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Synthesis of 2,5-Dihydrofurans via a Gold(I)-Catalyzed Formal [4 + 1] Cycloaddition of α-Diazoesters and Propargyl Alcohols

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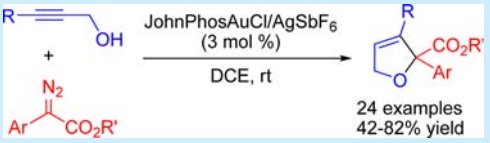
Supporting Information

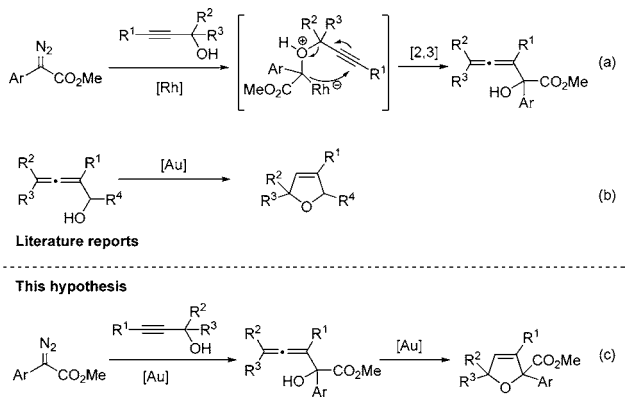
ABSTRACT: A gold(I)-catalyzed formal [4 + 1] cycloaddition of α-diazoesters and propargyl alcohols is disclosed, offering access to a variety of 2,5-dihydrofurans. The reaction shows a broad substrate scope and functional group tolerance. Preliminary mechanistic investigation indicates that this reaction most likely occurs through a 5-*endo-dig* cyclization of an α-hydroxy allene intermediate.



The transition-metal-catalyzed carbene transfer from diazo compounds serves as a powerful tool in organic synthesis.[1] Several metals have been reported to mediate this transformation effectively, among which rhodium[2] and copper[3] are mostly employed. In 2005, Nolan et al. reported the first example of gold-catalyzed carbene transfer from ethyl diazoacetate,[4] which was later followed by several gold-catalyzed transformations involving simple diazo substrates. For example, there have been reports on gold-catalyzed C−H insertion,[5] O−H insertion,[6] cycloadditions,[7] cyclopropenation,[8] cyclopropanation,[6,9] and cross-coupling of diazo compounds.[10] Despite the fact that gold complexes have shown specific catalytic activities in diazo chemistry, the application of gold catalysts is still less explored in diazo-based transformations. Herein we want to present an efficient gold-catalyzed [4 + 1] cycloaddition of α-diazoesters and propargyl alcohols leading to 2,5-dihydrofurans which serve as subunits in many bioactive natural products such as (+)-furanomycin,[11] diplobifuranylone B,[12] and cryptoresinol.[13]

The hypothesis comes from the Rh-catalyzed formation of α-hydroxy allenes from aryl diazoacetates and propargyl alcohols and the gold-catalyzed cyclization of α-hydroxy allenes to 2,5-dihydrofurans. As shown in Scheme 1, it was reported that α-hydroxy allenes would be generated from diazoacetates and propargyl alcohols in the presence of a Rh(II) catalyst via a tandem oxonium ylide formation/[2,3]-sigmatropic rearrangement cascade (Scheme 1a).[14] Interestingly, the resulting α-hydroxy allene was reported to undergo a 5-*endo-dig* cyclization giving 2,5-dihydrofuran in the presence of gold catalysts (Scheme 1b).[15] We hypothesized that, by the use of a gold catalyst, the oxonium ylide formation and the [2,3]-sigmatropic rearrangement would also occur to give α-hydroxy allene, which subsequently undergoes a 5-*endo-dig* cyclization delivering 2,5-dihydrofuran as a final product (Scheme 1c). By the use of a single catalyst to promote two reactions, this protocol would simplify the operations to provide an efficient method for the preparation of 2,5-dihydrofurans.

Scheme 1. Literature Reports and Our Hypothesis



Our initial studies examined the reaction between the phenyl diazoacetate **1a** and phenyl propargyl alcohol **2a** in the presence of [IPrAuCl]/$AgNTf_2$ (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethylsulfonyl). Pleasingly, as we expected, 2,5-dihyrofuran **3aa** was obtained after 3 h (Table 1, entry 1). Encouraged by the result, a search for suitable catalysts and solvents for the [4 + 1] cyclization was then conducted (Table 1). A variety of gold catalysts were examined first, among which JohnPhosAuCl (JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl) in combination with $AgNTf_2$ improved the reaction dramatically affording **3aa** in 76% yield in 5 min (Table 1, entry 4). In contrast, AuCl alone (Table 1, entry 5) as well as $AuCl_3$ (Table 1, enrty 6) only gave a trace amount of **3aa** after 3 h. Other transition metal catalysts were also examined. $AgNTf_2$ was also capable of catalyzing this reaction, but gave a mixture of 2,5-dihydrofuran **3aa**, the O−H insertion product **4a**, and cyclopropene derivative **6a** (Table 1, entry 7). In analogy to $AgNTf_2$, $Cu(OTf)_2$ did not improve this reaction (Table 1, entry 8). $CuBr_2$ afforded only O−H insertion product **4a** in 68% yield (Table 1, entry 9). No reaction was observed when PTSA (*p*-toluenesulfonic acid) was added to catalyze this reaction (Table 1, entry 10). Further optimization

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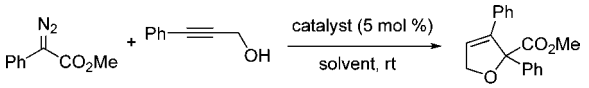
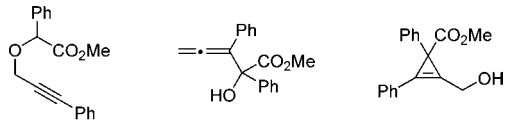
Table 1. Reaction Optimization[a]



1a 2a 3aa

entry	catalyst	solvent/time	yield (%)[b]
1	IPrAuCl/$AgNTf_2$	DCM/3 h	55
2	$Ph_3PAuCl/AgNTf_2$	DCM/10 h	25
3	SPhosAuCl/$AgNTf_2$	DCM/3 h	67
4	JohnPhosAuCl/$AgNTf_2$	DCM/5 min	76
5	AuCl	DCM/3 h	trace
6	$AuCl_3$	DCM/3 h	trace
7[c]	$AgNTf_2$	DCM/5 min	33
8[d]	$Cu(OTf)_2$	DCM/1 h	43
9[e]	$CuBr_2$	DCM/10 h	0
10	PTSA	DCM/3 h	0
11	JohnPhosAuCl/AgOTf	DCM/5 min	57
12	JohnPhosAuCl/$AgSbF_6$	DCM/5 min	78
13	JohnPhosAuCl/$AgSbF_6$	DCE/5 min	81
14	JohnPhosAuCl/$AgSbF_6$	THF/3 h	trace
15	JohnPhosAuCl/$AgSbF_6$	CH_3CN/3 h	trace
16	JohnPhosAuCl/$AgSbF_6$ (3 mol %)	DCE/30 min	80
17	JohnPhosAuCl/$AgSbF_6$ (1 mol %)	DCE/10 h	63

[a]The solution of **1a** (0.3 mmol) in 1 mL of solvent was introduced into the reaction mixture of the catalyst (0.003−0.015 mmol) and **2a** (0.45 mmol) in 2 mL of solvent by a syringe in 5 min. [b]Isolated yield. [c]**4a** and **6a** were obtained in 10% and 15% yield, respectively. [d]**4a**, **5a**, and **6a** were obtained in 9%, 20% and 12% yield, respectively. [e]**4a** was isolated in 68% yield.

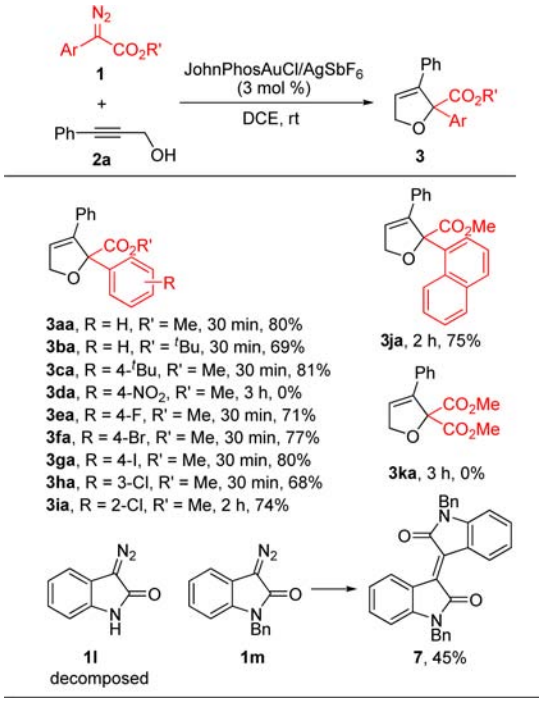


4a 5a 6a

of the reaction conditions including silver salts (Table 1, entries 11, 12), solvents (Table 1, entries 13−15), and catalyst loading (Table 1, entries 16, 17) revealed that 3 mol % of the JohnPhosAuCl/$AgSbF_6$ was able to efficiently induce the [4 + 1] cycloaddition in 1,2-dichloroethane at room temperature (Table 1, entry 16).

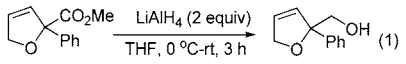
Having established optimized reaction conditions, the scope of the cycloaddition reaction with various α-diazoesters was explored (Scheme 2). The substituent on the ester group of **1** was first investigated. When the methyl group was replaced by a bulky *tert*-butyl group, the yield of the corresponding 2,5-dihydrofuran was dropped from 80% (**3aa**) to 69% (**3ba**). A electron-donating group in the *para*-position of the phenyl gave the product in good yield (**3ca**), while the substrate bearing a strong electron-withdrawing group afforded no 2,5-dihydrofuran product (**3da**). The installation of a halogen atom in the phenyl ring did not affect the yield dramatically (**3ea**−**3ia**) and, at the same time, makes further functionalizations possible. The α-naphth-1-yl α-diazoacetate also worked leading to corresponding product **3ja** in 75% yield. Attempts to get the corresponding 2,5-dihydrofurans from dimethyl 2-diazomalonate and diazooxindoles (**1l** and **1m**) failed. The decomposition of starting materials was observed when dimethyl 2-diazomalonate and diazooxindole **1l** were subjected to standard conditions. The reaction of **1m** gave a dimerization product **7** in moderate yield.

Scheme 2. Substrate Scope of α-Diazoesters[a]

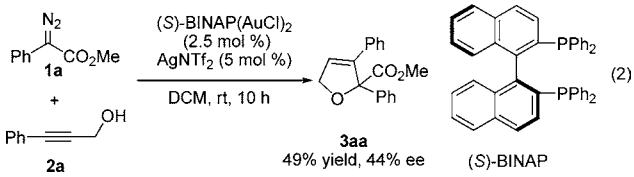


[a]The reactions were carried out on 0.3 mmol scale; the yields given are isolated yields.

Various propargyl alcohols were then examined to explore the substrate scope (Scheme 3). Moderate to good yields of the 2,5-dihydrofurans were obtained for most of the substrates with a substituted phenyl group on the alkyne terminal. It is worth pointing out that introduction of an −OH group on the phenyl group resulted in various reaction possibilities such as aromatic C−H insertion[5] and phenolic O−H bond insertion,[5,6] which rationalizes the relatively low yield of **3ac**. A strong electron-withdrawing group in the phenyl group renders the reaction incapable (**3af**). **3ai** was obtained in a relatively lower yield because of the bulky 1-naphthyl group. A heteroaromatic substrate also worked smoothly affording corresponding product in moderate yield (**3aj**). Substrates with two propargyl alcohol units delivered corresponding products in good yields (**3ak** and **3bk**). Notably, when the substituent R on the propargyl alcohols was a H atom and an *n*-butyl group, the corresponding products were obtained in 56% (**3al**) and 60% (**3am**) yields, respectively. Tertiary propargyl alcohols did not afford 2,5-dihydrofuran (**3an**) but the dimers of diazoester and the O−H insertion products. **3al** was easily transformed into the corresponding alcohol **8**,[16] a known compound, by addition of $LiAlH_4$ in THF (eq 1).



3al 57% 8



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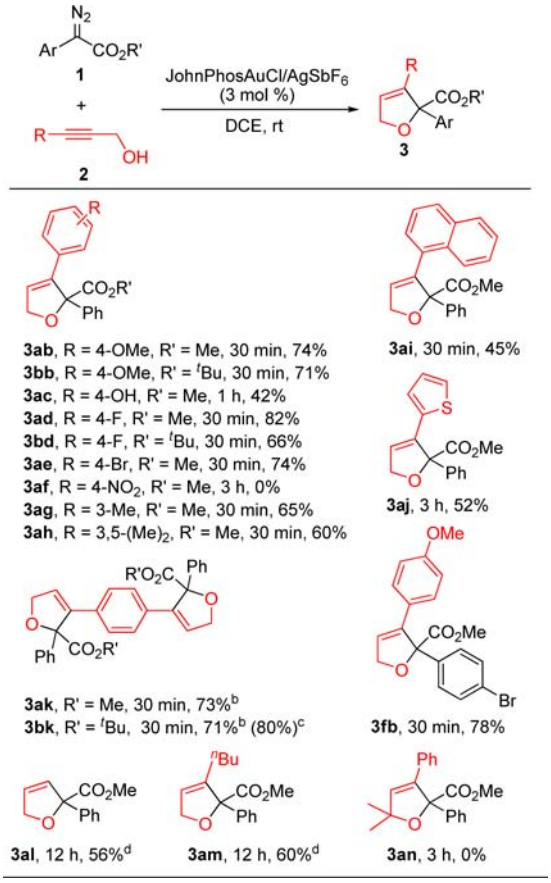
Scheme 3. Substrate Scope of Propargyl Alcohols[a]

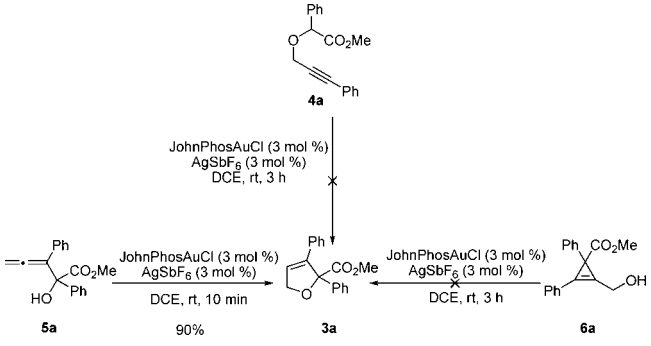


[a]The reactions were carried out on 0.3 mmol scale; the yields given are isolated yields. [b]The ratio of diazoester to propargyl alcohol was 3:1. [c]The ratio of diazoester to propargyl alcohol was 6:1. [d]3.0 equiv of propargyl alcohol were added.

Attempts to achieve the asymmetric catalysis have also been undertaken (eq 2). Various chiral ligands[17] were examined; however, only moderate enantioselectivity was achieved. Among the ligands examined, (*S*)-BINAP gave the best result delivering **3aa** with 44% ee. Although an acceptable enantioselectivity has not been achieved, the result indicated that this reaction is amendable to enantioselective catalysis.

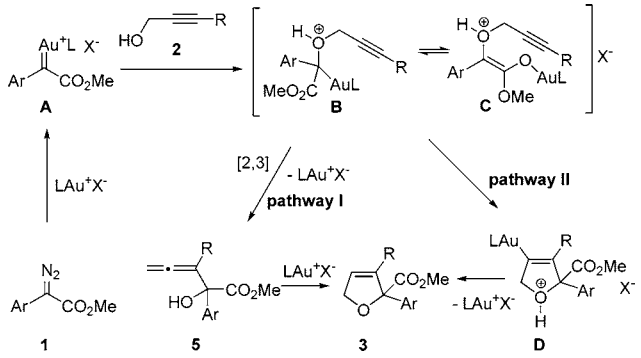
Several control reactions were conducted to gain insight into the mechanism of this reaction, as shown in Scheme 4. When subjected to the standard reaction conditions, α-hydroxy allene **5a** afforded 2,5-dihydrofuran **3a** in 90% yield, whereas neither **4a** nor **6a** led to the formation of **3a**. The results indicated that an α-hydroxy allene intermediate was possibly involved in the reaction pathway.

Scheme 4. Mechanistic Investigations



Based on the experimental observations and literatures,[18] a plausible reaction mechanism is proposed in Scheme 5. A

Scheme 5. Plausible Mechanisms for the [4 + 1] Cycloaddition



gold(I) carbene intermediate **A** was formed from α-diazoester **1** in the presence of a gold(I) catalyst. The following nucleophilic attack of the propargyl alcohol on the carbene center led to oxonium ylide **B**, which is in equilibrium with gold enolate **C**. In pathway **I**, as we hypothesized, a [2,3]-σ-rearrangement of oxonium ylide **B** afforded α-hydroxy allene **5**, which then delivered 2,5-dihydrofuran **3** via a gold(I)-catalyzed 5-*endo-dig* cyclization. Alternatively, in pathway **II**, the insertion of the C≡C triple bond into the Au−C bond led to the formation of a 2,5-dihydrofuran ring.[19]

NMR experiments were carried out to obtain further information on the reaction pathway.[20] As shown in Figure 1,

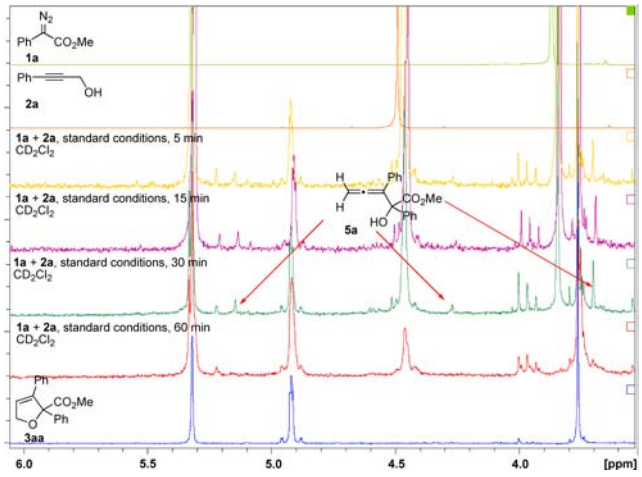


Figure 1. NMR experiments on the reaction mechanism.

α-hydroxy allene **5a** was indeed observed from the beginning of the reaction until **1a** was fully consumed. This result indicated that at least part of 2,5-dihydrofuran **3aa** was formed via pathway **I**. Additionally, the fact that only a trace amount of **5a** was observed in the whole process revealed that, in pathway **I**, the formation of α-hydroxy allene **5a** was slow whereas the conversion of **5a** to **3aa** was fast. However, pathway **II** is still not excluded by existing experimental results.

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In summary, we have established an efficient approach for the synthesis of 2,5-dihydrofurans from α-diazoesters and propargyl alcohols via a gold(I)-catalyzed [4 + 1] cycloaddition. The reaction showed a broad substrate scope and functional group tolerance. In addition, attempts to achieve the asymmetric catalysis indicated that this reaction is amendable to enantioselective catalysis. Mechanistic investigations revealed that two plausible pathways might be involved in the formation of 2,5-dihydrofurans. Further studies including asymmetric catalysis and synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02663.

Experimental procedures and detailed characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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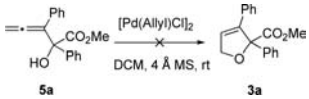
(17) For details on the chiral ligands examined, please see the Supporting Information.

(18) For a review for mechanistic studies on the gold chemistry of allenes, see: Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014**, *43*, 2941−2955.

(19) Another independent work by Prof. Hu and co-workers appeared recently while this manuscript was being prepared. They reported the same reaction which was catalyzed by $[Pd(Allyl)Cl]_2$. Comparably, the gold-catalyzed reaction showed a broad substrate scope and functional group tolerance, better yields, simplified operations (without protection from inner atmosphere, a syringe pump was not required), and differences in mechanisms. For example, the treatment of α-hydroxy allene with $[Pd(Allyl)Cl]_2$ did not afford the 2,5-dihydrofuran product.



5a 3a

For Hu's report, please see: Shi, T.; Guo, X.; Teng, S.; Hu, W. *Chem. Commun.* **2015**, DOI: 10.1039/C5CC05000F.

(20) For details on the NMR experiments, please see the Supporting Information.

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