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Gold-Catalyzed Cyclization of (*Z*)-2-En-4-yn-1-ols: Highly Efficient Synthesis of Fully Substituted Dihydrofurans and Furans

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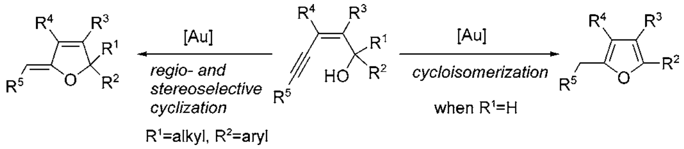
ABSTRACT



The gold-catalyzed cyclization of (*Z*)-enynols offers an efficient and straightforward route to stereodefined (*Z*)-5-ylidene-2,5-dihydrofurans and fully substituted furans under extremely mild reaction conditions. Importantly, the results indicated that both the oxyauration and the protodemetalation steps are highly stereoselective.

The furan or dihydrofuran rings widely occur as key structural subunits in numerous natural products, which can find a variety of applications as pharmaceuticals and flavor and fragrance compounds.[1] Furthermore, highly substituted furans are of significant interest since they are useful and versatile synthetic intermediates for access to heterocyclic and acyclic compounds.[2] As a consequence, much attention has been paid to the synthesis of furan derivatives. In addition to traditional methods (e.g., dehydration of γ-diketones, ring derivatization),[3] numerous transition-metal-catalyzed heteroannulation reactions have been developed with remarkable improvements in terms of efficiency and wide scope of application.[4] Nevertheless, the development of synthetic routes that allow the facile assembly of substituted furans under mild conditions still remains an important objective. A particularly attractive methodology is based on cycloisomerization of (*Z*)-2-en-4-yn-1-ols.[5] Cu(II)-catalyzed large-

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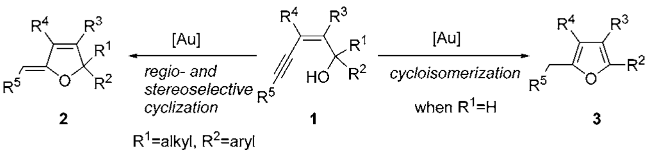
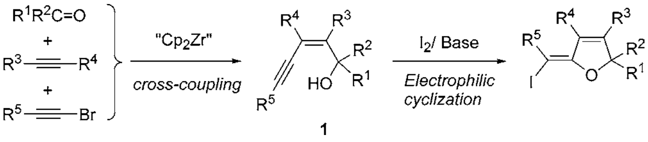
scale preparation of 2,3-dimethylfuran starting from (*Z*)-3-methylpent-2-en-4-yn-1-ol was disclosed some years ago.[5b] Base-promoted cyclization of (*Z*)-enynols was achieved under strongly basic conditions, i.e., KOBu^t in Bu^{t}OH−THF, in the presence of 18-crown-6, which was not suitable for the synthesis of base-sensitive furan.[5c,e,f] A Ru-catalyzed synthesis of furans by selective cyclization of (*Z*)-enynols using Ru(PPh$_3$)(*p*-cymene)Cl$_2$ as catalyst precursor was reported by Dixneuf et al., which was only suitable for terminal alkynes.[5g,h,l] An excellent K$_2$PdI$_4$-based catalytic system was reported to accomplish the cycloisomerization of a wide variety of (*Z*)-enynols under neutral conditions.[5a] This methodology was applicable to different substitution patterns in the starting materials (e.g., terminal and internal alkynes) and provided most of the corresponding furans in good to high yields. However, the reaction usually requires high temperature (100 °C) in a dipolar aprotic solvent such as DMA when (*Z*)-enynols bearing a substituent at C-3 and an internal triple bond were employed. Thus, the catalytic version of enynol-cyclization that proceeds at ambient temperature in combination with the efficient (*Z*)-enynol construction from simple, readily available starting materials would greatly enhance the utility of this reaction. It has recently been shown that gold(III) salts and gold(I) complex display considerable catalytic activity under moderate conditions.[6] Hashmi et al. reported that this catalyst was superiorly efficient in the cyclization of 2-methylpent-2-en-4-yn-1-ol to furans (only one substrate was tested).[7] Consequently, the use of gold catalysis in the conversion of highly substituted (*Z*)-enynols to furans remains largely unexplored. Herein, we report the utilization of gold as catalyst for cyclization of (*Z*)-enynols, which offers an efficient and straightforward route to highly substituted furans or dihydrofurans under extremely mild reaction conditions (Scheme 1).

Scheme 1



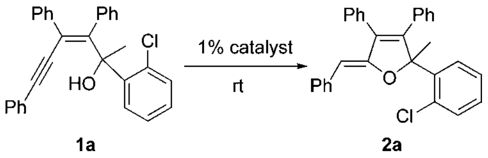
The preparation of (*Z*)-enynols is usually achieved through multistep transformations involving Pd/Cu-catalyzed coupling of the terminal alkynes with vinylic halides, addition of alk-1-ynes to vinyl ketones followed by acid-catalyzed allylic isomerization, and reduction of methyl (*Z*)-2-en-4-ynoates, etc.[5a,c] We recently reported an efficient synthetic approach to stereodefined (*Z*)-enynols **1** via zirconium-mediated cross-coupling reactions of three different components involving alkyne, ketone, and alkynyl bromide in a one-pot procedure (Scheme 2).[8] The subsequent electrophilic cyclization of the thus formed (*Z*)-enynols affords fully substituted (*Z*)-5-(1-iodoylidene)-2,5-dihydrofurans. In addition to ketones, aldehydes were also confirmed to be suitable substrates for this type of reaction.[9]

Scheme 2



Thus, a variety of (*Z*)-enynols with a tertiary or secondary alcoholic groups were readily synthesized by this method. With (*Z*)-enynols **1** in hand, we were interested in exploring the feasibility of using **1** in gold-catalyzed cyclization reactions. We began our investigation with enynol **1a** (R^1 = Me, R^2 = *o*-ClC$_6$H$_4$, R^3 = R^4 = R^5 = Ph) bearing phenyl group at C-5 and a tertiary alcohol group at C-1 (Scheme 3).

Scheme 3



catalyst	*yield of* ***2a***
(PPh$_3$)AuCl/AgOTf, CH$_2$Cl$_2$, 1 d	*70%*
(PPh$_3$)AuCl/AgOTf, THF, 3 h	*82%*
AuCl$_3$, CH$_2$Cl$_2$, 3 h	*97%*
0.1% AuCl$_3$, CH$_2$Cl$_2$, 4 h	*80%*
AuCl$_3$, in air, CH$_2$Cl$_2$, 6 h	*74%*

Treatment of **1a** with 1 mol % of (PPh$_3$)AuCl in refluxing CH$_3$CN for 5 days afforded (*Z*)-5-ylidene-2,5-dihydrofuran

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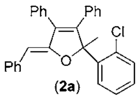
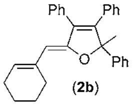
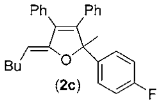
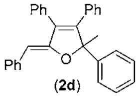
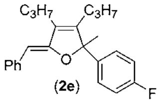
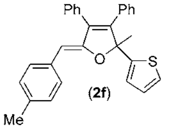
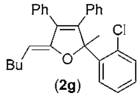
(7) Hashmi, A. S. K.; Schwarz, L.; Choi, J.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *112*, 2285.

(8) Liu, Y. H.; Song, F. J.; Cong, L. Q. *J. Org Chem.* **2005**, *70*, 6999−7002.

2a as anticipated in 77% yield. The situation, however, changed by using a cationic gold(I) complex $(PPh_3)AuCl/AgOTf$ as catalyst, and the yield was increased to 82% when the reaction was carried out in THF at room temperature for 3 h. Gold(III) chloride also showed excellent catalytic activities to afford quantitative yield of the desired product. Even with only 0.1 mol % of $AuCl_3$ used as the catalyst, the yield of **2a** still was as high as 80%. The yield was decreased to 74% when the reaction was carried out under an atmosphere of air in the presence of 1% $AuCl_3$. The results of the gold-catalyzed cyclization for the formation of dihydrofurans using various kinds of (*Z*)-enynol substrates are summarized in Table 1. The alkyne moiety in enynols **1** bearing an aromatic ring as well as alkyl substrate all reacted very well to provide the 5-*exo-dig* cyclization products in high yields (83−97%). The appearance of a vinylic group at C-5 in **1b** did not influence the efficiency of this reaction, in which the corresponding product **2b** was formed in 92% yield. Bulky substrates, such as **1a** and **1g** bearing the *o*-chlorophenyl group at C-1, underwent the reaction smoothly to give **2a** and **2g** in high yields.

Table 1. Gold-Catalyzed Cyclization of (Z)-enynols: Formation of (*Z*)-5-Ylidene-2,5-dihydrofurans

enynol	R^1	R^2	R^3	R^4	R^5	condition^a	product	yield^b
1a	Me	*o*-ClC_6H_4	Ph	Ph	Ph	A, 3 h	 **(2a)**	97%
1b	Me	Ph	Ph	Ph	Cy^c	A, 1 h	 **(2b)**	92%
1c	Me	*p*-FC_6H_4	Ph	Ph	Bu	A, 1 h	 **(2c)**	89%
1d	Me	Ph	Ph	Ph	Ph	A, 3 h	 **(2d)**	91%
1e	Me	*p*-FC_6H_4	C_3H_7	C_3H_7	Ph	B , 3 h	 **(2e)**	84%
1f	Me	2-thienyl	Ph	Ph	p-MeC_6H_4	B , 3 h	 **(2f)**	87%
1g	Me	*o*-ClC_6H_4	Ph	Ph	Bu	A, 1 h	 **(2g)**	83%

^{a} All of the reactions were carried out at room temperature using 1 mol % of catalyst. Condition A: 1% $AuCl_3$, in CH_2Cl_2.Condition B: 1% $(PPh_3)AuCl$, 1% AgOTf, in THF. ^{b} Isolated yields. ^{c} Cy is 1-cyclohexenyl group.

It is interesting to note that, in all cases, only 5-*exo-dig* cyclization occurred and stereoisomerically pure compounds (*Z*)-**2** were found to be the only reaction products, while the regioisomers of pyran derivatives derived from 6 *endo* cyclization and the stereoisomers of (*E*)-**2** were not observed. It is noteworthy that the geometrical selectivity of the substituent (R^5) on exocyclic double bond is in sharp contrast to that observed for electrophilic cyclization (see Scheme 2). The stereochemistry of the products was unambiguously established by 2D NMR spectroscopy and the single-crystal analysis of **2a** (Figure 1). The results suggested that the activation of the alkyne and the subsequent addition of the oxygen nucleophile was highly stereoselective. The similar *anti*-addition was observed through deuterium-labeling experiments in gold-catalyzed Conia-ene reaction and in cycloisomerization of propargylcarboxamides.[10] However, this is in contrast to the work of Teles et al., who calculated a *syn* mode for the gold(I)-catalyzed addition of alcohols to alkynes.[11]

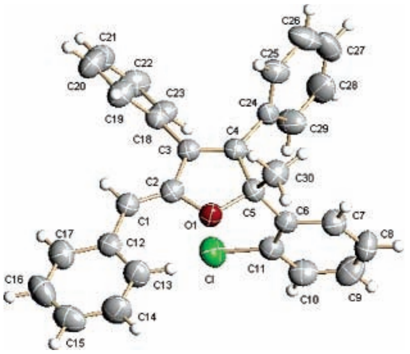


Figure 1. The X-ray crystal structure of **2a**.

More interestingly, gold can also catalyze cycloisomerization of (*Z*)-enynols with a secondary alcohol group at C-1. Under similar conditions as shown in Table 1, a wide range of (*Z*)-enynols participated in the cycloisomerization reactions. As shown in Table 2, alkyl, alkenyl, and aryl substitution at C1−C5 were all compatible with cyclization conditions, and high yields of the corresponding furans were obtained in each case (64−92%, except **3h**). In sharp contrast to the low reactivity of (*Z*)-enynols bearing an aryl group at C-3 in the Pd-catalyzed reaction, the gold-catalyzed cycloisomerization of the substrate **1k** proceeded well at ambient conditions, furnishing **3d** in 79% yield. Substitution at C-1 with an electron-withdrawing group *p*-$CF_3C_6H_4$, as in **1l**, led to the corresponding product **3e** in 64% yield. Enynol **1m** substituted at C-3 with a TMS group resulted in partial desilylation during the separation, the two products were

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(9) Unpublished results.

(10) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391.

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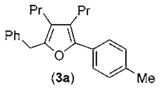
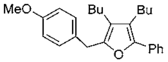
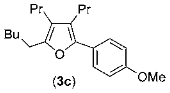
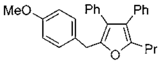
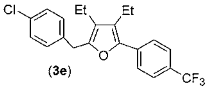
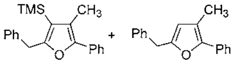
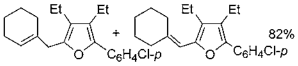
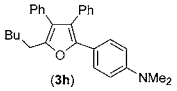
Table 2. Gold-Catalyzed Cyclization of (*Z*)-Enynols: Formation of Fully Substituted Furans

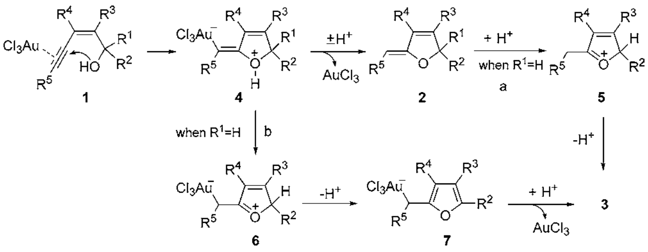
enynol	R^2	R^3	R^4	R^5	condition[a]	product	yield[b]
1h	*p*-MeC_6H_4	Pr	Pr	Ph	A, 4 h	 (**3a**)	92%
1i	Ph	Bu	Bu	*p*-$MeOC_6H_4$	B, 3 h	 (**3b**)	85%
1j	*p*-$MeOC_6H_4$	Pr	Pr	Bu	A, 2 h	 (**3c**)	85%
1k	Pr	Ph	Ph	*p*-$MeOC_6H_4$	A, 3 h	 (**3d**)	79%
1l	*p*-$CF_3C_6H_4$	Et	Et	*p*-ClC_6H_4	B, 2 h	 (**3e**)	64%
1m	Ph	CH_3	TMS	Ph	A, 1 h	 (**3f**) (2:1)	92%
1n	*p*-ClC_6H_4	Et	Et	Cy[c]	B, 3 h	 (**3g**) (2:1)	82%
1o	*p*-$NMe_2C_6H_4$	Ph	Ph	Bu	A, 3 h	 (**3h**)	12%[d]

[a] All of the reactions were carried out at room temperature using 1 mol % of catalyst. Condition A: 1% $AuCl_3$, in CH_2Cl_2. Condition B: 1% $(PPh_3)AuCl$, 1% AgOTf, in THF. [b] Isolated yields. [c] Cy is 1-cyclohexenyl group. [d] The reaction was carried out directly by adding $AuCl_3$ to a crude enynol solution containing zirconium (see the Supporting Information).

obtained in a ratio of 2:1 with a combined yield of 92%. When the alkyne moiety in **1n** terminated with 1-cyclohexenyl group, a double-bond isomerization to an exocyclic double bond was observed, owing to better conjugation with furan ring in product **3g**. A 2:1 mixture of isomers **3g** was obtained in 82% combined yield. Enynol **1o** bearing *p*-$NMe_2C_6H_4$ group at C-1 was confirmed to be unstable in the air, the cycloisomerization was carried out directly by adding $AuCl_3$ to a crude enynol solution containing zirconium (see the Supporting Information). The corresponding furan **3h** was obtained in a low yield of 12%. It is interesting to note that this strategy offers the additional flexibility to the existing methodology in the creation of regiochemical patterns around the furan nucleus.

We propose the following mechanism for this reaction, which is analogous to what has been previously reported on Pd-catalyzed cycloisomerization of (*Z*)-enynols[5a] (Scheme 4). In the first step, the coordination of the triple bond of enynol **1** to $AuCl_3$ enhances the electrophilicity of alkyne, and the subsequent *anti-exo-dig* nucleophilic attack of the hydroxy group on a Au(III)−alkyne complex would form the ate complex **4**. Protonolysis of **4** affords dihydrofuran **2** and regenerate $AuCl_3$. Furans **3** were formed either by isomerization of **2** (path a) or through isomerization/protonolysis pathway (path b). It should be noted that the associative mechanism proposed by Teles[11] is unlikely in this case, since it would involve a very constrained intermediate.

Scheme 4



In conclusion, we have developed a highly efficient Au(III)- or Au(I)-catalyzed cyclization of (*Z*)-enynols that proceeds under neutral conditions at room temperature. In combination with our zirconium-mediated one-pot protocol for (*Z*)-enynol formation, this methodology provides rapid access to stereodefined (*Z*)-5-ylidene-2,5-dihydrofurans and fully substituted furans in high yields from common starting materials. This method should find particular application in the regioselective synthesis of tetrasubstituted furans. We are currently exploring the new synthetic potential for gold-catalyzed C−C bond or C−X bond formation reactions.

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Supporting Information Available: Experimental details and characterization data of compounds **2a**−**g** and **3a**−**h** and crystallographic data of **2a** (CIF). Copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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