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Gold Catalyzed Synthesis of Substituted Furan by Intermolecular Cascade Reaction of Propargyl Alcohol and Alkyne

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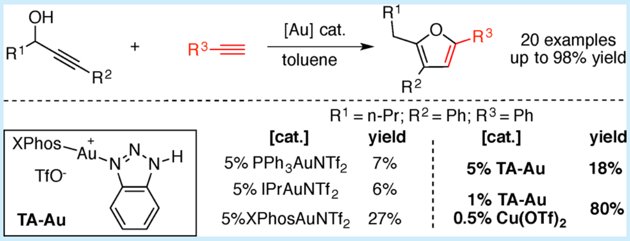
Supporting Information

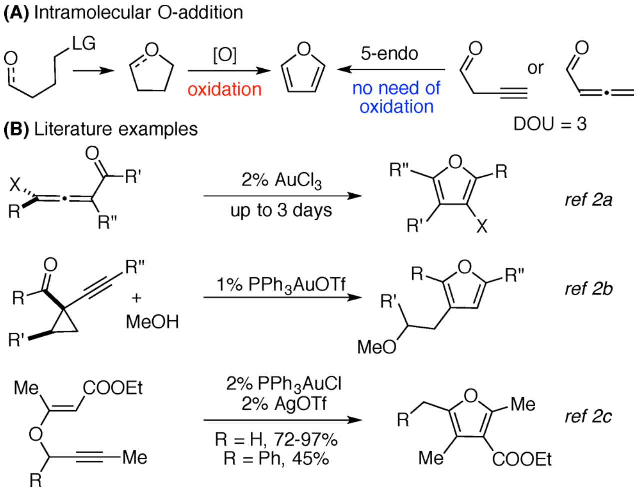
ABSTRACT: Using a combination of triazole-gold (TA-Au) and copper catalysts, the substituted furan was achieved in one pot through a three-step reaction cascade. The reaction tolerates a large substrate scope with simple starting materials. The desired di-, tri-, and tetrasubstituted furans were prepared in good to excellent yields.



Furan is one of the most important building blocks in chemical, material, and biological research.[1] Developing effective synthesis toward furan-containing products is of general interest to organic chemists. One of the general synthetic strategies toward furan is oxygen promoted cyclization.[2]

As shown in Scheme 1A, oxygen nucleophiles (from ketone or alcohol) can conduct intramolecular nucleophilic substitution to form the cyclic structures. Further oxidation will achieve the furan products. To avoid the oxidation step, substrates with the right oxidation state are needed. For example, both allene-ketone and alkyne-ketone (ynone) have three degrees of unsaturation, the same as furan. Thus, they may give the furan product upon cyclization with no need for further oxidation. The general concern is how to facilitate the unfavored 5-endo cyclization.

Scheme 1. Furan Synthesis from Intramolecular O-Addition



Homogeneous gold catalysis has seen a drastic advancement during the past decade. Gold catalysts proved to be highly effective toward alkyne, alkene, and allene activation.[3] As a result, they have been applied in catalyzing a wide range of reactions. They have also been used in promoting this type of cyclization reaction. Several reported examples from the literature are shown in Scheme 1B. First, Gevorgyan reported the $AuCl_3$ catalyzed allene-ketone cyclization.[2a] Due to the unfavored 5-endo cyclization, slow reactions were observed (some substrates took up to 3 days for completion). The 1,3-ynone is another viable substrate for the synthesis of furan through cyclization reported by Schmalz et al. 1,3-Ynones were effective substrates for the preparation of furan through alcohol promoted cyclopropane ring opening.[2b] However, α-substituted ynones are required to prevent triple bond isomerization (formation of conjugated alleneone).

Another interesting example is the gold catalyzed propargyl-vinyl ether rearrangement reported by Kirsch et al.[2c] In this case, gold catalyzed 3,3-rearrangement of propargyl-vinyl ether to form the 1,3-ynone in situ and subsequently furans. Although it showed an interesting cascade design, this approach has some limitations. First, due to the difficulty in the synthesis of vinyl ether, only substrates with electron-withdrawing groups (esters) were suitable, which significantly limits the scope of this transformation. Second, the reaction performance was greatly influenced by the substituted group at the propargyl position. When R = Ph, a significantly lower yield was observed (45%). Overall, considering the importance of furan in chemistry research, new catalytic systems that facilitate the synthesis of substituted furan with simple starting materials, high efficiency, and a broad reaction scope are highly desirable.

In recent years, our group has investigated gold catalyzed reactions.[4] In particular, we demonstrated that triazole-coordinated gold complexes (TA-Au) can give unique reactivity in promoting alkyne activation. Compared with other conven-

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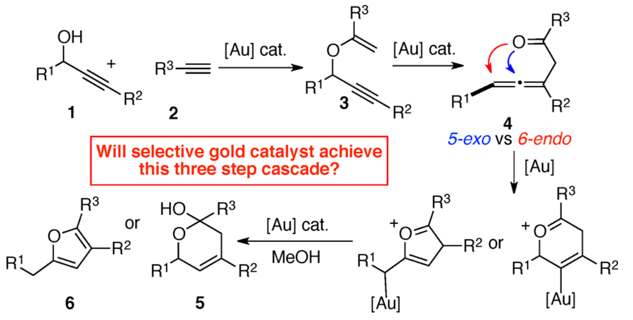
tional $[L\text{-}Au]^+$ catalysts, TA-Au gives significantly improved stability and excellent chemoselectivity (activating alkyne over allene).[5] With interest in developing a new efficient synthesis for complex organic compounds, we focused our attention on the intermolecular reaction between propargyl alcohol and a simple alkyne as a potential new approach for the synthesis of substituted furans.

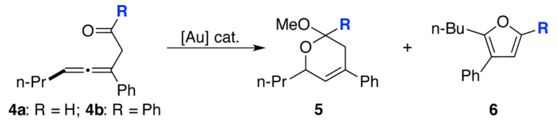
As shown in Scheme 2, our general design was a tandem reaction of three sequential gold catalyzed processes: (1) alcohol addition to alkyne **2**; (2) Saucy–Marbet rearrangement,[6] and (3) cyclization of allene-ketone **4**. Clearly, this new design offers much better overall efficiency toward furan when compared to current literature reported methods. However, there are some big challenges. First, as required in any cascade processes, orthogonal reactivity is crucial to ensure the reaction proceeds in a sequential fashion. Based on the design, a precise gold catalytic system must have good chemoselectivity such that reactivity proceeds by activation of a terminal alkyne followed by an internal alkyne and concluding with an allene. No successful gold catalysts have been reported that can achieve this type of selectivity in a single reaction fashion. The other challenge was the allene-ketone cyclization. Although both 5-exo and 6-endo cyclizations of allene-carbonyl **4** have been reported, the 6-endo pathway is much more prevalent.[7] This is likely due to the formation of a more stable vinyl-gold intermediate over the formation of alkyl gold (allylic gold) from the 5-exo cyclization. The only example in literature undergoing 5-exo cyclization is the work done by Kirsch as shown in Scheme 1B. Thus, to develop a successful example of the proposed three-step cascade, understanding the basic control factors that influence the allene-ketone cyclization is crucial.

Scheme 2. Furan Synthesis from Intramolecular O-Addition



The TA-Au catalysts developed in our group have shown excellent chemoselectivity toward alkynes. However, they indicated almost no reactivity toward allenes.[8] This property makes TA-Au a potential catalyst for the synthesis of allene **4** from simple starting materials **1** and **2**. Moreover, to reach furan **5**, allene activation is required. Thus, an alternative strategy needs to be applied to convert TA-Au as an operable catalyst toward allene activation.

Through the reaction kinetic evaluation, our group recently explored the mechanism of the TA-Au catalyzed Saucy–Marbet rearrangement. The alkyne replacement of the triazole (TA) ligand was revealed as the turnover-determining step in this TA-Au catalyzed reaction.[9] Based on this discovery, we postulated that the addition of a Lewis acid as a cocatalyst might help the TA-dissociation from gold, which will increase the reactivity of the TA-Au catalysts. Moreover it was recently reported that Lewis acids as cocatalysts are effective in increasing the efficiency of the gold catalyst by Hammond and Xu.[10] To investigate this hypothesis, we prepared allene-aldehyde **4a** and allene-ketone **4b** and charged them under various gold catalyzed conditions. The results are summarized in Figure 1.



4a: R = H; **4b**: R = Ph

5

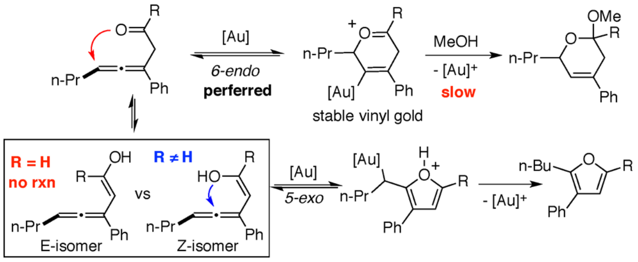
6

substrate	cat.	condition	conv **4** (%)	yield **5** (%)	yield **6** (%)
4a or **4b**	5% $[PPh_3Au(TA)]OTf$	tol or MeOH, rt, 24 h	trace	-	-
4a	5% PPh_3AuNTf_2	tol, rt, 5 h (no further conversion)	50	messy rxn	
4a	5% PPh_3AuNTf_2	MeOH, rt, 5 h	100	95	0
4b	5% PPh_3AuNTf_2	tol, rt, 4 h	100	0	80
4b	5% PPh_3AuNTf_2	MeOH, rt, 3 h	100	45	55
4b	5% $[PPh_3Au(TA)]OTf$, 5% $Cu(OTf)_2$	tol, rt, 6 h	100	0	75
4b	5% $Cu(OTf)_2$	tol, rt, 6 h	trace	-	-

Figure 1. TA-Au catalyzed allene-carbonyl cyclization.

First, TA-Au will not activate allenes. Treating allene aldehyde **4a** with PPh_3AuNTf_2 in dry toluene gave a very messy reaction with no major product identified. Notably, gold decomposition was observed with no further reaction progression after hours. Switching the solvent from toluene to methanol resulted in the formation of **5a** in 95% yield with no furan product **6a** observed. Interestingly, treating allene-ketone **4b** with PPh_3AuNTf_2 in dry toluene gave the formation of desired furan product **6a** in 80% yield. However, switching the solvent to MeOH generated a mixture of **5a** and **6a** (45% vs 55%). These results suggested that allene-ketone is a generally more acceptable substrate for the desired 5-exo cyclization (formation of furan). To test our hypothesis on Lewis acid activation of TA-Au catalysts, we performed reactions of **4b** and TA-Au with various different Lewis acids (see details in SI). With the combination of TA-Au and $Cu(OTf)_2$, furan **6a** was obtained in good yield. A plausible mechanism supporting why allene-ketone prefers the 5-exo cyclization is proposed in Scheme 3.

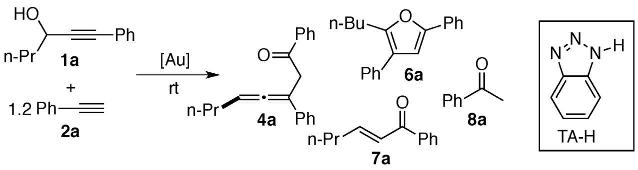
Scheme 3. Proposed Mechanism



First, the 6-*endo* cyclization is likely the preferred path due to the formation of more stable vinyl-gold. However, the turnover-limiting step is often the protodeauruation of a relatively stable vinyl-gold intermediate. The 5-*exo* cyclization may require the formation of *Z*-enol. Thus, with an allene aldehyde, the more stable trans isomer (E-enol) will be formed, which cannot undergo the cyclization step. As a result, dihydro pyrane was formed with protic solvent.

Encouraged by those results, we started to explore the proposed three-step cascade reactions using the combination of the TA-Au catalyst and Lewis acid. A summary of screening conditions is shown in Table 1.

Table 1. Screening Conditions[a]



entry	cat.	cond	Time (h)	conv (%)	yield (%) 4a	6a	7a	8a
1	$PPh_3AuCl/AgOTf$ (5%)	tol. rt	6	50	0	0	41	39
2	PPh_3AuNTf_2 (5%)	tol. rt	12	66	0	7	28	65
3	$IPrAuNTf_2$ (5%)	tol. rt	12	67	0	6	18	65
4	$XphosAuNTf_2$ (5%)	tol. rt	12	76	0	27	16	85
5	$(ArO)_3PAuNTf_2$ (5%)	tol. rt	12	77	0	6	24	60
6	$[(Ph_3PAu)_3O]^+SbF_6^-$ (5%)	tol. rt	14	25	12	<5	<5	<5
7	[XphosAu(MeCN)]OTf (5%)	tol. rt	14	70	25	20	25	25
8	[XphosAu(TA-H)]OTf (5%)	tol. rt	14	100	55	18	<5	<5
9	[XphosAu(TA-H)]OTf (5%) $Ga(OTf)_3$ (5%)	tol. rt	14	100	47	30	<5	12
10	[XphosAu(TA-H)]OTf (5%) $Cu(OTf)_2$ (5%)	tol. rt	14	100	22	63	<5	15
11	[XphosAu(TA-H)]OTf (1%) $Cu(OTf)_2$ (1%)[b]	tol. 45 °C	12	100	6	71	0	27
12	[XphosAu(TA-H)]OTf (**1%**) $Cu(OTf)_2$ (**0.5%**)[b]	tol. 45 °C	16	100	8	**80**	0	27

[a] Reaction conditions: **2a** (0.6 mmol) and catalyst(s) (0.025 mmol) in toluene (0.7 mL) were added to a solution of **1a** (0.5 mmol). See detailed screening conditions in the Supporting Information. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [b] 1.8 equiv of alkyne **2a** was used.

First, fast decomposition of gold and silver mixtures was observed (entry 1) with only 50% conversion of **1a**. A silver-free gold catalyst, PPh_3AuNTf_2, resulted in a slower decomposition rate (entry 2), with increased conversion of **1a**. However, significant **1a** hydration was observed (formation of enone **4a**). Notably, furan **6a** was observed under this condition, though with a low yield (7%). XPhos showed to be the most efficient primary ligand, producing more furan **6a** (entry 4, 27%). This suggests that the desired intermolecular addition occurred. Low conversion was observed using the gold-oxo complex with no desired furan product, and the catalyst decomposed over a longer reaction period. The echavarren catalyst (entry 7) gave incomplete conversion with 25% hydration of propargyl alcohol. XphosAu(TA-H)OTf gave almost no hydration of **5a** and **7a** and 55% allene product, likely due to its good stability toward allene activation. Using $Ga(OTf)_3$ as a Lewis acid cocatalyst (entry 9) increased the furan yield suggesting that the Lewis acid helped to increase TA-Au reactivity toward allene activation. Screening of Lewis acids gave $Cu(OTf)_2$ as the optimal choice with furan **6a** formed in 63% yield. Notably, addition of the $Cu(OTf)_2$ cocatalyst caused the formation of propargyl alcohol dimerization and enhancement of a hydration side product (**8a**). Therefore, decreasing the copper loading and increasing the reaction temperature to 45 °C gave the desired furan with improved yield (71%). Finally, the optimal result was obtained using 1% of [XphosAu(TA-H)]OTf and 0.5% $Cu(OTf)_2$ at 45 °C with an 80% yield of the desired furan (1.8 equiv of terminal alkyne was necessary). To the best of our knowledge, this is the first example of furan synthesis through the intermolecular propargyl alcohol addition.

Other metal catalysts such as Pd(II), Ag(I), Cu(I/II), Rh(I), and Ru(III) and propionic acid have also been tested. Propargyl alcohol addition to an alkyne was not observed in those cases (see SI). The scope of substrates for this cascade reaction is summarized in Figure 2.

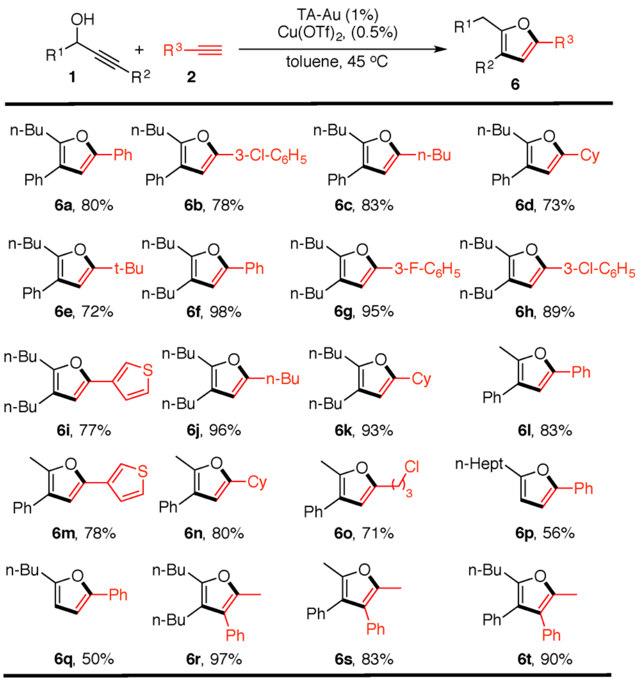


Figure 2. Reaction scope. General reaction conditions: **2a** (1.8 mmol) and gold catalyst (0.01 mmol) in toluene (1.5 mL) were added to a solution of **1a** (1 mmol), followed by addition of a copper catalyst (0.005 mmol). The resulting mixture was heated to 45 °C and monitored by TLC until full conversion was observed. See detailed reaction conditions in the SI. Isolated yields are shown.

This approach facilitated the synthesis of various furans with a large substrate scope. Good to excellent isolated yields were obtained in most of the cases. This reaction tolerated aromatic alkynes (**6a** and **6b**), aliphatic alkynes (**6c**), and heteroaromatic alkynes (**6m**). Linear (**6c**) and branched (**6d**) aliphatic alkynes also worked well under this catalytic system. Primary alkyl chlorides have also been tolerated well (good leaving group, **6o**). Bulky alkynes also gave good results in this condition (**6e**). However, internal alkynes did not work for this furan formation because of its very poor reactivity even when 15% of the catalysts were used. Also, increasing the temperature resulted in a complex reaction mixture likely caused by the similar reactivity of the two alkynes (hard to differentiate).

The reaction scope of propargyl alcohol also showed good functional group tolerability. First, with aliphatic groups at the R^1 position, both primary (**6l−6m**) and secondary (**6a−6k**) propargyl alcohols worked well under the standard conditions. At the R^2 position, both aliphatic and aromatic alkynes were suitable. Yet, terminal propargyl alkynes (**6p**, **6q**) gave lower yields due to the increasing amount of hydration.

Under the optimal conditions, tertiary propargyl alcohols failed to produce furans, likely due to the formation of stable and bulky fully substituted allenes (Figure 3A). To overcome this problem, a sequential "one-pot" process was developed. Initially,

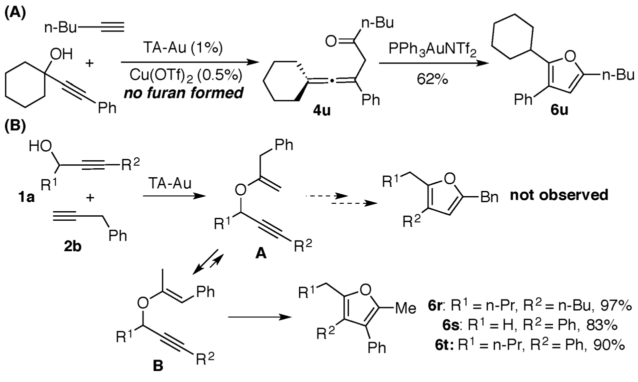


Figure 3. Challenging substrates.

TA-Au/Cu(OTf)$_2$ catalyzed propargyl alcohol addition to alkynes occurs, giving the allene **4u**. Treating the allene with the more reactive PPh$_3$AuNTf$_2$ catalyst gave the desired furan **6u** in good yield. Complex reaction mixtures were received with an aromatic group at the R^1 position likely due to formation of benzylic carbocation, which facilitated propargyl alcohol dimerization.

Another surprising result arose from the reactions using benzyl alkyne **2b**. Under the standard conditions, reactions of alcohol **1a** and benzyl alkyne **2b** gave products occurring through "migration" (**6r**, **6s**, and **6t**). This interesting "carbon migration" could be explained by the vinyl ether rearrangement as summarized in Figure 3B. Propargyl vinyl ether **A** isomerized to a more stable compound **B** prior to the 3,3 rearrangement, which results in yielding fully substituted furans. As discussed above, internal alkynes were not suitable substrates for this transformation due to their poor reactivity. Thus, fully substituted furan could not be prepared using this method. However, this pseudo carbon migration from benzyl alkyne **2b** provided an interesting alternative approach to achieve the fully substituted furan, which further enhanced the scope of this new transformation.

In conclusion, we report herein the first successful example of intermolecular propargyl alcohol addition to alkynes as a general approach for the synthesis of substituted furans in good to excellent yields. This method used simple starting materials and required mild conditions (1% gold loading). On the other hand, other catalysts (gold or other metals) gave almost no desired products due to the lack of stability and inevitable gold-catalyzed propargyl alcohol hydration side reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02980.

Experimental details and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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