**10a**	87
2	**8b**	Ph	H	Ph	p-ClC_6H_4	Me	1.5	**10b**	82
3	**8c**	Ph	H	Ph	p-$MeOC_6H_4$	Me	2	**10c**	66
4	**8d**	Ph	H	Ph	n-C_4H_9	Me	1.5	**10d**	80
5	**8a**	Ph	H	Ph	Ph	Ph	1	**10e**	87[b]
6	**8a**	Ph	H	Ph	Ph	TMS	1.2	**10f**	66[c,d]
7	**8e**	Ph	H	COOEt	Ph	Ph	1.5	**10g**	67[b]
8	**8f**	Ph	H	CH_2OCH_3	Ph	Ph	1	**10h**	77[b]
9	**8g**	Ph	H	n-C_4H_9	Ph	Ph	1	**10i**	66
10	**8h**	p-ClC_6H_4	H	Ph	Ph	Me	1	**10b**	91
11	**8i**	p-$MeOC_6H_4$	H	Ph	Ph	Me	1	**10c**	89
12	**8j**	2-thienyl	H	Ph	Ph	Me	1	**10j**	84
13	**8k**	n-C_3H_7	H	Ph	Ph	Ph	1.5	**10k**	77[b]
14	**8l**	Ph	$-(CH_2)_3-$		Ph	Ph	1	**10l**	80[b]
15	**8m**	Ph	$-(CH_2)_4-$		Ph	Me	1.3	**10m**	33

[a] Isolated yields. Unless noted, all of the reactions were carried out using 5 mol % of $(PPh_3)AuNTf_2$ and 2.0 equiv of furans at room temperature. [b] 1.2 equiv of furans was used. [c] First, **8a** reacted with 10 equiv of 2-trimethylsilylfuran in the presence of 5 mol % of $(PPh_3)AuCl/AgOTf$ to afford the arylated intermidiate **9f** with the elimination of the TMS group, and then **9f** was subjected to standard conditions. [d] Compound **10f** is an enal in which R^5 = H in the represented structure.

with 5 mol % of gold(I) complex PPh_3AuNTf_2 resulted in the clean formation of enone **10a** in 87% yield. It is interesting to note that in this reaction, the C1−C5 in enynol **8a** together with the C-5 carbon of furan are smoothly transferred to the arene skeleton, while the remaining C2−C4 carbons of furan are converted into the enone moiety in product **10**. Remarkably, only (*Z*)-enone was observed (coupling constant of two olefinic hydrogens is 12.4 Hz); the (*E*)-isomer was not detected according to the ^1H NMR of the crude reaction mixture. The α,β-unsaturated aldehydes or ketones (without arene formation) have been observed as side products by Echavarren; these were formed by hydrolysis of a platium carbenoid intermediate; however, they observed the (*E*)-isomer exclusively.[4b] A mixture of (*Z*)- and (*E*)-isomers of α,β-unsaturated ketones have been isolated also by Hashmi et al. as side products in gold-catalyzed phenol synthesis.[3m] The formation of (*Z*)-isomer in their report is in accordance with the *cis*-carbenoid **3** that is suggested to be generated through rearrangement of cyclopropyl carbenoids **2** in the proposed reaction mechanism.

The present method could be applied successfully to various enynols **8**, whether acyclic or bearing a cyclic ring, to provide the corresponding (Z)-enones or -enals in generally good to high yields (Table 2). The substituent effects on the alkyne terminus were first investigated. The aromatic ring of R^4 bearing an electron-withdrawing group (−Cl) or an electron-donating group (−OMe) were all compatible, furnishing the corresponding enones **10b** and **10c** in 82% and 66% yields, respectively (Table 2, entries 2 and 3). The alkyl-substituted enynol **8d** underwent cyclization smoothly, leading to **10d** in 80% yield (entry 4). 2-Phenylfuran could also be used in the reaction, and a 87% yield of **10e** was achieved (entry 5). When 2-trimethylsilylfuran was employed, the product could not be isolated as a pure form. We then tried to carry out the reaction in a stepwise manner. Thus, by stirring the reaction mixture in the presence of 5 mol % of $(PPh_3)AuCl/AgOTf$ and 10 equiv of 2-trimethyisilylfuran for 2 h, the intermediate of (*Z*)-2-(1,3,5-triphenylpent-2-en-4-ynyl)furan **9f** with the elimination of a TMS group was isolated in 70% yield. When **9f** was subjected to the gold-catalyzed reaction, the expected cyclization occurred to generate enal **10f** in 66% yield (entry 6). The substituent effects on C-3 and C-1 of enynols have also been examined, and a wide range of substituents, including alkyl-, aryl-, and heteroaryl-substituted ones, are suitable in these domino reactions (entries 7−13). Furthermore, the functionalities of $-CO_2Et$ and $-CH_2OCH_3$ were well tolerated during the reaction, affording **10g** and **10h** in 67% and 77% yields, respectively (entries 7 and 8). It should be noted that the substrates of **8b** and **8h** afforded the same product **10b**, and also **8c** and **8i** led to the same enone **10c**. Enynols **8l** and **8m** fused with 5- or 6-membered rings generated the enones **10l** and **10m** in 80% and 33% yields, respectively (entries 14 and 15). The structure of **10e** was unambiguously confirmed by X-ray crystallographic analysis, which clearly showed the (*Z*)-configuration of the enone (Figure 2). In the solid structure, the C═C−C═O unit is oriented approximately perpendicular to the central benzene ring.

To understand the reaction mechanism, the arylated product **9e** has been isolated in 82% yield by $AuCl_3$-catalyzed

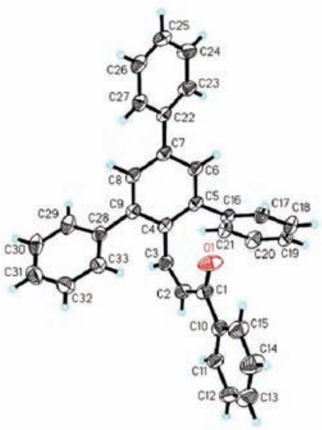
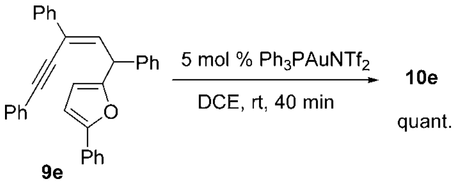


Figure 2. X-ray crystal structure of enone **10e**.

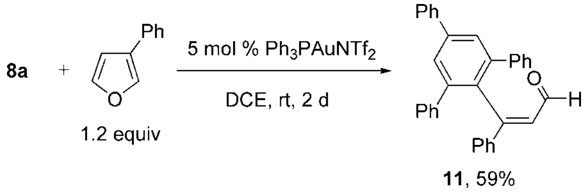
substitution reaction. The intramolecular cyclization of **9e** catalyzed by (PPh$_3$)AuNTf$_2$ proceeded smoothly to provide the same product of **10e** as observed in the tandem process (Scheme 3). The results strongly supported our assumption that the enone **10** was formed through Au(I)-catalyzed furan/alkyne cyclization of intermediate **9** in the one-pot procedure.

Scheme 3



Interestingly, when 3-phenylfuran was used, the expected 2-phenylacrylaldehyde was not obtained; instead, 3-phenylacrylaldehyde **11** was isolated in 59% yield[8] (Scheme 4).

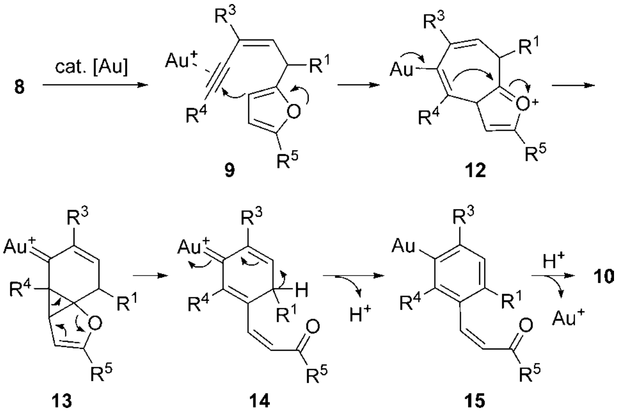
Scheme 4



The results indicated that arylation took place selectively at the C-2 position of furan, which might relate to an electronic effect of the 3-phenyl substituent.

We propose the following reaction mechanism for this tandem sequence (Scheme 5). The reaction is initiated by Au$^+$-catalyzed Friedel−Crafts reaction with 2-substituted furan through the electrophilic attack of the furan C5 to afford the enyne **9**. Coordination of gold complex to the triple bond of **9** followed by the intramolecular nucleophilic attack of the furan ring results in a 7-endo cyclization intermediate **12**. Next, a cyclopropyl gold carbenoid **13** is formed, which is analogous to the reaction intermediate **2** proposed in Hashmi's work. Rearrangement of **13** by cleavage of a C−C and C−O bond affords carbonyl compound **14** with a *cis*-configuration of the double bond. Elimination of a proton followed by deauration leads to the enone **10**.

Scheme 5



In summary, we have developed an efficient domino approach for the synthesis of arylated (Z)-enones or -enals through gold(I)-catalyzed reactions of enynols with furans. PPh$_3$AuNTf$_2$ was found to be an excellent catalyst to catalyze both the Friedel−Crafts and furan/alkyne cyclization reactions in the same vessel. This method offers several advantages such as high stereoselectivities, mild reaction conditions, and easily accessible starting materials. Further studies to extend the scope of synthetic utility for this Au-catalyzed cascade reaction are in progress in our laboratory.

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Supporting Information Available: Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compound **10e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The geometry of the double bond in **11** is tentatively assigned to be the (*Z*)-configuration.