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Gold-Catalyzed Intramolecular Oxidative Cross-Coupling of Nonactivated Arenes

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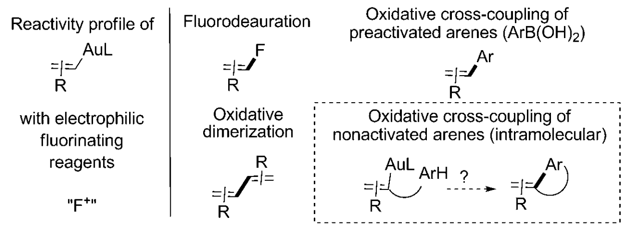
Homogeneous catalysis by gold has received considerable interest in recent years.[1] The isolation of a gold(I) fluoride complex stabilized by an N-heterocyclic carbene (NHC) ligand led to the first Au^I-catalyzed hydrofluorination of alkynes, a transformation carried out in the presence of $Et_3N{\cdot}3HF$, a mildly acidic fluoride source.[2] In 2008, our group explored the chemistry of Au^I complexes with electrophilic fluorinating reagents. Trifluorodihydropyranones were obtained upon Au^I-catalyzed cyclization–fluorodeauration of β-hydroxy-α,α-difluoroynones, a reaction performed with Selectfluor.[3] In more recent studies by Zhang and co-workers, Selectfluor was found to be a suitable oxidant for the gold-catalyzed oxidative dimerization of propargylic acetates and for oxidative cross-coupling reactions with preactivated arylboronic acids.[4] The development of gold-catalyzed oxidative cross-coupling reactions that do not require preactivated arenes is more challenging and, to date, is restricted to homocoupling reactions with $PhI(OAc)_2$.[5] We recently sought to investigate whether the gold-catalyzed oxidative cross-coupling of nonactivated arenes might be accomplished with electrophilic N–F reagents, such as Selectfluor. We herein report the successful gold-catalyzed oxidative intramolecular C–H arylation using allenoate esters as model substrates (Scheme 1).



Scheme 1. Reactivity of vinylgold(I) species with "F^+".

The benzyl-substituted *tert*-butyl allenoate ester **1a** was treated with Selectfluor (2.5 equiv) and AuCl (5 mol %) in acetonitrile. Three products were formed, none of which were fluorinated (Scheme 2). The major product obtained in 36 % yield was unambiguously identified by X-ray analysis as the tricyclic 8,8a-dihydro-2*H*-indeno[2,1-*b*]furan-2-one (**2a**). The separable dimeric butenolides (±)-(2*S*,2′*S*)-**3a** and (2*R*,2′*S*)-**3a** were also formed and isolated in 20 and 15 % yield, respectively. X-Ray diffraction analysis of analytically pure samples confirmed that the dimeric butenolides were, indeed, diastereomers. The butenolide **4a** resulting from cyclization–protodeauration was not detected in the crude reaction mixture. In a control experiment performed with AuCl (5 mol %) in acetonitrile, but omitting Selectfluor, compound **4a** was formed as the only product after 6 days (Scheme 2).[6,7] The formation of **2a** from **1a**, a new addition to the list of gold-catalyzed oxidative cross-coupling reactions reported to date,[4,5,8] is a challenging operation. Under the same reaction conditions, but with $PtCl_2$, CuOAc, H_2SO_4, or AgOTf as the catalyst, **2a** and **3a** were not observed and with $Pd(OAc)_2$ (5 mol %) the dimers **3a** were formed as the only products with no trace of **2a**.[9,10]

Following extensive optimization studies, $Ph_3PAuNTf_2$[11] (10 mol %) was identified as the catalyst of choice when used in acetonitrile and H_2O (10 equiv), a suitable solvent system for Selectfluor (2.5 equiv) (Table 1, entry 5).[10] Under these conditions, compound **2a** was isolated in 62 % yield. Although Selectfluor was the best oxidant to access dihydroindenofuranones from allenoates, *N*-fluorobenzenesulfonimide (NFSI) was also suitable, but less efficient (Table 1, entry 6). With the latter fluorinating reagent, the

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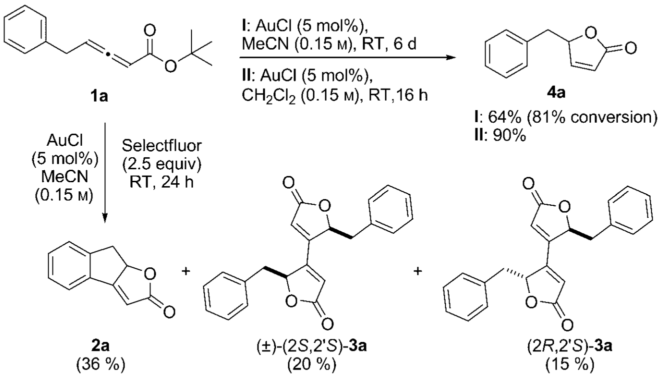


Scheme 2. Gold(I)-catalyzed cyclization of **1a** with and without Selectfluor.

Table 1. Optimization studies for oxidative cyclization of **1a**.

Entry	Catalyst	Conditions[a]	Product ratio[b] **2a**/**3a**[c]/**4a**/**1a** (Yield [%])[d]
1	$AuCl_3$[e]	Selectfluor, MeCN, 5 d	26:74:0:0 (**2a** = 20) (**3a** = 41)
2	$SIPrAuNTf_2$[e]	Selectfluor, MeCN, 5 d	no reaction
3	AuCl	Selectfluor, MeCN, 24 h	57:43:0:0 (**2a** = 56)
4	AuCl	Selectfluor, MeCN, H_2O, 24 h	67:33:0:0 (**2a** = 58)
5	$Ph_3PAuNTf_2$	Selectfluor, MeCN, H_2O, 4 h	80:20:0:0 (**2a** = 62)
6	$Ph_3PAuNTf_2$	NFSI, MeCN, H_2O, 72 h	38:62:0:0 (**2a** = 20) (**3a** = 45)
7	$Ph_3PAuNTf_2$	NFSI, CH_2Cl_2, 16 h	0:0:100:0 (**4a** = 57)
8	$Ph_3PAuNTf_2$	**A**, MeCN, H_2O, 5 d	no reaction
9	$Ph_3PAuNTf_2$	*t*BuOOH, MeCN, H_2O, 6 d	0:0:50:50
10	$Ph_3PAuNTf_2$	Ph_2SO, MeCN, H_2O, 6 d	0:0:69:31
11	$Ph_3PAuNTf_2$	$PhI(OAc)_2$, MeCN, H_2O, 48 h	0:100:0:0[f] (**3a** = 23)
12	$Ph_3PAuNTf_2$	Oxone, MeCN, H_2O, 6 d	12:88:0:0 (**2a** = 10) (**3a** = 46)
13	$Ph_3PAuNTf_2$	Selectfluor, MeCN (0.01 M), H_2O, 4.5 h	100:0:0:0 (**2a** = 95)

[a] All reactions at RT; catalyst (10 mol%) unless otherwise stated; [**1a**] = 0.15 M unless otherwise stated, H_2O (10 equiv), oxidant (2.5 equiv); **A** = 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] (±)-(2*S*,2'*S*)-**3a** and (2*R*,2'*S*)-**3a**. [d] Yield of the isolated product where appropriate. [e] 5 mol%. [f] Significant decomposition of **1a** was observed.

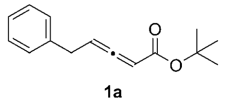
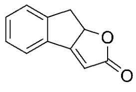
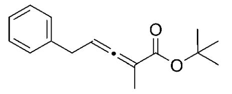
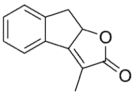
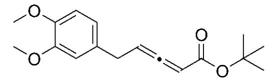
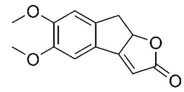
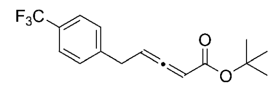
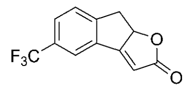
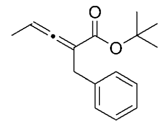
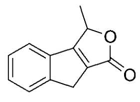
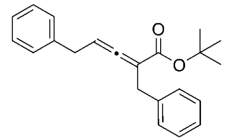
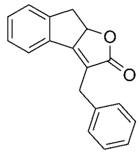
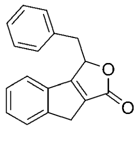
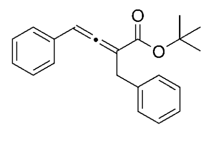
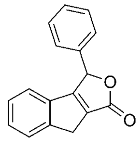
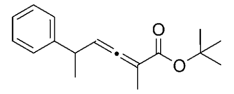
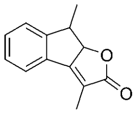
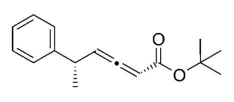
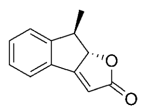
reaction performed in dichloromethane afforded 57% of the butenolide **4a** as the only product (Table 1, entry 7).[7] 1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate led to recovery of the starting material (Table 1, entry 8). Alternative oxidants, such as *t*BuOOH, Ph_2SO, and $PhI(OAc)_2$, did not lead to **2a**, but typically led to **4a** or **3a** (Table 1, entries 9–11). With Oxone, compound **2a** was isolated in 10% yield (Table 1, entry 12).[10] Pleasingly, by using $Ph_3PAuNTf_2$ with Selectfluor, the formation of the dimeric butenolides **3a** was completely suppressed upon lowering the reaction concentration from 0.15 to 0.01 M. Under these optimized conditions, compound **2a** was formed within 4.5 h and isolated in 95% yield (Table 1, entry 13).[12] The structural core of **2a** is surprisingly uncommon,[13] but presents similarities with cadinane sesquiterpenes isolated from *Heritiera littoralis*.[14]

Experiments to probe the scope of the allenoate substrates are summarized in Table 2. Access to all of the substrates **1a–1i** was achieved by the Wittig olefination of ketenes by following literature procedures.[6a,10] The trisubstituted allenoate **1b** was responsive to cyclization delivering compound **2b** in 70% yield (Table 2, entry 2). The reaction proceeded rapidly (1.5 h) with allenoate **1c**, which has electron-donating groups on the phenyl ring and led to **2c** in 84% yield (Table 2, entry 3). The trifluoromethyl-substituted allenoate **1d** cyclized successfully, but this substrate required a longer reaction time (16 h) and **2d** was isolated in much lower chemical yield (Table 2, entry 4). Under our optimized reaction conditions, substrate **1e** with the benzyl group geminal to the *tert*-butyl ester gave access to an alternative structural motif, the tricyclic 3,8-dihydro-1*H*-indeno-[2,1-*c*]furan-1-one (**5e**) (Table 2, entry 5). With allenoate **1f** presenting two benzyl groups that could compete for the C–C coupling event, the dihydroindenofuranones **2f** and **5f** were obtained in 70% overall yield (Table 2, entry 6). The successful cyclization of **1a–1h** prompted us to investigate the efficiency of the transfer of stereochemical information. Pleasingly, for (2*S*,5*S*)-**1i**, which was prepared enantiopure (enantiomeric excess (*ee*) >97%) and as a single diastereomer, complete axis-to-center chirality transfer for the C–O bond forming event followed by arylation delivered the single diastereomer (8*R*,8a*S*)-**2i** in 80% yield and >97% *ee* (Table 2, entry 9).

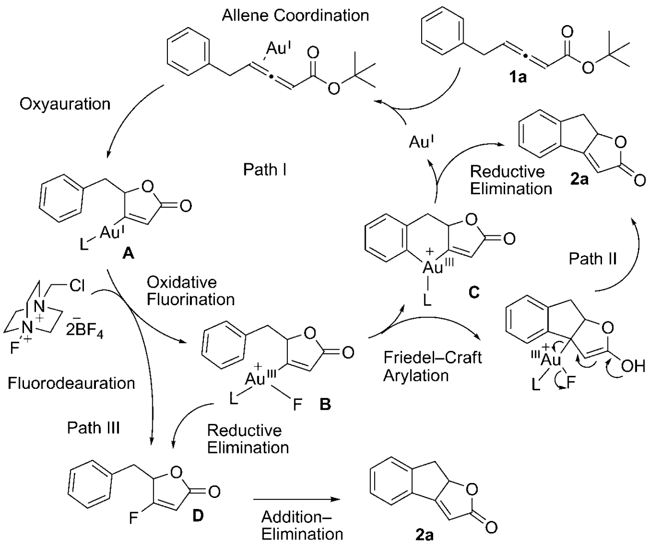
Mechanistically, we envisage initial Au^I coordination to the allene and addition of the pendent *tert*-butyl ester to afford intermediate **A**, two elementary steps for which experimental evidence has been provided by Hammond and co-workers.[6b,c] In one case, oxidative fluorination to the Au^{III} species **B** followed by Friedel–Crafts-type arylation with fluoride displacement would lead to the auracycle **C**, an intermediate susceptible to Au^{III}/Au^I reductive elimination (Path I). A conjugated addition–reductive elimination mechanism from **B** leading to **2a** is also plausible (Path II). Alternatively, the oxidative fluorination may lead to the β-fluorinated γ-butenolide **D** either directly by fluorodeauration of **A** or by reductive elimination of **B**. This fluorinated intermediate could subsequently undergo intramolecular arylation upon addition–elimination (Path III). γ-Butenolide **4a** was unreactive under the standard oxidative cyclization conditions, ruling out a mechanism involving the protodeaurated product (Scheme 3).

To support a mechanistic scenario involving the vinyl gold complex **A**, this intermediate (**A**; L = PPh_3) was prepared independently[6b,c] and treated with Selectfluor in CD_3CN/D_2O. Pleasingly, the conversion of this complex into **2a** and **3a** was complete within 2 h with no detectable formation of

Table 2. Gold(I)-catalyzed oxidative cyclization of allenoates **1a–1i**.

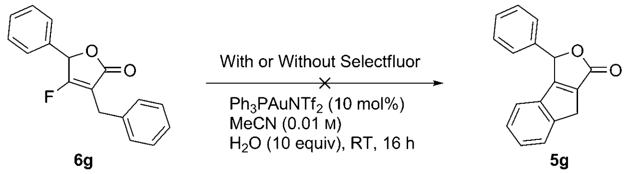
Entry[a]	Allenoate	Product(s)	Yield[b] [%]
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	70
3	 **1c**	 **2c**	84
4	 **1d**	 **2d**	37
5	 **1e**	 **5e**	57
6	 **1f**	 **2f**	27
		 **5f**	43
7	 **1g**	 **5g**	46
8	 **1h** d.r. 1:1.1	 **2h** d.r. 1:1.2	81
9	 (2*S*,5*S*)-**1i** d.r. >20:1 *ee* >97%	 (8*R*,8a*S*)-**2i** d.r. >20:1 *ee* >97%	80

[a] Reaction conditions: Selectfluor (2.5 equiv), $Ph_3PAuNTf_2$ (10 mol %), MeCN (0.01 M), H_2O (10 equiv), RT, 1.5–24 h. [b] Yield of the isolated product.



Scheme 3. Plausible mechanism.

protodeaurated butenolide **4a**. The preference for electron-rich over electron-poor aryl-substituted allenoates supports a mechanism based on a Friedel–Crafts arylation and argues against a pathway involving an S_NAr-type step by a nucleophilic organogold species.[15] The suitability of $AuCl_3$ as a catalyst for the reaction (Table 1, entry 1) is consistent with the proposed mechanism. Initial activation of the allenoate by Au^{III} could lead directly to an intermediate of type **B**, which, upon conversion to the product, generates the proposed catalytic species, Au^I. The formation of the dimeric butenolides **3a** can be accounted for, by evoking transmetalation from **A** to **B** followed by reductive elimination of the resulting diorganogold(III) species.[16] This was the major pathway observed when **1a** was treated with a stoichiometric amount of $AuCl_3$ without Selectfluor.[10,17] In the course of our studies, in no case could a fluorinated product be isolated from the reaction mixtures.[18] To discriminate between paths I/II and III, the β-fluorinated γ-butenolide **6g** was prepared independently[19] and treated in acetonitrile with $Ph_3PAuNTf_2$ (10 mol %) in the presence or in the absence of Selectfluor. These experiments led to recovery of the starting material with no detectable trace of the tricyclic product **5g**,[20] which suggests that Path III is not operating (Scheme 4).[21]



Scheme 4. Reactivity of fluorinated butenolide **6g**.

In conclusion, we have developed a novel cascade cyclization cross-coupling process leading to tricyclic dihydroindenofuranone-type products. This is the first example of a gold-catalyzed intramolecular C–C cross-coupling reaction involving aryl C–H functionalization with Selectfluor as the oxidant. Axis-to-center chirality transfer has been demonstrated with no erosion of enantiomeric excess. Mechanistic investigations suggest that a pathway involving fluorodeauration is not operating. This reaction is a new addition to the shortlist of oxidative cross-coupling processes performed under gold catalysis known to date. Efforts aimed at expanding the scope of this chemistry and its mechanistic aspects are ongoing and will be reported in due course.

Experimental Section

General procedure for oxidative cyclization of *tert*-butyl allenoates: PPh$_3$AuNTf$_2$ (10 mol %) and Selectfluor (2.5 equiv) were added to a solution of the allenoate (1 equiv) in acetonitrile (0.01 M) and water (10 equiv). The reaction was stirred at room temperature until TLC analysis showed complete consumption of the allenoate (1.5–24 h). The reaction mixture was then diluted with dichloromethane and filtered through Celite. After drying over anhydrous sodium sulfate and filtration, the solvent was removed in vacuo. The resulting crude mixture was purified by flash column chromatography on a short pad of silica gel.

X-ray crystallographic analysis: CCDC-765540, 765541, 765542, 765543, 765544 and 765545 contain the supplementary crystallographic data for **2a**, **2d**, (8*R*,8a*S*)-**2i**, (±)-(2*S*,2′*S*)-**3a**, (2*R*,2′*S*)-**3a**, and **5f**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: allenes · arylation · cross-coupling · cyclization · gold

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[7] The solvent has a significant effect on the efficiency of protodeauration. The gold-catalyzed cyclization of **1a** to **4a** was much slower in MeCN than CH$_2$Cl$_2$ (Scheme 2). The oxidative coupling with NFSI was only successful in MeCN. Compound **4a** was the only product observed in CH$_2$Cl$_2$. For details, see the Supporting Information.

[8] For a recent review on oxidative coupling reactions with gold, see: a) H. A. Wegner, *Chimia* **2009**, *63*, 44–48; for selected examples of gold-catalyzed cross-coupling reactions with substrates as oxidants, see: b) C. González-Arellano, A. Corma, M. Iglesias, F Sánchez, *J. Catal.* **2006**, *238*, 497–501; c) C. González-Arellano, A. Abad, A. Corma, H. García, M. Iglesias, F. Sánchez, *Angew. Chem.* **2007**, *119*, 1558–1560; *Angew. Chem. Int. Ed.* **2007**, *46*, 1536–1538; d) P. Li, L. Wang, M. Wang, F. You, *Eur. J. Org. Chem.* **2008**, 5946–5951; for a report on the gold-catalyzed oxidative homodimerization of coumarins with an external oxidant, see: e) H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310–11313.

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[12] The cyclization of **1a** with Ph$_3$PAuNTf$_2$ but without Selectfluor afforded **4a** as the only product; for details, see the Supporting Information.

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