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# Gold-Catalyzed Cascade Cyclization−Oxidative Alkynylation of Allenoates

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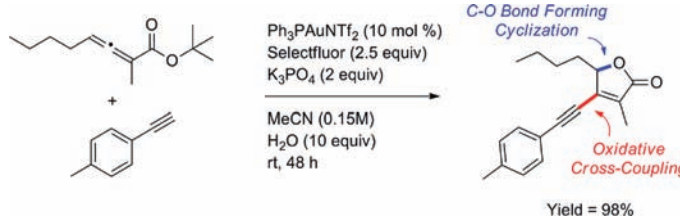
## ABSTRACT




**A gold(I)-catalyzed cascade cyclization−oxidative cross-coupling process has been applied to prepare β-alkynyl-γ-butenolides directly from allenoates and various terminal alkynes. Following an initial gold-catalyzed C−O bond forming allenoate cyclization, a mechanism based on a $Au^{I}/Au^{III}$ redox cycle has been proposed with Selectfluor acting as the external oxidant.**

The homogeneous catalysis of organic reactions by gold has received significant attention in recent years.[1] In contrast to other late transition metals, gold rarely changes oxidation state during the course of a reaction and instead most commonly acts as a tunable soft π-acid, activating multiple bonds toward nucleophilic attack. In the past few years, however, several gold-catalyzed homo- and cross-coupling reactions proceeding via proposed $Au^{I}/Au^{III}$ redox cycles have been reported.[2] In many cases, the key oxidation of gold(I) to gold(III) is performed by an external oxidant precluding the need for preactivation of the starting materials.[3] In 2009 Zhang et al. reported the cascade rearrangement−oxidative homocoupling of propargyl acetates catalyzed by gold(I) complexes in the presence of the electrophilic fluorinating reagent Selectfluor.[4,5] This methodology has

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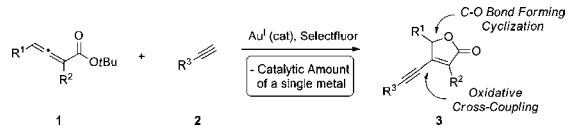
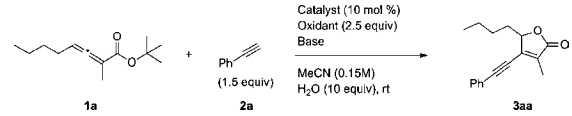
also been successfully applied to oxidative cross-coupling with benzoates[6] and preactivated arylboronic acids.[7] In 2008, we disclosed that oxidative fluorination of an organogold intermediate is feasible using Selectfluor.[8] More recently, we showed that benzyl-substituted *tert*-butyl allenoates are amenable to cascade cyclization−oxidative intramolecular arylation using the same oxidant.[9,10] This process, involving direct aryl C−H functionalization, led to the facile synthesis of indenofuranones from substrates not requiring preactivation. We sought to investigate whether this methodology could be applied to effect a cascade cyclization−intermolecular alkynylation delivering $\beta$-alkynyl-$\gamma$-butenolides directly from allenoates and unfunctionalized alkynes. Currently, these compounds are accessed via a two-step protocol where the allene cyclization and subsequent alkynylation are performed separately.[11,12] This novel transformation, relying on gold catalysis only, combines the well-established reactivity of gold with an oxidative cross-coupling event (Scheme 1).

**Scheme 1.** Cascade Cyclization−Oxidative Alkynylation




As a preliminary experiment, the alkyl-substituted *tert*-butyl allenoate **1a** was treated with phenylacetylene **2a** (1.5 equiv), Selectfluor (2.5 equiv), and $Ph_3PAuNTf_2$ (10 mol %)[13] in acetonitrile (0.15 M) and water (10 equiv) at room temperature.[14] Pleasingly, the desired $\beta$-alkynyl-$\gamma$-butenolide **3aa** was isolated in 44% yield after 4 days (Table 1, entry 1). Notably, no products resulting from cyclization−protodeauration of the allenoate or homocoupling of either **1a** or **2a** were observed.[15] The yield of **3aa** was increased to 94%, and the reaction time

**Table 1.** Optimization Studies for Oxidative Alkynylation of **1a**




| entry | catalyst | oxidant | base | time | yield[a] |
|---|---|---|---|---|---|
| 1 | $Ph_3PAuNTf_2$ | Selectfluor | none | 4 d | 44% |
| 2 | $Ph_3PAuNTf_2$ | Selectfluor | $K_3PO_4$ | 4 h | 94% |
| 3 | no catalyst | Selectfluor | $K_3PO_4$ | 10 d | NR |
| 4 | AuCl[b] | Selectfluor | $K_3PO_4$ | 48 h | NR |
| 5 | AgOTf | Selectfluor | $K_3PO_4$ | 10 d | NR |
| 6 | $PtCl_2$ | Selectfluor | $K_3PO_4$ | 10 d | NR |
| 7 | CuOAc | Selectfluor | $K_3PO_4$ | 10 d | NR |
| 8 | $H_2SO_4$ | Selectfluor | $K_3PO_4$ | 10 d | NR |
| 9 | SIPrAuCl/AgOTf[c] | Selectfluor | $K_3PO_4$ | 10 d | NR |
| 10 | $Pd(OAc)_2$/ CuOAc | Selectfluor | $K_3PO_4$ | 24 h | decomp. |
| 11 | $AuCl_3$ | Selectfluor | $K_3PO_4$ | 6 d | 22% |
| 12 | $Ph_3PAuNTf_2$[b] | Selectfluor | $K_3PO_4$ | 24 h | 72% |
| 13 | $Ph_3PAuNTf_2$ | no oxidant | $K_3PO_4$ | 5 d | NR |
| 14 | $Ph_3PAuNTf_2$ | $PhI(OAc)_2$ | $K_3PO_4$ | 7 d | NR |
| 15 | $Ph_3PAuNTf_2$ | *t*BuOOH | $K_3PO_4$ | 7 d | NR |
| 16 | $Ph_3PAuNTf_2$ | Oxone[d] | $K_3PO_4$ | 7 d | NR |
| 17 | $Ph_3PAuNTf_2$ | NFSI[e] | $K_3PO_4$ | 7 d | 54%[f] |

[a] Isolated yield. [b] 5 mol %. [c] SIPr = 1,3-Bis(2,6-diisopropylphenyl) imidazolin-2-ylidene. [d] Oxone = $KHSO_5$•1/2$KHSO_4$•1/2$K_2SO_4$. [e] NFSI = *N*-Fluorobenzenesulfonimide. [f] Conversion estimated by $^1H$ NMR.

shortened to 4 h upon addition of potassium phosphate tribasic (2 equiv, entry 2). After extensive optimization studies,[16] $Ph_3PAuNTf_2$ was identified as the catalyst of choice for this transformation, while AuCl, AgOTf, $PtCl_2$, CuOAc, $H_2SO_4$, and SIPrAuCl/AgOTf all led to recovered allenoate (entries 3−9). The combination of $Pd(OAc)_2$/CuOAc, a common catalytic system for Sonogashira coupling, led to decomposition of the starting materials (entry 10). $AuCl_3$ was a suitable catalyst for the cascade cyclization−oxidative alkynylation process but was significantly less efficient, delivering **3aa** in only 22% yield after 6 days of reaction (entry 11). Alternative oxidants such as $PhI(OAc)_2$, *t*BuOOH, and Oxone led to no reaction with complete recovery of **1a** (entries 13−16). *N*-Fluorobenzenesulfonimide (NFSI), a mild electrophilic fluorinating reagent, did lead to **3aa** but with low conversion after an extended reaction time (54% conversion after 7 days, entry 17).

With optimized reaction conditions in hand, the effect of the alkyne substitution on the reaction efficiency was investigated (Scheme 2). The transformation was compatible with a wide range of arylacetylenes including *para*-, *meta*-, and *ortho*-substituted derivatives. Alkyne **2e**, bearing an electron-donating *para*-OMe group on the benzene ring, reacted readily, affording **3ae** in 88% yield. Electron-neutral and electron-poor arylacetylenes were also tolerated, delivering the cross-coupled butenolide products **3af**−**ah** bearing *para*-F, *para*-$CF_3$, and even *para*-

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(10) For examples of palladium-catalyzed cross-coupling reactions of stoichiometric (butenolide)gold(I) complexes, see: (a) Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics* **2009**, *28*, 1275. (b) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022.
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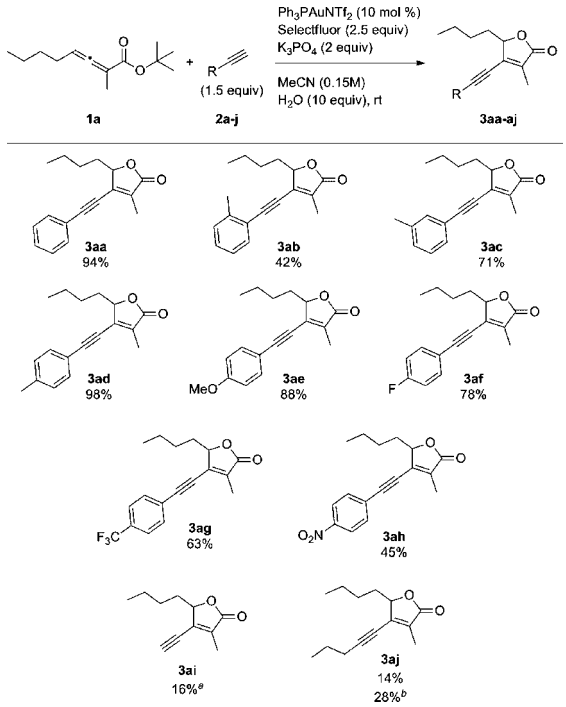
(13) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.
(14) The addition of water (10 equiv) aids the solubility of the reagents.

(15) By contrast, treating **1a** with $Ph_3PAuNTf_2$ (10 mol %) in dichloromethane afforded 5-butyl-3-methylfuran-2(5*H*)-one (**8a**) resulting from cyclization−protodeauration as the only product in 76% yield after 24 h. In acetonitrile and water (10 equiv), **8a** was produced in 39% yield after 6 days. See also ref 9.
(16) For details, see the Supporting Information.

**Scheme 2.** Oxidative Alkynylation of **1a** with **2a−j** Isolated Yields

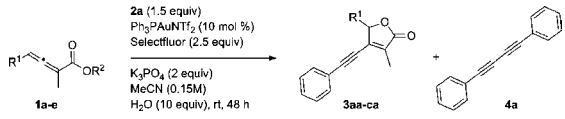



[a] Reaction performed with NaOH (2 equiv) as base. [b] Reaction performed with CuOAc (10 mol %) cocatalyst at 80 °C.

$NO_2$ substituents in moderate to good yields. While the trimethylsilyl-protected alkyne **2i** was amenable to the cascade cyclization−cross-coupling process, the isolated yield of the corresponding butenolide **3ai**, resulting from subsequent deprotection of the silyl group, was low (16%). The reaction with 1-pentyne **2j** was similarly low yielding, delivering **3aj** in only 14% yield. Following screening of conditions for this substrate, the isolated yield could be improved to 28% upon heating to 80 °C in the presence of added CuOAc (10 mol %) cocatalyst.

To probe the effect of the allenoate substitution, substrates **1a−g** were synthesized according to literature procedures[9,17] and reacted with phenylacetylene **2a** (Table 2). The allyl-substituted allenoates **1b** and **1c** cyclized successfully,

**Table 2.** Oxidative Alkynylation of **1a−e** with **2a**



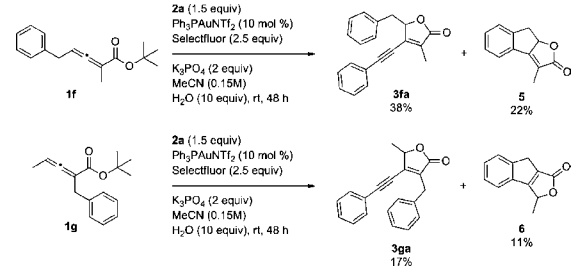

| entry | allenoate | $R^1$ | $R^2$ | **3** (yield)[a] | **4a** (yield)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | *n*Bu | *t*Bu | **3aa** (94%) | --- |
| 2 | **1b** |  | *t*Bu | **3ba** (45%) | 29% |
| 3 | **1c** dr = 1:1 |  | *t*Bu | **3ca** (33%) dr = 1:1.2 | 23% |
| 4 | **1d** | Ph | *t*Bu | --- | --- |
| 5 | **1e** | *n*Bu | Et | **3aa** (29%) | 88% |

[a] Isolated yield. [b] Isolated yield relative to **2a**.

affording cross-coupled products **3ba** and **3ca** in moderate yields (entries 2 and 3). In these reactions, diyne **4a** resulting from oxidative homocoupling of the alkyne was also isolated in 29% and 23% yield, respectively, relative to **2a**. Phenyl-substituted allenoate **1d** failed to react and led to complete recovery of the allenoate after 48 h (entry 4).

The transformation was successful with ethyl allenoate **1e**, delivering **3aa** in 29% yield (entry 5). The drop in efficiency with this substrate in comparison with **1a** can be attributed to a less favorable cyclization step involving the loss of an ethyl cation. In this reaction, competitive alkyne homocoupling was the major reaction pathway. The benzyl-substituted allenoates **1f** and **1g** led to mixtures of products resulting from both intermolecular oxidative alkynylation (**3fa** and **3ga**) and intramolecular oxidative arylation (**5** and **6**) with the alkynylation process slightly favored (Scheme 3).[9] Butenolides **3fa** and **5** were

**Scheme 3.** Competitive Alkynylation and Arylation of **1f** and **1g**




crystalline solids and allowed for the unambiguous assignment of the structures by X-ray crystallography (Figure 1).[16,18]

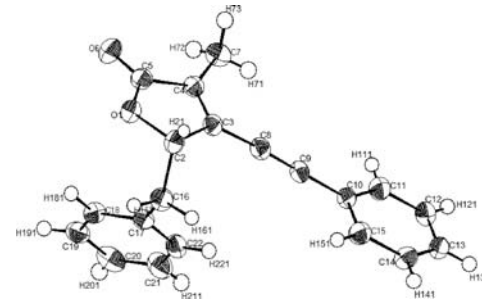


**Figure 1.** X-ray crystal structure of **3fa**.

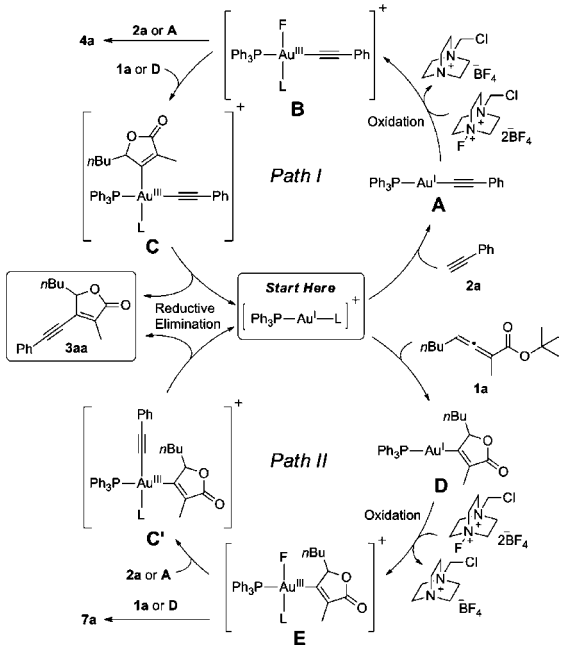
Mechanistically, we envisage two plausible pathways for the cascade allenoate cyclization−oxidative alkynylation process, both involving a $Au^I/Au^{III}$ redox cycle.[19] In the presence of base, initial deprotonation of the alkyne and subsequent coordination to the cationic gold(I) catalyst could lead to the alkynylgold(I) intermedi-

(17) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431.

(18) CCDC-795566 and CCDC-795567 contain the supplementary crystallographic data for **3fa** and **5**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

ate **A**. Oxidation at the gold center by Selectfluor would afford the square planar gold(III) cationic intermediate **B**. A similar gold(III) fluoride complex was recently observed by Toste et al. upon treating gold(I) methyl complexes with the electrophilic fluorinating reagent $XeF_2$.[20] Coordination of this species to the allene followed by nucleophilic attack of the pendant *tert*-butyl ester would lead to the gold(III) complex **C** bearing both butenolide and alkyne substituents. After reductive elimination, this species delivers the cross-coupled product and regenerates the cationic gold(I) catalyst (Scheme 4, path I).[3e] Alternatively, the allenoate

**Scheme 4.** Plausible Reaction Mechanism



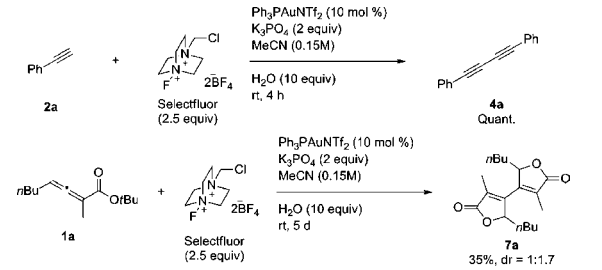

cyclization could occur prior to the alkyne coordination step. In this case, oxidation of the organogold(I) intermediate **D** by Selectfluor would lead to the gold(III) complex **E**. Reductive elimination from intermediate **C′**, formed after alkynylation, would afford the product and regenerate the catalyst (Scheme 4, path II).[21]

To investigate the proposed mechanisms, several control reactions were performed. Treatment of **2a** under the optimized reaction conditions but in the absence of **1a** afforded the product of oxidative homocoupling **4a**, in quantitative yield after 4 h (Scheme 5). The formation of this product is consistent with path I, invoking a second alkynylation to intermediate **B** followed by reductive elimination. Allenoate **1a** afforded the diastereomeric bibutenolides **7a**, resulting from oxidative homocoupling, in 35% yield after 5 days when reacted in the absence of **2a** (Scheme 5). Again, coordination and cyclization of a second molecule of the allenoate to intermediate **E** (path II) followed by reductive elimination can

(19) While a mechanism involving a $\beta$-fluoro-$\gamma$-butenolide intermediate cannot be unequivocally ruled out for this transformation, such a pathway was ruled out in the related cascade allenoate cyclization−intramolecular arylation reaction (see ref 9). In addition, no fluorinated organic species were isolated from any reaction mixture in the course of our studies.

(20) Mankad, N. P.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 12859.

**Scheme 5.** Oxidative Homocoupling of **1a** and **2a**




explain the observed reactivity. The long reaction time and low yield of this reaction in comparison with that above suggests that path I could be more favored. This observation is consistent with the scope and limitation studies where diynes were observed as minor side products of the reactions. To support a mechanism involving the intermediates **A** and **D**, these complexes were synthesized according to literature procedures[22,23] and subjected to the reaction conditions with **1a** and **2a**, respectively. After 1 h at rt, complete consumption of each complex was observed with the formation of **3aa**, **4a**, and **7a** in both reactions, suggesting that both path I and path II are feasible. Additionally, if ligand exchange between the gold complexes is sufficiently fast under the reaction conditions, each product **3**, **4**, or **7** could be formed regardless of the initial coordination and oxidation steps.[24] The observed product distribution, in this case, would be a function of the rate of ligand exchange and reductive elimination at each diorganogold(III) complex.[25]

In conclusion, a novel, gold-catalyzed cascade cyclization−oxidative cross-coupling process has been used to synthesize $\beta$-alkynyl-$\gamma$-butenolides directly from starting materials not requiring preactivation. This process provides a basis for the development of novel cascade reactions combining traditional gold catalysis and intermolecular oxidative alkynylation.

**Acknowledgment.** We thank GlaxoSmithKline and the EPSRC for financial support, Dr. B. Odell (University of Oxford) for NMR studies, and Dr. A. L. Thompson (Oxford Chemical Crystallography Service) for crystallographic services.

**Supporting Information Available:** Experimental procedures and characterization data for all compounds, optimization table, and X-ray crystal data for **3fa** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642.

(24) The formation of diyne **4a** from **A** in the absence of alkyne **2a** and the formation of bibutenolides **7a** from **D** in the absence of allenoate **1a** are best explained by such intermolecular ligand exchange processes.

(25) Tamaki, A.; Kochi, J. K. *J. Organomet. Chem.* **1974**, *64*, 411.