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Gold(I)- and Platinum(IV)-Catalyzed Intramolecular Annulations of Allenes towards Furans†‡

Cheng-Hang Liu and Zhi-Xiang Yu*

Intramolecular annulations of allenes towards furans to give six-membered ring fused furans with gold and platinum catalysts have been developed. It was found that allenes can be activated by gold catalyst and attacked by the furan rings to generate six-membered rings. When $PtCl_4$ was used as catalyst, the annulation also gives six-membered ring fused furans, but the carbon-carbon double bond in the products has been shifted to form conjugation with the furan ring with a high *Z*/*E* ratio.

Six-membered ring fused furans are widely found in natural products with biological properties. Figure 1 shows some selected examples of these natural products.[1] These furanosesquiterpenes and furanoditerpenes are ubiquitous metabolites found in varieties of marine invertebrates. For example, (+)-pallescensin A is suggested to be involved in the defensive mechanisms employed by opisthobranch molluscs[1b] and (-)-furodysinin shows significant activity against parasitic stages of *Nippostrongylus brasiliensis*.[1d] Therefore, there is a high demand to develop new methods and strategies for the synthesis of six-membered ring fused furans, which could further be used in target- and function-oriented synthesis of biologically and pharmaceutically interesting natural products with the six-membered ring fused furan skeletons.

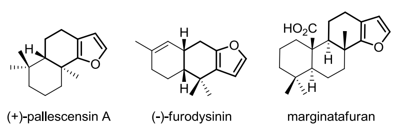
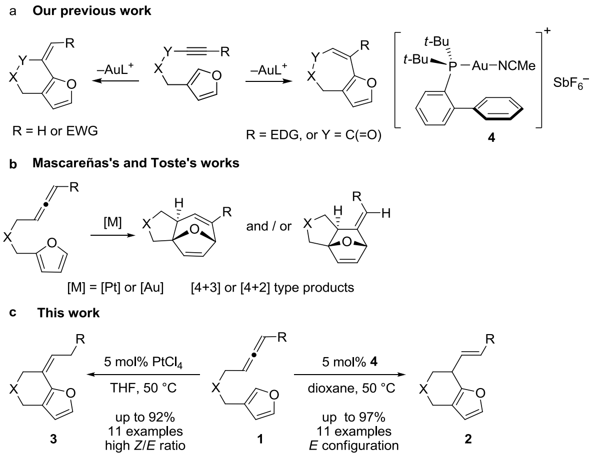


Figure 1 Natural products with six-membered ring fused furans



Scheme 1 a) Our previous work about the α-alkenylation of β-yne-furans. b) [4+2] and [4+3] type reactions of α-allenyl-furans. c) The annulation of β-allenyl-furans.

Recently we developed an efficient gold-catalyzed *endo*-selective intramolecular α-alkenylation of furans with internal alkynes to synthesize the challenging seven-membered ring fused furans (Scheme 1a).[2] This strategy was based on the higher reactivity of α-position over β-position of furan[3] and consequently alkenylation can be realized. We found that six-membered ring fused furans can also be obtained through the intramolecular α-alkenylation strategy via *exo*-selective cyclization of furans with terminal alkynes or alkynes terminated by electron-withdrawing groups. It was reported that allenes can also be activated and then react with aromatic rings,[4] such as electron-rich benzenes,[5] indoles,[6] and pyrroles,[7] to give Friedel–Crafts (F–C) products. We wondered whether the alkynes in our previous substrates can be replaced by allenes so that either six- or seven-membered ring fused furans could be accessed using gold or platinum catalyst (Scheme 1c). Herein we report our experimental results of achieving the synthesis of α-alkylated furans from β-allenyl-furans through the gold-catalyzed annulation of allenes towards furans (or hydroarylation of allenes with furans). The method is of high stereoselectivity and only the *E* configuration products were obtained. We also noticed that the carbon-carbon double bond can shift to the position conjugated with the furan ring with a high *Z*/*E* ratio when $PtCl_4$ was used. This reaction is different from previous reports from Mascareñas[8] and Toste,[9] who

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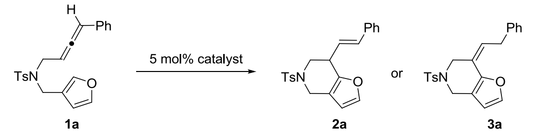
† Dedicated to Professor Max Malacria on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Synthetic procedures and analytical data; CIF file for single crystal X-ray structural analysis. CCDC 1018190. See DOI: 10.1039/c000000x

independently showed that α-substituted allenyl-furans under gold and platinum catalysis gave [4+2] and [4+3] type products,[10] not the alkylation products (Scheme 1b).[11]

We commenced our investigation by subjecting compound **1a** to the standard conditions for α-alkenylation of β-yne-furans using catalyst **4** (Echavarren's catalyst), finding that the desired product **2a** can be isolated in a modest yield (65%) and a very long reaction time (60 h) was needed (Table 1, entry 1). This transformation was highly stereoselective because only annulation product with the *E* configuration was observed. The reaction yield can be further increased to 86% and the reaction time can be shortened to 7 h when the reaction was carried out at 50 °C (Table 1, entry 2). Then we screened various gold complexes as catalysts (Table 1, entry 3–7). No desired product was obtained when using Au(JohnPhos)Cl as catalyst, indicating that 'naked' gold cation was required. When using cationic gold catalyst generated from Au(IPr)Cl and $AgSbF_6$ for the annulations reaction, we found that substrate **1a** was consumed after 4 h, but the reaction yield was low. Other gold catalysts including the simple $AuCl_3$, AuCl have also been tested, showing that only a trace amount of **2a** was detected by TLC (Table S1, entry 9–10). Several widely used Brønsted acids and Lewis acids such as TfOH, $AlCl_3$, $BF_3 \cdot OEt_2$ and $InCl_3$ were proved to be ineffective for the target transformation (Table S1, entry 12–15). We then investigated how solvents affect the reaction outcome, finding that dioxane turned out to be the best solvent and the product **2a** can be isolated in 91% yield, whereas no product was detected in MeCN (Table 1, entry 8–12). A catalytic amount of water is required for this transformation (no desired product was observed when 4Å MS was added to the reaction system), which is similar to our previous gold-catalyzed α-alkenylation reaction of β-yne-furans (Table S1, entry 23).[2]

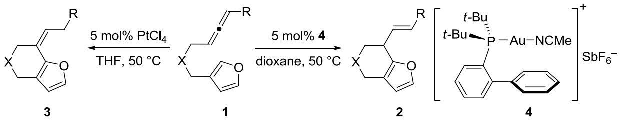
Table 1 Optimization studies on the annulation of β-allenyl-furans using Au and Pt catalysts

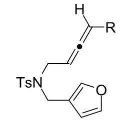
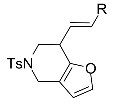
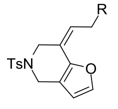
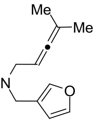
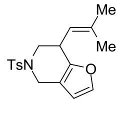
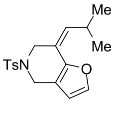
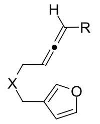
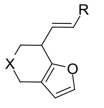
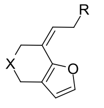
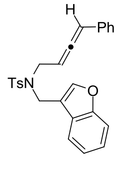
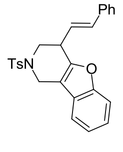
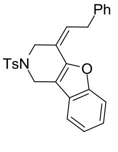
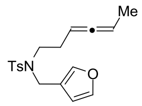


entry	solvent[a]	catalyst	temp	time [h]	product	yield[%][b]
1	DME	$[Au(NCMe)JohnPhos]SbF_6$	rt	60	**2a**	65
2	DME	$[Au(NCMe)JohnPhos]SbF_6$	50°C	7	**2a**	86
3	DME	Au(JohnPhos)Cl	50°C	12	-	no reaction
4	DME	$Au(PPh_3)Cl/AgSbF_6$[c]	50°C	24	**2a**	49[d]
5	DME	$Au(IPr)Cl/AgSbF_6$[c]	50°C	4	**2a**	83
6	DME	$Au[P(OPh\text{-}2,4\text{-}t\text{-}Bu)_3]Cl/AgSbF_6$[c]	50°C	15	**2a**	71
7	DME	$Au(XPhos)NTf_2$	50°C	48	**2a**	48[e]
8	MeCN	$[Au(NCMe)JohnPhos]SbF_6$	50°C	7	-	no reaction
9	DCE	$[Au(NCMe)JohnPhos]SbF_6$	50°C	42	**2a**	76[f]
10	toluene	$[Au(NCMe)JohnPhos]SbF_6$	50°C	13	**2a**	88
11	THF	$[Au(NCMe)JohnPhos]SbF_6$	50°C	9	**2a**	36
12	dioxane	$[Au(NCMe)JohnPhos]SbF_6$	50°C	6	**2a**	91
13	DME	$PtCl_2$	50°C	17	**3a**	73
14	DME	$PtCl_4$	50°C	2	**3a**	74
15	dioxane	$PtCl_4$	50°C	2	**3a**	76
16	toluene	$PtCl_4$	50°C	4	**3a**	40[f]
17	THF	$PtCl_4$	50°C	2	**3a**	92

[a] Concentration: 0.05M. [b] Isolated yield, the Z/E ratio of **3a** was above 20/1. [c] Gold and silver salts were added at radio of 1:1. [d] 27% **1a** was recovered. [e] 28% **1a** was recovered. [f] Yield based on NMR.

Table 2 Scope of this intramolecular annulation reaction of β-allenyl-furans



Entry	Substrate	Product 2 yield[%][a], time	Product 3 yield[%][a], time
			
1	**1a**, R = Ph	**2a**, 91, 6 h	**3a**, 92, 2 h
2	**1b**, R = *p*-BrPh	**2b**, 78, 7 h	**3b**, 79, 2.5 h
3	**1c**, R = *p*-OMePh	**2c**, 67, 3 h	**3c**, 58[b], 2 h
4	**1d**, R = Me	**2d**, 79, 5 h	**3d**, 80, 1 h
5	**1e**, R= *n*-Pr	**2e**, 91, 4 h	**3e**, 80, 2 h
6	**1f**, R = H	decomposed	decomposed
			
7	**1g**	**2g**, 97, 4 h	**3g**, 88[c], 4 h
			
8	**1h**, X = NBs, R = *p*-BrPh	**2h**, 93, 8 h	**3h**, 84, 2 h
9	**1i**, X = O, R = Ph	**2i**[d], 83, 8 h	**3i**[e], 67, 4 h
10	**1j**, X = $C(CO_2Me)_2$, R = Ph	**2j**, 86, 4 h	**3j**, 89[f], 2 h
11	**1k**, X = $C(CO_2Me)_2$, R = H	**2k**[d], 63, 3 h	**3k**[e], 72[g], 2 h
			
12	**1l**	**2l**[d], 85, 5 h	**3l**[e], 83[h], 1 h
		-	-
13	**1m**	no reaction	no reaction

[a] Isolated yield. The *Z*/*E* ratio of **3** was above 20/1 if not mentioned. [b] 3c/2c = 4.3/1 based on NMR. [c] 3g/2g = 1/2.4 based on NMR. [d] Carried out at 80 °C using 10 mol% catalyst. [e] Carried out at 80 °C in dioxane instead of THF using 10 mol% catalyst. [f] *Z*/*E*=10/1 based on NMR. [g] *Z*/*E*=1.3/1 based on NMR. [h] *Z*/*E*=8/1 based on NMR.

Interestingly, a new product **3a**, which is the isomer of **2a** and has the double bond in conjugation with furan, was isolated when we used $PtCl_2$ as the catalyst (Table 1, entry 13). Compound **3a** has a high *Z*/*E* ratio (>20:1). We also found that the reaction time can be dramatically shortened to 2 h without loss of reaction yield when using $PtCl_4$ instead of $PtCl_2$ as catalyst (Table 1, entry 14). We screened several common solvents using $PtCl_4$ as catalyst (Table 1, entry 14–17), finding that product **3a** can be obtained in 92% yield in THF. Consequently, THF was chosen as the optimal solvent for the annulations reaction under the catalysis of $PtCl_4$.

With the optimized reaction conditions in hand, the scope of this intramolecular annulation reaction of β-allenyl-furans was studied. At first, we investigated the influence of the substitutions in the allene moiety, finding that other aryl groups such as *para*-bromo phenyl, phenyl, *para*-methoxyl phenyl could also be used in the substrates for both gold and platinum catalyzed reactions, giving their corresponding products **2** and **3**, respectively (Table 2, entry 2–3). Treating compound **1c** with $PtCl_4$, a mixture of the alkene shifted product **3c** and unshifted product **2c** (the ratio of **3c**/**2c** is 4.3:1) was obtained in a combined reaction yield of 58%. The allene moiety of the substrate can be substituted by simple aliphatic groups such as methyl and *n*-propyl groups, finding that the desired products in high yields were generated under both gold and platinum catalysis (Table 2, entry 4–5). Unfortunately, monosubstituted substrate **1f** decomposed under the standard reaction conditions (Table 2, entry 6). For trisubstituted allene substrate **1g,** the annulation product **2g** could also be formed in an excellent yield using the gold catalyst **4**. But a mixture of **2g** and **3g** was obtained using $PtCl_4$ as the catalyst (Table 2, entry 7).

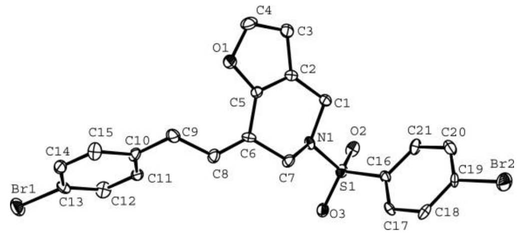
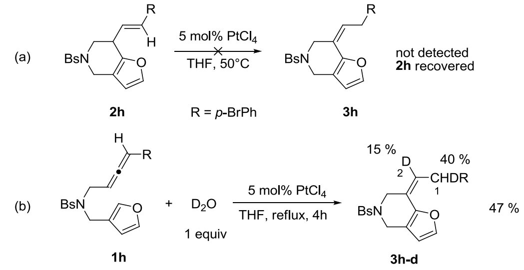


Figure 2 ORTEP representation of crystallized compound **3h (**hydrogen atoms are omitted).

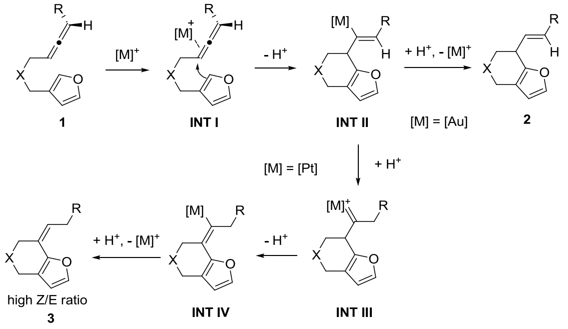
The tether in β-allenyl-furans can be NBs, O and $C(CO_2Me)_2$ for the annulation reactions using gold and platinum catalysts (Table 2, entries 8–11). The *Z* configuration of the double bond in **3** was further confirmed by single X-ray crystallography analysis of product **3h** (Figure 2). For substrates **1i** and **1k,** the desired annulation reactions had to be carried out at 80 ℃ in dioxane, considering that their reactions were too slow upon using the above-mentioned standard optimized reaction conditions (Table 2, entries 9 and 11). We observed that the *Z*/*E* ratios of the final product were not satisfying for C-tethered substrate when $PtCl_4$ was used as the catalyst (Table 2, entry 10–11). The furan moiety could also be replaced by benzofuran, but the corresponding annulation reaction for β-allenyl-benzofuran substrate **1l** had to be carried out at 80 ℃ in order to get a reasonable reaction yield (Table 2, entry 12). Finally, we tested the influence of the tether length, showing that no seven-membered ring fused furans were observed for substrate **1m,** even though the reactions were performed at 80 ℃ (Table 2, entry 13). This further demonstrated that synthesis of seven-membered ring fused furan was not trivial.

We hypothesized that the annulation reaction using gold and platinum catalysts gave the same product **2**, but **2** could further isomerize to **3** under the platinum catalysis. When we treated **2h** with $PtCl_4$, no alkene shifted product **3h** was detected (Scheme 2a), showing that compound **3** was not generated through olefin isomerization from **2**. To get more information about the detail of the platinum catalysis, we tried to add additive D_2O to the platinum-catalyzed reaction system (Scheme 2b). We found that **3h-d** with 15% D incorporation at the C-2 position and 40% D incorporation at the C-1 position was obtained, which indicated that D_2O is involved in the olefin isomerization process.



Scheme 2 Preliminary mechanistic study.

Based on the experiments, we proposed the following mechanisms to account for the annulation reactions of allenes towards furans using gold and platinum catalysts (Scheme 3). The annulation reaction begins with the coordination of the allene part of the substrate to the metal catalyst, generating a metal-allene complex, intermediate **INT I**. Then nucleophilic *anti*-attack of the α-position in the furan rings on the metal-complexed allene of intermediate **INT I** gives rise to the intermediate **INT II**.[12] When the catalyst used is the cationic gold complex, intermediate **INT II** will undergo a protodeauration process to form the six-membered ring fused furan product **2** and release the gold catalyst for the next catalytic cycle. When the catalyst is a platinum complex, we propose that there is a water-assisted proton transfer process via the platinum carbene intermediate **INT III**.[13] Finally, the alkene shifted product **3** can be afforded with a high *Z*/*E* ratio after the protodeplatination process from **INT IV**. However, the reason why different products can be achieved using diverse catalysts is still not known.



Scheme 3 Proposed mechanism.

In conclusion, an efficient intramolecular annulation of allenes towards furans has been developed to synthesize six-membered ring fused furans in good yields and high stereoselectivity. To the best of our knowledge, this is the first report of the intramolecular Friedel–Crafts-type annulation of allenes with furans. Two different products can be generated under gold and platinum catalysis. Under gold catalysis, a nucleophilic *anti*-attack mechanism was involved and the products with *E* configuration were generated. While using $PtCl_4$ as the catalyst, alkene shifted products **3** were isolated with a high *Z*/*E* ratio, especially for N- and O-tethered substrate.

Experimental section

General procedure

A solution of β-allenyl-furan substrate and catalyst (5 mol% or 10 mol%, [Au(NCMe)JohnPhos]SbF_6 or $PtCl_4$) in anhydrous solvent (dioxane or THF, 0.05 M) was stirred under an argon atmosphere at 50 ℃ (or 80 ℃). When TLC indicated the disappearance of the starting material, the reaction mixture was cooled to room temperature and concentrated. The crude mixture was submitted to flash column chromatography on silica gel to afford the corresponding product.

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