

Gold-Catalyzed Cascade Cyclization—Oxidative Alkynylation of Allenates

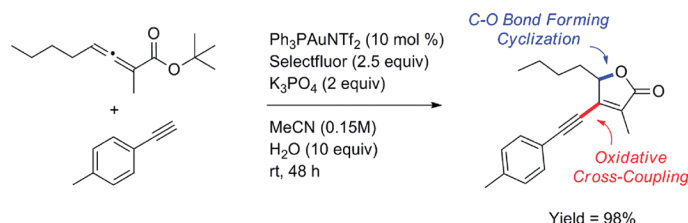
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ABSTRACT



A gold(I)-catalyzed cascade cyclization—oxidative cross-coupling process has been applied to prepare β -alkynyl- γ -butenolides directly from allenates and various terminal alkynes. Following an initial gold-catalyzed C–O bond forming allenate cyclization, a mechanism based on a $\text{Au}^{\text{I}}/\text{Au}^{\text{III}}$ 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 $\text{Au}^{\text{I}}/\text{Au}^{\text{III}}$ 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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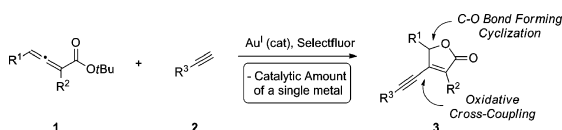
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also been successfully applied to oxidative cross-coupling with benzoates⁶ and preactivated arylboronic acids.⁷ In 2008, we disclosed that oxidative fluorination of an organogold intermediate is feasible using Selectfluor.⁸ More recently, we showed that benzyl-substituted *tert*-butyl allenates 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 β -alkynyl- γ -butenolides directly from allenates 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 allenate **1a** was treated with phenylacetylene **2a** (1.5 equiv), Selectfluor (2.5 equiv), and Ph₃PAuNTf₂ (10 mol %)¹³ in acetonitrile (0.15 M) and water (10 equiv) at room temperature.¹⁴ Pleasingly, the desired β -alkynyl- γ -butenolide **3aa** was isolated in 44% yield after 4 days (Table 1, entry 1). Notably, no products resulting from cyclization—protodeauration of the allenate 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 ₃ PAuNTf ₂	Selectfluor	none	4 d	44%
2	Ph ₃ PAuNTf ₂	Selectfluor	K ₃ PO ₄	4 h	94%
3	no catalyst	Selectfluor	K ₃ PO ₄	10 d	NR
4	AuCl ^b	Selectfluor	K ₃ PO ₄	48 h	NR
5	AgOTf	Selectfluor	K ₃ PO ₄	10 d	NR
6	PtCl ₂	Selectfluor	K ₃ PO ₄	10 d	NR
7	CuOAc	Selectfluor	K ₃ PO ₄	10 d	NR
8	H ₂ SO ₄	Selectfluor	K ₃ PO ₄	10 d	NR
9	SIPrAuCl/AgOTf ^c	Selectfluor	K ₃ PO ₄	10 d	NR
10	Pd(OAc) ₂ /CuOAc	Selectfluor	K ₃ PO ₄	24 h	decomp.
11	AuCl ₃	Selectfluor	K ₃ PO ₄	6 d	22%
12	Ph ₃ PAuNTf ₂ ^b	Selectfluor	K ₃ PO ₄	24 h	72%
13	Ph ₃ PAuNTf ₂	no oxidant	K ₃ PO ₄	5 d	NR
14	Ph ₃ PAuNTf ₂	PhI(OAc) ₂	K ₃ PO ₄	7 d	NR
15	Ph ₃ PAuNTf ₂	<i>t</i> BuOOH	K ₃ PO ₄	7 d	NR
16	Ph ₃ PAuNTf ₂	Oxone ^d	K ₃ PO ₄	7 d	NR
17	Ph ₃ PAuNTf ₂	NFSI ^e	K ₃ PO ₄	7 d	54% ^f

^a Isolated yield. ^b 5 mol %. ^c SIPr = 1,3-Bis(2,6-diisopropylphenyl)imidazolin-2-ylidene. ^d Oxone = KHSO₅·1/2KHSO₄·1/2K₂SO₄. ^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 Ph₃PAuNTf₂ was identified as the catalyst of choice for this transformation, while AuCl, AgOTf, PtCl₂, CuOAc, H₂SO₄, and SIPrAuCl/AgOTf all led to recovered allenate (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). AuCl₃ 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*-Fluorobenzene-sulfonimide (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*-CF₃, and even *para*-

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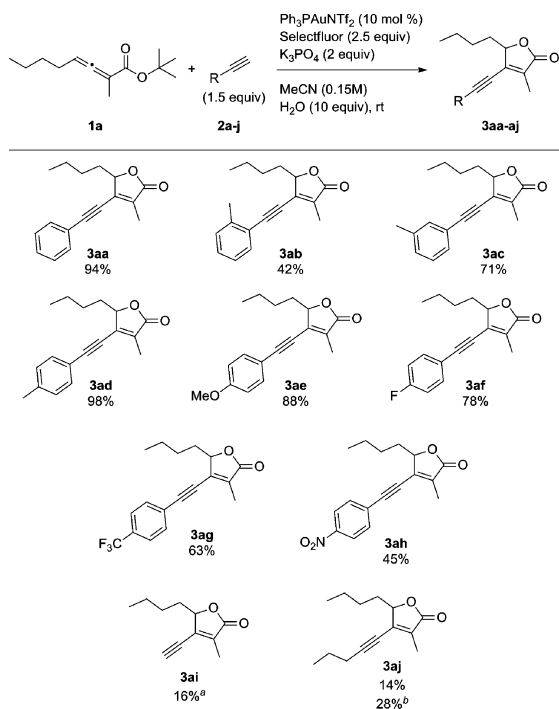
(13) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

(14) The addition of water (10 equiv) aids the solubility of the reagents.

(15) By contrast, treating **1a** with Ph₃PAuNTf₂ (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 allenolate substitution, substrates **1a–g** were synthesized according to literature procedures^{9,17} and reacted with phenylacetylene **2a** (Table 2). The allyl-substituted allenolates **1b** and **1c** cyclized successfully,

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

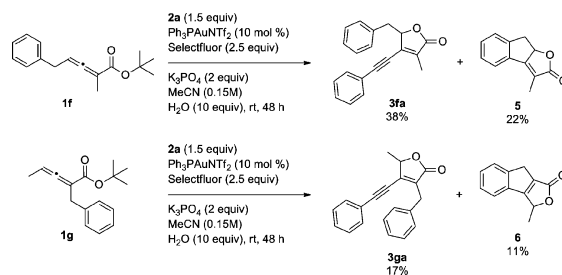
entry	allenolate	R ¹	R ²	3 (yield) ^a	4a (yield) ^b
1	1a	<i>n</i> Bu	<i>t</i> Bu	3aa (94%)	---
2	1b	<i>n</i> Bu	<i>t</i> Bu	3ba (45%)	29%
3	1c	<i>t</i> Bu	<i>t</i> Bu	3ca (33%)	23%
	dr = 1:1			dr = 1:1.2	
4	1d	Ph	<i>t</i> Bu	---	---
5	1e	<i>n</i> Bu	Et	3aa (29%)	88%

^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 allenolate **1d** failed to react and led to complete recovery of the allenolate after 48 h (entry 4).

The transformation was successful with ethyl allenolate **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 allenolates **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}

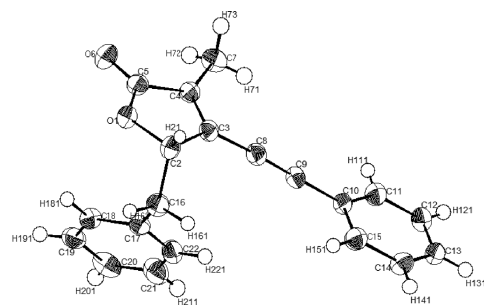


Figure 1. X-ray crystal structure of **3fa**.

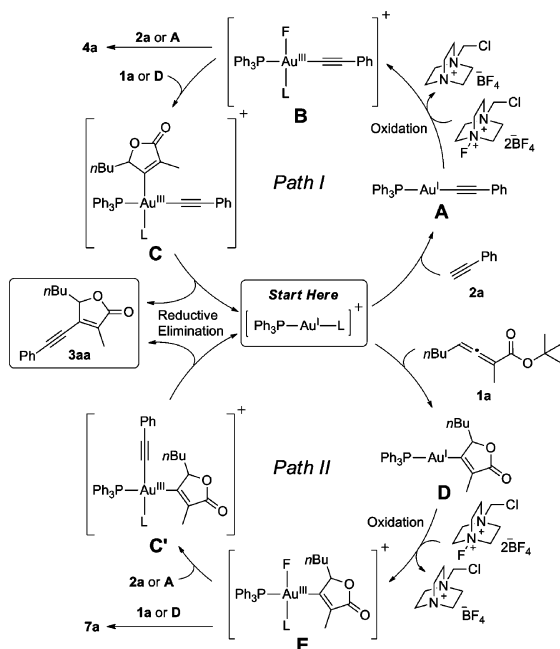
Mechanistically, we envisage two plausible pathways for the cascade allenolate cyclization–oxidative alkynylation process, both involving a $\text{Au}^{\text{I}}/\text{Au}^{\text{III}}$ redox cycle.¹⁹ In the presence of base, initial deprotonation of the alkyne and subsequent coordination to the cationic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

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(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 XeF₂.²⁰ 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).^{3c} Alternatively, the allenolate

Scheme 4. Plausible Reaction Mechanism



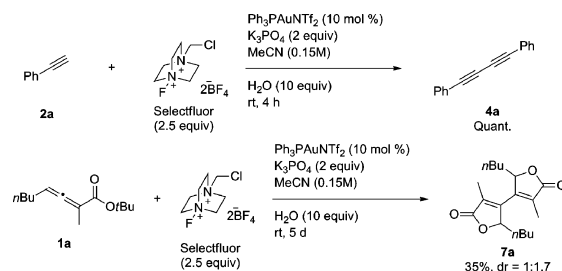
cyclization could occur prior to the alkyne coordination step. In this case, oxidation of the organogold(I) intermediate **D** by Selectfluor would lead to the gold(III) complex **E**. Reductive elimination from intermediate **C'**, formed after alkynylation, would afford the product and regenerate the 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. Allenolate **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 allenolate to intermediate **E** (path II) followed by reductive elimination can

(19) While a mechanism involving a β -fluoro- γ -butenolide intermediate cannot be unequivocally ruled out for this transformation, such a pathway was ruled out in the related cascade allenolate 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.

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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 β -alkynyl- γ -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 alkylation.

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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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(21) 5-Butyl-3-methylfuran-2(5H)-one (**8a**) was unreactive under the optimized reaction conditions ruling out a mechanism involving the protodeaured product.

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(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 allenolate **1a** are best explained by such intermolecular ligand exchange processes.

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