ACS Catalysis
Letter
Cite This: ACS Catal. 2019, 9, 10339−10342
pubs.acs.org/acscatalysis

Efficient Synthesis of α-Allylbutenolides from Allyl Ynoates via Tandem Ligand-Enabled Au(I) Catalysis and the Claisen Rearrangement

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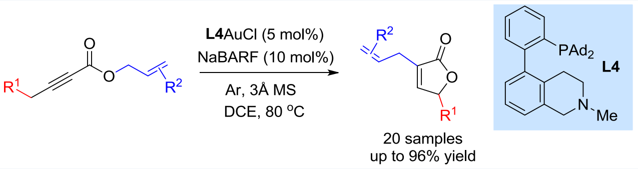
Supporting Information

ABSTRACT: A facile construction of α-allylbutenolides from readily available allyl ynoates has been developed via tandem gold-catalyzed alkyne isomerization to allene and cycloisomerization, the Claisen rearrangement and a double bond migration. The gold catalysis is enabled by a bifunctional phosphine ligand featuring a critical remote tertiary amino group, and the reaction tolerates a range of substituents and exhibits yields up to 96%.



KEYWORDS: *gold, cycloisomerization, catalysis, the Claisen rearrangement, bifunctional phosphine ligand*

Over the past few years, we have embarked on the development of new bifunctional phosphine ligands[1] specifically designed for homogeneous gold catalysis.[2] These ligands share the well-studied and privileged biphenyl-2-ylphosphine framework, yet are distinguished by the featured remoted basic substituents that can engage beneficial interactions with gold-activated alkynes/allenes or incoming nucleophiles, because of the rather unique linear ligand−Au(I)-substrate organization (see Scheme 1A). Examples of these ligands are shown in Scheme 1B. We have recently engineered their chiral versions for novel asymmetric gold catalysis.[1g,j] By using the amine-based ligands **L1−L4**, we have demonstrated that alkyne can be isomerized into allene in a reversible manner.[1a,e,j] As shown in Scheme 1C, the allene intermediates can further undergo irreversible isomerization[1a,c,e] to afford different types of dienes or cyclization to form dihydrofurans with good to excellent stereoselectivities[1j] and electron-rich 2-aminofurans en route to their Diels−Alder adducts.[3] Notably, these ligand-enabled gold catalysis could not been achieved in the presence of conventional phosphine and NHC ligands[1a,c,e,j] or were markedly superior.[1h,i]

To further expand the synthetic utility of the isomerization of alkynes into allenes, we envisioned, as shown in Scheme 2A, that our catalytic system can isomerize an ynoate (i.e., **1**) into an allenoate, which could undergo known cyclization to form the cationic intermediate **A**. It was anticipated that, because of the presence of the remote basic group, a facile deprotonative aromatization of **A** to afford alkoxyfuranylgold **B** might occur, similar to the alkynamide case that we just reported.[3] Subsequent protodeauration would deliver an electron-rich 2-alkoxyfuran as the product. We reasoned that if the R′ group is an allyl, the product would subsequently undergo the Claisen rearrangement and a double bond migration to afford the α-allylbutenolide product **2**. As such, the anticipated gold catalysis would permit the transformation of a readily available allyl ynoate into an α-functionalized butenolide. Notably, we are not aware of any example of such a Claisen rearrangement and, moreover, there is no precedent of direct cycloisomerization of ynoates to valuable electron-rich 2-alkoxylfuran, although the related ynone cases leading to 2-alkylfurans have been realized via Pd catalysis[4] or Cu catalysis.[5]

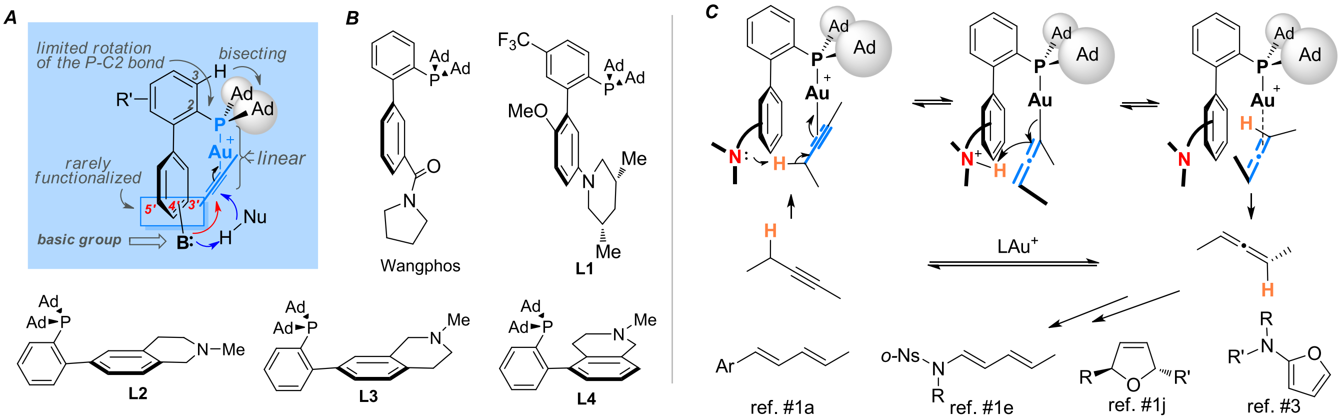
Although gold-catalyzed formations of butenolides from allenoates have been reported,[6] the reactions do not proceed through the intermediacy of 2-alkoxyfuran but rather undergo direct fragmentation of the O-R′ bond of the intermediate of type **A** to arrive at the butenolide structure. As a result, they do not lead to functionalization at the α-carbon. Of interest is a combined Au/Pd catalysis reported by Blum (Scheme 2B),[6c] where allyl α-methylallenoates are isomerized to isomeric β-allylbutenolides.

At the outset, we chose allyl but-2-ynoate (**1a**) as the substrate. After some exploration of the reaction conditions, we determined the following optimal reaction conditions: **L4**AuCl (5 mol %), NaBARF (10 mol %), 3 Å MS, DCE, 80 °C, 4 h, and under argon (see Table 1). Under these conditions, the desired α-allylbutenolide **2a** was formed in 95% NMR yield and 90% isolated yield (entry 1 in Table 1). Notably, as expected, various commonly used ligands including IPr, Ph$_3$P, JohnPhos, and the bulky phosphite [(2,4-^{t}Bu$_2$C$_6$H$_3$)O]$_3$P, and 1,10-phenanthroline were totally ineffective, and most **1a** remained unreacted (entry 2 in Table 1). Even with the addition of Et$_3$N or pyridine (2 equiv to Au; entry 3 in Table

Received: August 17, 2019
Revised: September 27, 2019
Published: October 17, 2019

DOI: 10.1021/acscatal.9b03501

Scheme 1. Development of Biphenyl-2-ylphosphines Featuring Remote Basic Groups for Gold Catalysis: (A) Design; (B) Selected Examples, and (C) Gold-Catalyzed Reversible Isomerization of Alkyne into Allene Enabled by Designed Bifunctional Ligands and Further Transformations



Scheme 2. Formation of 2-Allylbutenolides from Allyl Ynoates: (A) Design and (B) a Related Literature Precedent

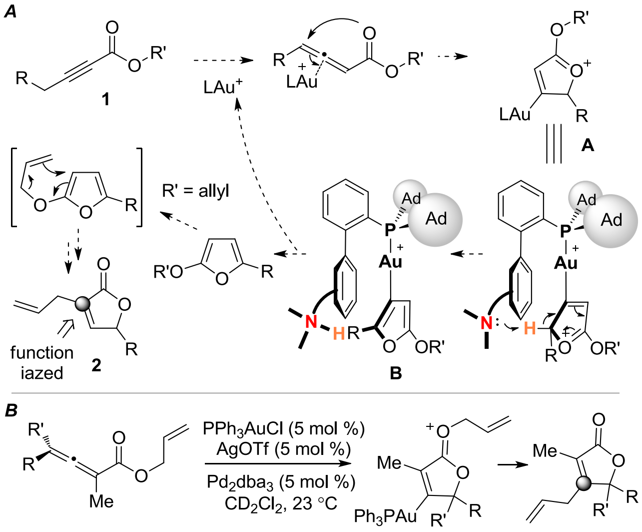
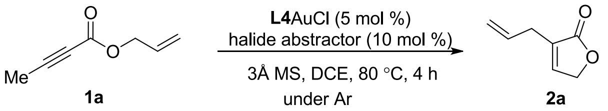


Table 1. Optimization of the Reaction Conditions[a]



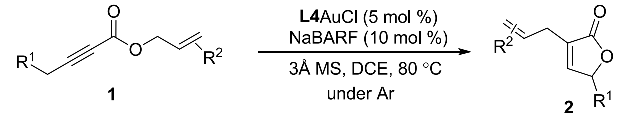
entry	deviation from optimized conditions	yield[a] (%)
1	–	**95 (90[b])**
2	IPr, Ph_3P, $[(2,4\text{-}^tBu_2C_6H_3)O]_3P$, JohnPhos, or 1,10-phenanthroline as ligand	0
3	JohnPhos or Ph_3P as ligand, Et_3N or pyridine (10 mol %) added to reaction	<2
4	**L1** as a gold ligand	68
5	**L2** as a gold ligand	50
6	**L3** as a gold ligand	70
7	$AgSbF_6$ as the chloride abstractor	15
8	$AgNTf_2$ as the chloride abstractor	15
9	AgOTf as the chloride abstractor	7
10	no Ar protection	65
11[c]	2.5 mol % gold loading	92
12	reaction temperature: 60 °C	14

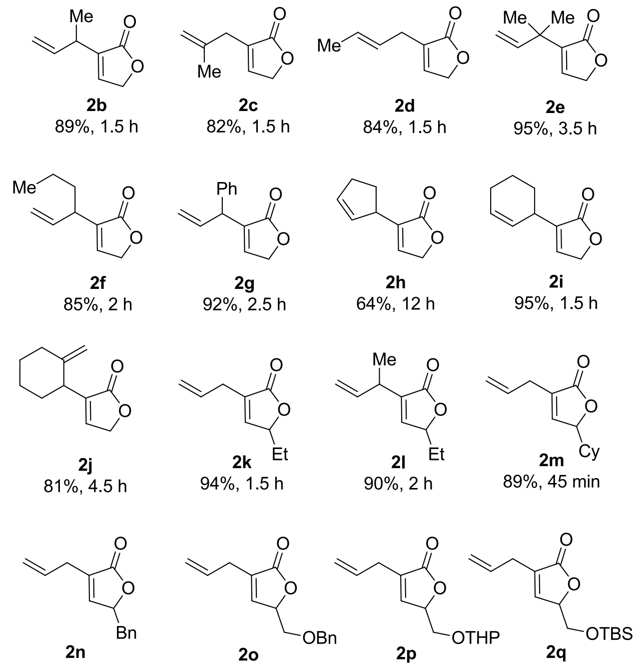
[a]The reaction run at an initial **1a** concentration of 0.05 M. Yield was determined by ^1H NMR. [b]Isolated yield. [c]The reaction was performed for 8 h.

1), little product was observed in the presence of either JohnPhos or Ph_3P. With the aniline-functionalized biphenyl-2-ylphopshine **L1**,[1a] the reaction did occur, albeit in a lower yield (entry 4 in Table 1). The tertiary amine-functionalized ligands **L2** and **L3**,[1c] isomeric to the optimal ligand **L4** by the location of the basic nitrogen, could also promote the reaction, despite with lower efficiencies (entries 5 and 6 in Table 1). These ligand screening results highlight (a) the indispensable and enabling nature of the tethered remote amino group in promoting this reaction and (b) the locale of the remote basic group affecting the reaction efficiency. The counteranion of the in situ generated cationic gold(I) catalyst is also of critical importance. Only $BARF^-$ works well. The use of other commonly used anions such as SbF_6^- (entry 7 in Table 1), NTf_2^- (entry 8 in Table 1) and OTf^- (entry 9 in Table 1) resulted in poor yields.[7] When the reaction was not protected by an Ar atmosphere, the yield suffered (entry 10 in Table 1), which can be attributed to the oxidative decomposition of the 2-allyloxyfuran intermediate by oxygen and hence offer circumstantial evidence for the intermediacy of this electron-rich species. Reducing the catalyst loading by 50% led to a long reaction time (8 h) and a slightly lower yield (entry 11 in Table 1). At 60 °C, the reaction conversion was even lower, and only 14% of **2a** was formed (entry 12 in Table 1).

With the optimal reaction conditions in hand, we set out to investigate the reaction scope (see Table 2). First, but-2-ynoate substrates (R^1 = H) with various allyl groups were examined. In the cases of **2b**–**2d**, a methyl substituent at all three allyl carbons is allowed, and the butenolides were formed in excellent yields. A quaternary allylic carbon center in **2e** was generated smoothly from prenyl but-2-ynoate. The products **2f** and **2g** featuring a *n*-propyl and a phenyl group, respectively, at the allylic position were formed in high yields. With the allyl group embedded in a 5-membered ring, the reaction leading to **2h** was much slower, but it was still formed in an acceptable yield. We attribute the sluggishness to a hampered Claisen rearrangement involving the cyclopentene ring. In the case of a 6-membered ring, the reaction was much faster and more efficient, affording **2i** in 95% yield. With cyclohex-1-en-1-ylmethyl but-2-ynoate as the substrate, the product **2j** featuring an exocyclic double bond was isolated in 81% yield. Second, the R^1 group of **1** was modified. An ethyl (**2k** and **2l**), a bulkier

Table 2. Au-Catalyzed Synthesis of 3-Allylfuran-2(5*H*)-one 2[a,b]



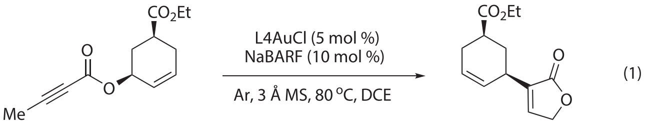


2b 89%, 1.5 h	**2c** 82%, 1.5 h	**2d** 84%, 1.5 h	**2e** 95%, 3.5 h
2f 85%, 2 h	**2g** 92%, 2.5 h	**2h** 64%, 12 h	**2i** 95%, 1.5 h
2j 81%, 4.5 h	**2k** 94%, 1.5 h	**2l** 90%, 2 h	**2m** 89%, 45 min
2n 84%, 1 h	**2o** 92%, 1 h	**2p** 96%, 1 h	**2q** 87%, 40 min

[a]The reaction run at an initial concentration of 0.05 M. [b]Isolated yields are reported.

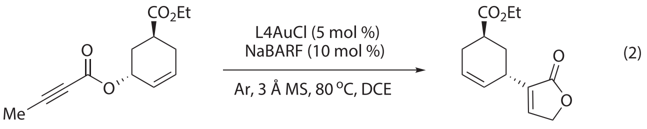
cyclohexyl (**2m**), a benzyl group (**2n**), and a benzyloxymethyl (**2o**) were all readily tolerated, and the reactions were of high efficiencies. An acid-labile THP (**2p**) and a TBS group (**2q**) in place of the benzyl in **2o** had little impact on the reaction outcome, highlighting the broad functional group tolerance and mild nature of the reaction system.

We also prepared *cis*- and *trans*-**1r**, where the placeholder ethoxycarbonyl group is *cis* and *trans* to the 2-butynoate moiety on the cyclohexene ring. As shown in eqs 1 and 2, the gold catalysis is mostly stereospecific, and, in both cases, the butenolide moiety ends up overwhelmingly on the same side of the ring as the but-2-ynoate moiety in the substrates. These results are consistent with the allyl migration being a concerted Claisen rearrangement process.



cis-1r

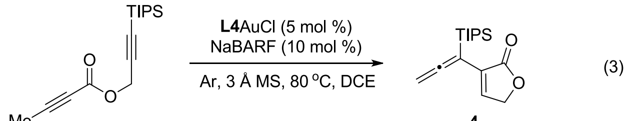
cis-2r
88%, 4 h



trans-1r : cis-1r = 1:0.13

trans-2r : cis-2r = 1:0.13
87%, 4 h

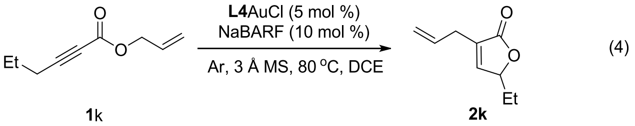
The replacement of the allyl group of **1** with a propargyl group was mostly unsuccessful, likely due to the interference of the 3,3-rearrangement of propargylic esters.[8] But, as shown in eq 3, with a bulky TIPS group at the C−C triple bond terminus, such a side reaction is hampered by sterics. As such, this gold-catalyzed tandem transformation of **3** occurred smoothly to deliver the allenylbutenolide **4** in a serviceable 61% yield.



3

4
61%

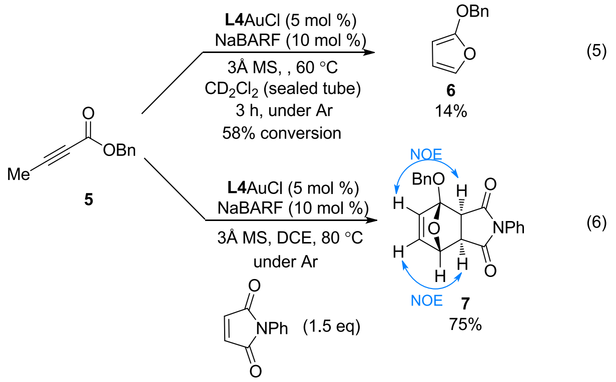
We also performed the reaction in a half-gram scale. As shown in eq 4, it proceeded without event, and the yield remained excellent.



1k
0.5 g

2k
0.46 g 92 %

To support the mechanistic aspect of this designed chemistry, we prepared the benzyl ester **5**, which could not undergo the Claisen rearrangement. It is anticipated that 2-benzyloxyfuran (**6**) should be formed. As shown in eq 5, it was indeed detected. The low yielding of this compound is consistent with its electron-rich and, hence, likely labile nature. By adding *N*-phenylphthalimide to trap **6** in situ, the Diels−Alder adduct, *exo*-cycloadduct **7** was formed in 75% isolated yield. The relative stereochemistry of **7** is assigned based on the related literature precedent[9] and the observation of the indicated NOEs.



5

6
14%

7
75%

In summary, we have developed an expedient construction of α-allylbutenolides from readily available allyl ynoates. The reaction entails multiple transformations including ligand-enabled gold-catalyzed isomerization of alkyne into allene and cycloisomerization of allenoate to 2-allyloxyfuran, the Claisen rearrangement, and a double bond migration. Despite its complex nature, the reaction is of rather broad scope and exhibits high to excellent yields. Our preliminary mechanistic studies support the intermediacy of a 2-allyloxyfuran, and the concerted nature of the Claisen rearrangement. This chemistry represents a facile access to versatile butenolides with valuable α-functionalization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b03501.

Experimental procedures, characterization data including ^{1}H and ^{13}C NMR spectra, IR spectra and HR-MS, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

H.-Y.W. is grateful to the financial support of Jiangsu Overseas Training Program for Universities and Lianyungang Haiyan Project. L.Z. thanks NSF (No. CHE 1800525) for financial support.

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