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# Gold-Catalyzed $sp^2$-sp C-C Coupling by Alkynylation via Oxidative Addition of Bromoalkynes

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## Abstract

A gold(I)-catalyzed cascade cyclization/alkynylation of allenoates using alkynyl bromide to generate $\beta$-alkynyl-$\gamma$-butenolides was investigated. While alkynyl iodides afforded significant amounts of the homo-coupling of two lactone units, alkynyl bromides led to a selective reaction, and a broad functional group tolerance was observed. Under optimized reaction conditions it was possible to directly synthesize a large range of $\beta$-alkynyl-$\gamma$-butenolides in moderate to good yields without the need for any external oxidant.

## Keywords

Allenes; cross-coupling; gold catalysis; heterocycles; oxidative addition

Due to the high redox potential of the Au(I)/ Au(III) (1.41 V) compared to those of Pd(0)/Pd(II) (0.91 V) or Pt(0)/Pt(II) (1.18 V),[1] the development of methodologies on the oxidative addition of Au(I) has attracted much attention.[2] In the last years, some general oxidizing agent were used in the gold-catalyzed redox coupling involving oxidation of Au(I) to Au(III). First, in 2009, Waser *et al.* developed the gold-catalyzed C-H alkynylation of indole with ethynyl-benziodoxolone (EBX) reagents, followed by a series of methodologies for alkynylation of (hetero)arenes (Scheme 1a).[3] Second, in 2013, Glorious and coworkers expanded Au(I) oxidation with aryldiazonium salt

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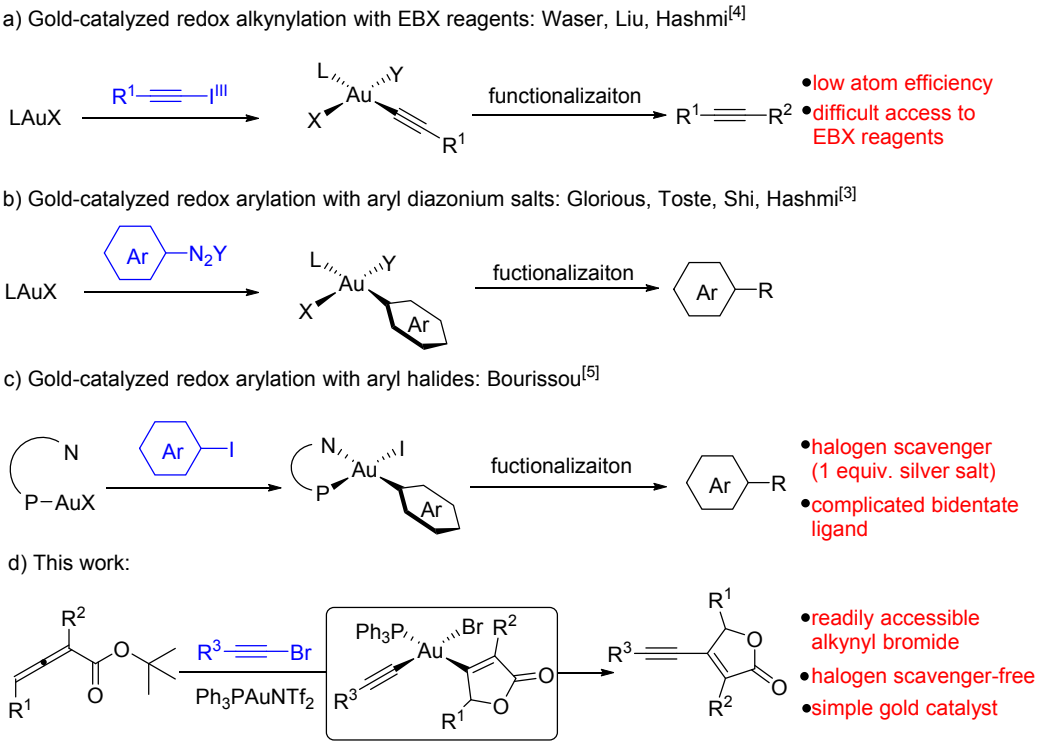
combined with a Ru photoredox catalyst, leading to the explosion of new methodologies for gold-catalyzed arylation (Scheme 1b).[4] Third, in 2017, in Bourissou's group, aryl halides was used in the gold-catalyzed arylation of electron-rich arenes by hemilabile (P,N) ligand-promoted oxidative addition of gold(I) (Scheme 1c).[5] However, these strategies suffered from some drawbacks, for example the steps for the synthesis of the hypervalent iodine regents, the low atom efficiency (only a small part of the reagent is transferred or more than one equivalent of silver is needed)[5] and the need of complicated bidentate ligands.




Scheme 1. a), b) and c) previous work on the gold-catalyzed redox coupling with general oxidizing agents; d) this work for the gold-catalyzed cyclization/ alkynylation with alkynyl bromides.

Haloalkynes, readily accessible oxidizing agents in transition metal-catalyzed cross-couping, are widely used in synthetic chemistry.[6] However, the development of gold catalysis with haloalkynes is hampered by some challenges. First, the lower oxidative potential compared to EBX reagents makes an oxidative addition of the haloalkynes to the gold(I) center difficult. Second, simple gold catalysts such as $Ph_3AuX$ and IPrAuX (X = halogen) are sluggish in the oxidative addition of Csp/$Csp^2$-X bond.[7] Finally, the halogen could block the active gold catalyst by the formation of thermodynamically stable LAuX.[8] The common solution for halogen poisoning is by the addition of more

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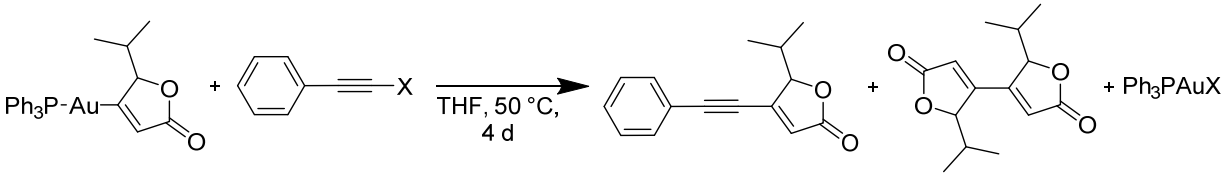
than one equivalent of halogen scavenger, which however, largely decreases the atom efficiency of these gold catalyses.[5]

Due to the strong Lewis acidity of gold catalyst, a sequential cyclization and functionalization is an advantage for gold catalysis.[3,4] In 2010, Gouverneur *et al.* developed a cascade cyclization – oxidative alkynylation of allenoates with terminal alkynes by using Selectfluor as external oxidant.[9] It provided an efficient method for the synthesis of $\beta$-alkynyl-$\gamma$-butenolides, which was previously conducted by a two-step procedure based on the *stoichiometric* cyclization of the allenoate with gold(I) complex and a subsequent palladium-catalyzed cross-coupling.[10] However, this strategy still suffered from the use of a strong external oxidant. Herein, we sought to combine the gold(I)-induced cyclization of allenoates with a mild oxidative addition of gold(I), a gold-catalyzed cyclization/cross-coupling alkynylation reaction with haloalkynes (Scheme 1d).

In initial experiments, *stoichiometric* reactions of lactonyl gold(I) complex **1a** with phenylacetylene and the corresponding halogenated derivatives were examined (Table 1). The organogold(I) complexes **1a-c**, which were first reported by Hammond *et al.* in 2008,[11] are characterized by a remarkable stability and the feature that they can conveniently be obtained by a cyclization reaction.[9,10,12] One equivalent of the organogold(I) complex **1a** was treated with 1.1 equivalents of the alkynes **2a-d** in THF at 50 °C. After stirring for 4 days, no reaction occurred using the non-halogenated phenylacetylene **2a** (Table 1, entry 1). But the brominated phenylacetylene **2c** yielded 74 % of the desired $\beta$-alkynyl-$\gamma$-butenolide **3a** without significant amounts of homo-coupling product **4** (Table 1, entry 3) while in case of the iodinated alkyne **2d** only 47 % of the desired product **3a** were gained (Table 1, entry 4) accompanied by 37 % of the homo-coupled lactone **4**. A low reactivity was observed with the chlorinated phenylacetylene **2b** (Table 1, entry 2).

Table 1. Stoichiometric reactions.[a]




**1a** **2a-d** **3a** **4**

| Entry | Alkyne | X | Yield 3a [%][b] | Yield 4 [%] |
|---|---|---|---|---|
| 1 | **2a** | H | no reaction | |
| 2 | **2b** | Cl | 3[c] | - |

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| 3 | 2c | Br | 74 | traces |
|---|---|---|---|---|
| 4 | 2d | I | 47[c] | 37 |

[a] *Reaction conditions:* Organogold(I) complex **1a** (55 µmol, 0.55 mmol/ml), alkyne **2a-d** (60 µmol), THF at T = 50 °C. [b] Yield determined by $^1$H NMR spectroscopy of the crude reaction mixture using 1,4-dinitrobenzene as an internal standard. [c] An ill-defined decomposition was observed, too.

Based on these results, studies concerning the gold-*catalyzed* cascade cyclization/alkynylating cross-coupling were conducted with brominated alkynes (See supporting information Table S1). The *tert*-butyl allenoate **5a** was treated with 1.1 equivalents of brominated phenylacetylene **2c**, 2 equivalents of base and a gold(I) catalyst (10 mol%) in a mixture of THF/$H_2O$ (1/2) at 50 °C. Pleasingly, the gold(I) complex $Ph_3PAuNTf_2$ in combination with $NaHCO_3$ led to the desired $\beta$-alkynyl-$\gamma$-butenolide **3a** in 72 % yield after 4 days (Table S1, entry 3). Compared to the stoichiometric experiment (Table 1, entry 3) the gold-catalyzed reaction (Table S1, entry 3) delivered a similarly high yield. The reaction of the gold(I) catalyst $Ph_3PAuNTf_2$ under exclusion of base delivers a 44 % yield (Table S1, entry 16). This emphasizes the importance of the usage of base. Further efforts for an optimization of the gold(I) catalyst only led to significantly decreased yields (Table S1, entries 1, 2, 4 – 12). This included various counter anions such as $Cl^-$, $Br^-$, $OTf^-$, $SbF_6^-$, $BF_4^-$ and $OTs^-$ and different ligands such as other phosphines ($Mes_3P$, ($p$-$CF_3Ph)_3P$), Buchwald ligands (SPhos, BrettPhos) and one NHC ligand (IPr). Especially, in case of Buchwald ligands, an unselective reaction was observed. Alternative bases (Table S1, entries 13 – 15) such as $K_2CO_3$, $K_3PO_4$ and $Cs_2CO_3$ reduced the turnover number up to 1/4. The control experiment with only $NaHCO_3$ showed no conversion (Table S1, entry 17).

Under the optimized reaction conditions the compatibility of the domino cyclization – alkynylation and the effects on the reaction efficiency were investigated with a wide range of substituted allenoates **5a-d** and arylacetylenes including *para*-, *meta*- and *ortho*-substituted derivatives **2c,e-m** as well as one alkylacetylene **2n** (Table 2). Allenoate **5b** with a methyl-substitutent in $R^2$-position almost afforded a full conversion of the starting material within a reaction time of 4 days. The cross-coupled butenolide **3b** was obtained in 80 %, the highest yield in the study of the scope of the reaction. A variation of the side chain $R^1$ to butyl (**5c**) or benzyl (**5d**) delivered the products **3c** and **3d** in only moderate yields. The effect of different substitution patterns of chlorinated phenyl groups in **2** on the reactivity was examined on the basis of the alkynes **2e-g**.

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Obviously, there is a significant effect on the yield. Here, the *p*-Cl substituent on the benzene ring provided **3e** in 53 % isolated yield, whereas, the *m*-Cl-substituted arylalkyne delivered a NMR yield of **3f** of 9 % after a reaction time of 4 days. Especially electron-poor arylbromoalkynes, bearing *p*-$CF_3$, *p*-$NO_2$ and even *p*-$COOCH_3$ on the aryl group, produced the corresponding butenolides **3i,j,l** in low yields. On the other hand, the electron-donating *p*-$CH_3O$-Ph-substituted alkyne **2m** afforded **3m** in 69 % yield and thus showed a slightly higher reactivity than the unsubstituted alkyne **2c**. The reaction with 1-bromohex-1-yne **2n** as alkylalkyne was extremely slow, however, the isolation of **3n** succeeded after an extended reaction time of 12 days. A trityl-substituted bromo alkyne did not show any conversion, after 4 days allenoate **5a** could be completely recovered. In the conversion of all these substrates no homo-coupling could be detected. For the highly crystalline cross-coupled butenolide **3h** a single crystal X-ray structure analysis could be obained.[13]

Table 2. Scope of the reaction.[a]

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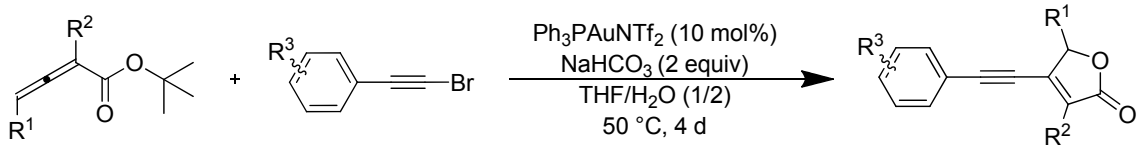
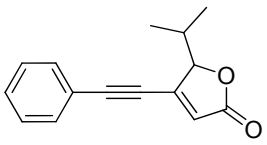
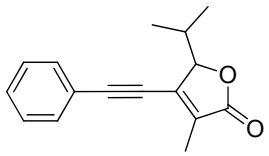


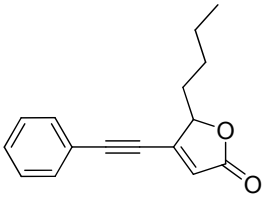

**5a-d** **2c,e-n** **3a-n**



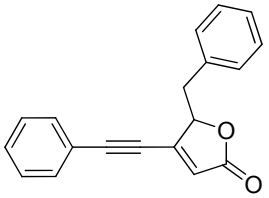
**3a**
64 % (72 %)



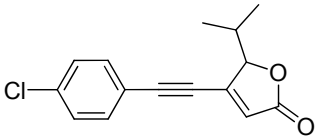
**3b**
80 % (95 %)



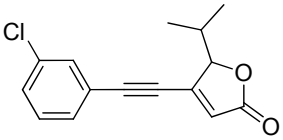
**3c**
37 % (45 %)



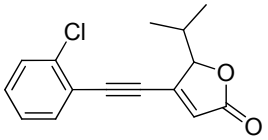
**3d**
25 % (31 %)



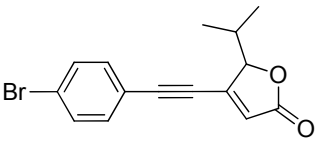

**3e**
53 % (56 %)



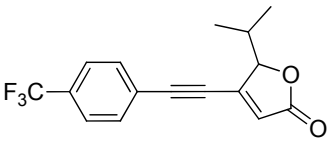

**3f**
32 % (9 %)[b]



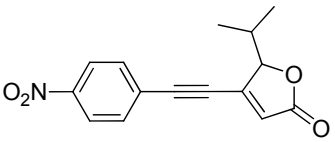

**3g**
17 % (30 %)



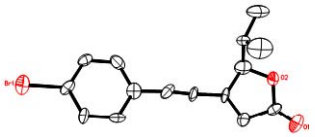

**3h**
48 % (53 %)



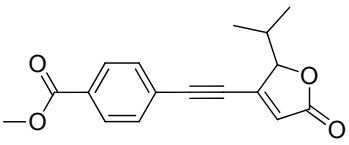

**3i**
5 % (8 %)



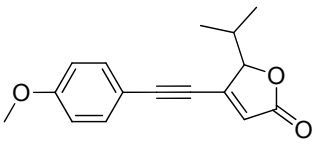

**3j**
38 % [c]



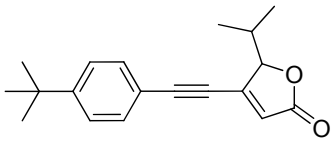
**3h**[13]



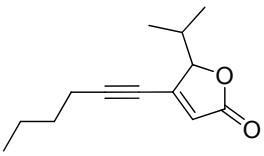
**3l**
10 % (10 %)



**3m**
69 % (77 %)



**3k**
28 % (34 %)



**3n**
23 % (2 %)[b]

[a] *Reaction conditions:* Allenoate **5a-d** (110 µmol, 1.1 mmol/ml THF), bromoalkyne **2c,e-n** (121 µmol), $NaHCO_3$ (219 µmol), $Ph_3PAuNTf_2$ (10 mol%), THF/$H_2O$ (1/2) at T = 50 °C. Yield of isolated product. Yield as determined by $^1H$ NMR spectroscopy of the crude reaction mixture using 1,4-dinitrobenzene as an internal standard is given within parentheses. [b] Purification and isolation of the product after a reaction time of 12 d. [c] No yield determined by $^1H$ NMR due to its poor solubility.

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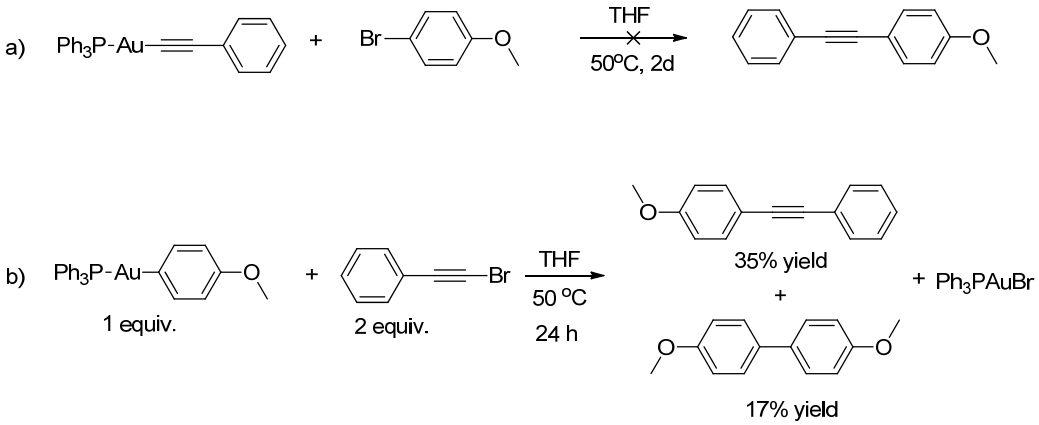
The mechanism of this reaction can be rationalized by four alternative pathways including: a) carbometalation[14], b) halogen metal exchange and c/d) two alternative $Au^{I}/Au^{III}$ redox cycles (Scheme 3, for details, see Scheme S1). Path **I** is a sequential Au-catalyzed cyclization, followed by carbometalation and anti-$\beta$-bromide elimination. In path **II**, a $\sigma$-bond metathesis was proposed. Furthermore, two other paths **III** and **IV**, involving a sequential Au-catalyzed cyclization/oxidative addition/reductive elimination or and oxidative addition/cyclization/reductive elimination are conceivable. A series of experiments were carried out to investigate these four pathways. In the event that this cross-coupling proceeds via carbometalation to form intermediate vinylgold(I) **B**, followed by anti-$\beta$-bromide elimination, a homo-coupling product (like **4**) should not be fromed. However, **4** was experimetally observed in the stoichiometric reaction, opposing path **I**. Path **II**, involving transition state **C,** was excluded by the absence of the cross-coupling product in a stoichiometric experiment with alkynylgold(I) substrate **7** and 1-bromo-4-methoxybenzene (Scheme 2a), in which the cross-coupling product was expected. Oppositely, mixing 1-(bromoethynyl)-4-benzene **2c** and 4-methoxyphenylgold(I) **6** afforded the cross-coupling product in 35% yield, along with 17% of homo-coupling product (Scheme 2b).




Scheme 2. Stoichiometric experiments to exclude bromo-gold exchange mechanism.

Alternatively, the reaction mechanism of $Au^{I}/Au^{III}$ redox cycles are in agreement with the presence of the homo-coupling product from group scrambling.[15] In path **III**, initially, the oxidative addition with 1-(bromoethynyl)-4-benzene **2c** yields the gold(III) complex **E**. The subsequent cyclization of the allenoate **5a** leads to the gold(III) complex **D**, followed by a reductive elimination, regenerating the active catalyst species and releasing $\beta$-alkynyl-$\gamma$-butenolide **3a**. An alternative pathway is shown in path **IV** (Scheme 3). First, the gold(I) species coordinates to the allenoate **5a**, and in

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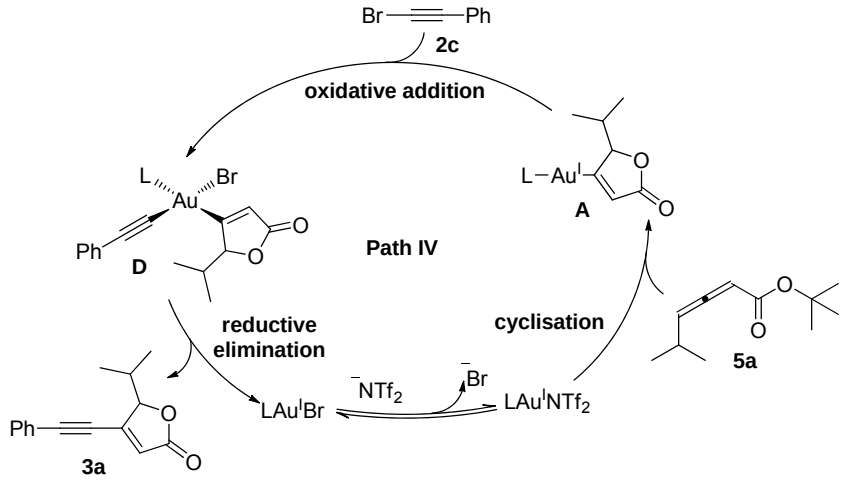
the presence of base and water the cyclization leads to the organogold(I) complex **A**. The oxidative addition of 1-(bromoethynyl)-4-benzene **2c** affords the gold(III) complex **D**, and a subsequent reductive elimination regenerates the active catalyst and sets free the $\beta$-alkynyl-$\gamma$-butenolide **3a** by the formation of the new C–C bond.




Scheme 3. The mechanism of path **IV**.

The mechanistic research on the Au(I)/Au(III) cycle is hampered by some challenges. First, precedents on the fast reductive elimination of alkynylgold(III) complex suggested that the life of the gold(III) intermediate **E** is expected to live extremely short, preventing the isolation of the gold(III) intermediate or detection by NMR spectrometry.[16] Secondly, the slow oxidative addition (4 days needed in the stoichiometric reaction) also fundamentally increases the difficulty for the detection of gold(III) intermediate. Indeed, efforts to isolate the gold(III) complex in combination with the ligands IPr, $Ph_3P$ and (2-(2-(diphenylphosphanyl)phenyl)pyridine) all failed (Scheme S2). Moreover, the gold intermediate being uncharged, prevents the detection by ESI-MS spectrometry, a method fast and sensitive enough to detect of the gold intermediate.[17] By introducing a pyrrolidinium to a remote position of the alkynyl bromide, the intermediates become accessible to ESI(+) MS. As shown in Scheme 4, in the mixture of the alkynyl bromide **2o** with organogold(I) complexes **1a** in THF/ $H_2O$, an ion with m/z 906.1984 was detected in high-resolution mass spectrometry (electrospray ionization, positive mode), which is in agreement with the calculated *m/z* for the gold(III) cation **8a** (906.1981). In the catalytic reaction with 10 mol% of $Ph_3PAuNTf_2$, an ion of the gold(III) intermediate **8b** from oxidative addition was also observed (calcd. 920.2137, found 920.2146). The gold(III) compound **8c** from the oxidative addition of arylgold(I) complex with alkynyl bromide was also found in the

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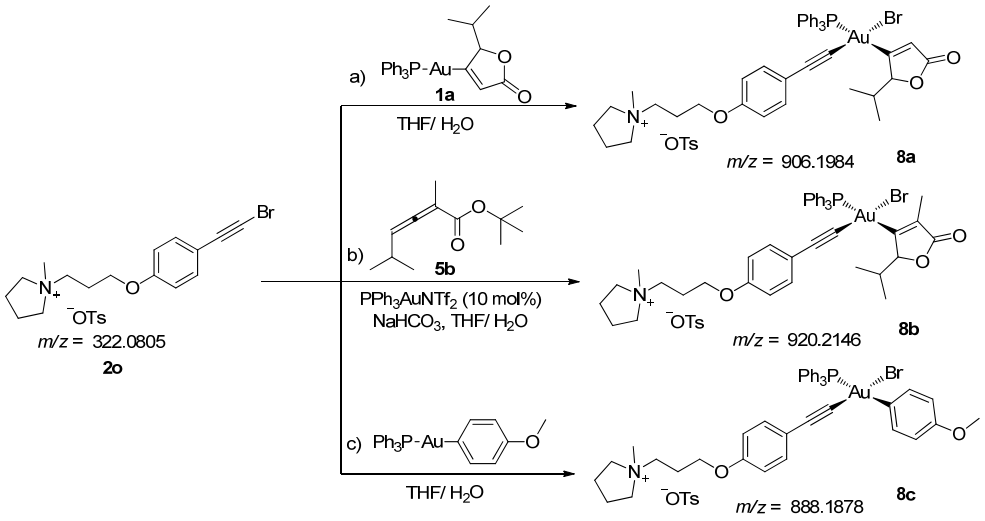
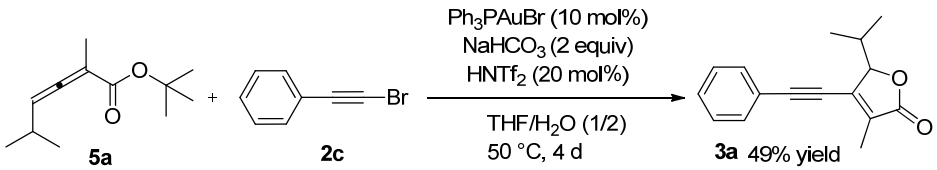
ESI-MS spectrum (calcd. 888.1875, found 888.1878). These data strongly support the Au(I)/Au(III) cycle in this gold-catalyzed cross-coupling by alkynylation with bromoalkynes. Moreover, in the ESI-MS spectrometry, the absence of the dibromogold(III) intermediate **F** in the mixture of $Ph_3PAuBr$ with alkynyl bromide **2o** excludes the path **III** with a sequential oxidative addition, followed by gold(III)-induced cyclization.




Scheme 4. Exploring the reaction intermediates with ESI-MS (LIFDI)

Next, the potential halogen poisoning by the formation of the $Ph_3PAuBr$ (followed by the first catalytic cycle), which is inactive in the cyclization, was investigated. Due to the specificity of $Ph_3PAuNTf_2$ (see Table S1) in the catalytic reaction and the stronger binding of $NTf_2$ to gold than other counter anions,[5] we think there might be an equilibrium between $Ph_3PAuBr$ and $Ph_3PAuNTf_2$, which enables the followed catalytic cycles. This assumption was firstly supported by the addition of NaBr to the reaction mixture (Table S2). Obviously, the addition of NaBr to the reaction mixture reduces the catalytic efficiency stepwise but, as expected because the catalytic reaction works, more than one equivalent of bromide with respect to the catalyst is tolerated. Additionally, the catalytic reaction with the combination of $Ph_3PAuBr$ and $NTf_2^-$ gave the desired product in 49% yield (Scheme 5). This strongly supports the existence of an equilibrium between $Ph_3PAuBr$ and $Ph_3PAuNTf_2$.



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Scheme 5. Effect of $NTf_2^-$ on the catalytic reaction.

Overall, a novel cascade cyclization/alkynylation reaction of allenoates was established for various alkynyl bromides. It was demonstrated that the use of simple, easily accessible alkynyl bromides, ideal for organic synthesis, shows a broader functional group tolerance than hypervalent iodine reagents or other related oxidants. In consideration of the optimized reaction procedure, the $\beta$-alkynyl-$\gamma$-butenolide could be isolated depending on the electronic properties of the substituents in low to good yields (5 – 80 %). Moreover, the mechanistic investigation strengths the proposed reaction mechanism of an $Au^I/Au^{III}$ redox cycle even. This unique reactivity may open new opportunities in gold catalysis.

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## TOC Graphic