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Homogeneous Catalysis

Gold(I)-Catalyzed Alkoxyhalogenation of β-Hydroxy-α,α-Difluoroynones**

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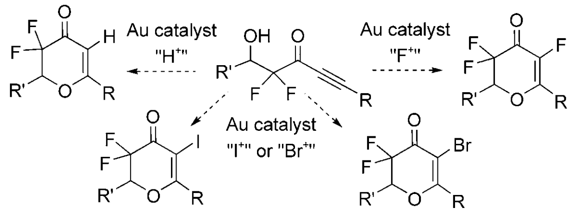
Dedicated to Professor Léon Ghosez

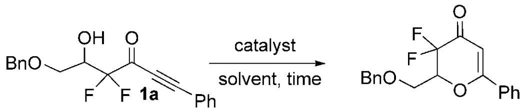
The presence of fluorine substituents can significantly impact the physicochemical properties of organic compounds.[1] Novel methods for the preparation of fluorinated molecules based on fluorinated building blocks or C–F bond forming reactions are therefore in great demand. New approaches to dihydro- or tetrahydropyranones featuring two or more fluorine substituents are valuable, as these compounds may be manipulated to enable, among other things, the synthesis of fluorinated carbohydrate analogues.[2] The number of synthetic routes to difluorinated dihydropyranones remains limited, a notable exception being the hetero-Diels–Alder reaction of difluorinated Danishefsky dienes.[2a] Although gold catalysis has brought forth spectacular achievements,[3] the usefulness of gold complexes has not been explored with reactions involving fluorinated starting materials or to promote C–F bond forming reactions. A rare example of gold-catalyzed fluorination is the *trans*-hydrofluorination of alkynes catalyzed by N-heterocyclic carbene gold(I) complexes.[4] This process relies on the use of a gold catalyst with a nucleophilic source of fluorine. The ability of gold catalysts to activate alkynes towards nucleophilic addition led us to hypothesize that di- and trifluorinated dihydropyranones may be accessible from β-hydroxy-α,α-difluoroynones, the key event being a gold-catalyzed 6-*endo-dig* ring closure (Scheme 1). A gold-catalyzed 6-*endo-dig* cyclization also offers the possibility to capture the gold intermediate with electrophiles other than H^+.[5,6] We were particularly intrigued by the prospect of developing a cyclization–halogenation sequence including a process that features an unprecedented oxidative fluorination of a transient vinylgold species. Herein, we report that gold(I)-catalyzed alkoxyhalogenations of β-hydroxy-α,α-difluoroynones are feasible, including a cyclization–fluorination cascade, a reaction combining for the first time a gold catalyst with an electrophilic source of fluorine.



Scheme 1. Gold(I)-catalyzed alkoxyhalogenation (and -protonation) of ynones.

Initial investigations focused on validating the ring closure in the absence of an additional electrophile. This study was aimed at comparing the efficiency of gold catalysts with alternative catalytic systems.[7] For substrate **1a** (Table 1) featuring the key *gem*-difluoro motif, the ring closure did not proceed (or was not efficient) under basic or acidic conditions or using catalytic systems other than gold catalysts. The poor reactivity of this substrate is likely the result of the deactivating effect of the *gem*-difluoro group that reduces the nucleophilicity of the proximal hydroxy group. The desired 6-*endo-dig* ring closure took place efficiently in the presence of 5 mol% AuCl in CH_2Cl_2. No product resulting

Table 1: 6-*Endo-dig* cyclizations of ynone **1a**.



1a **2a**

Entry	Catalyst	Loading [mol%]	Conditions	Yield [%]
1	$[(MeCN)_2PdCl_2]$	10	CH_2Cl_2, 18 h	–[a]
2	$[(MeCN)_4Pd](BF_4)_2$	8	CH_2Cl_2, 18 h	15
3	amberlyst-15	–[b]	CH_2Cl_2, 18 h	–[a]
4	NaH	100	CH_2Cl_2, 5 h	–[c]
5	HCl	100	CH_3CN, 40 h	–[a]
6	TfOH	50	CH_2Cl_2, 29 h	–[c]
7	$PtCl_2$	5	CH_2Cl_2, 18 h	–[a]
8	$InCl_3$	5	CH_2Cl_2, 18 h	–[a]
9	$AgNO_3$	5	THF, 18 h	–[a]
10	$AgSbF_6$	5	CH_2Cl_2, 18 h	25
11	$AuCl_3$	5	CH_2Cl_2, 18 h	79
12	AuCl	5	CH_2Cl_2, 18 h	93
13	$[Au(PPh_3)OTf]$	5	CH_2Cl_2, 18 h	90

[a] Starting material recovered. [b] 2 wt equiv. [c] Decomposition. OTf = CF_3SO_3, Bn = benzyl.

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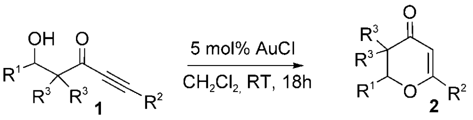
from a 5-*exo-dig* ring closure or other side products were detectable in the crude reaction mixtures (Table 1).

We investigated the scope and limitations of this reaction using the difluorinated ynones **1b–i** as starting materials (Table 2).[8,9] The cyclization was performed with 5 mol% AuCl in CH_2Cl_2 at room temperature. Numerous structural variations were tolerated for the difluorinated ynones, both on the alkyne and on the group flanking the alcohol. The aldol product **1g** with the silyl-protected alkyne was the only ynone that failed to cyclize (entry 6, Table 2). The unfluorinated ynones **1j–k** were successfully cyclized under gold(I) catalysis with yields of isolated product reaching 89% (entries 9 and 10, Table 2). For the enantioenriched β-hydroxyynone (*R*)-**1k**, the product (*R*)-**2k** was formed with no erosion of enantiomeric excess.

Table 2: Gold-catalyzed cyclization of β-hydroxyynones **1b–k**.

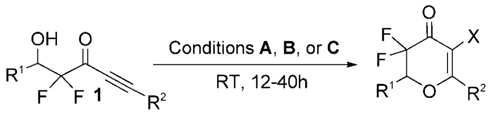


Entry	Ynone	R^1	R^2	R^3	Yield **2** [%][a]
1	**1b**	Ph	Ph	F	92
2	**1c**	4-$CF_3C_6H_4$	Ph	F	94
3	**1d**	4-$MeOC_6H_4$	Ph	F	92
4	**1e**	cyclohexyl	Ph	F	94
5	**1f**	cyclohexyl	*n*Pr	F	90
6	**1g**	$BnOCH_2$	$SiMe_3$	F	<5[b]
7	**1h**	$BnOCH_2$	Me	F	83[c]
8	**1i**	$BnOCH_2$	H	F	75[d]
9	**1j**	$PhCH_2CH_2$	Ph	H	89
10	(*R*)-**1k**	*p*-$NO_2C_6H_4$	Et	H	65[e]

[a] Yields of isolated products. [b] Decomposition. [c] Reaction in MeCN. [d] Reaction carried out with 10 mol% $AuCl_3$. [e] *ee* = 74% for **1k** and **2k**.

We next investigated the possibility of coupling the 6-*endo-dig* cyclization with an iodination of the presumed vinylgold intermediate (Table 3). Literature precedent indicates that electrophilic iodinating reagents can capture in situ generated organogold species.[6] The difluoroiodopyranones were successfully formed when treating the β-hydroxyynones with 1.2 equivalents of *N*-iodosuccinimide (NIS) in the presence of 5 mol% AuCl. The yields ranged from 65 to 92% (entries 1–5, Table 3). The structure of **3b** was confirmed by X-ray analysis.[9] Crude reaction mixtures showed no trace of dihydropyranones resulting from a competing protodeauration. As unfluorinated dihydropyranones are known to undergo iodination upon treatment with iodine and pyridine,[10] we performed control experiments to probe the reactivity of the protodeaurated difluorinated dihydropyranone **2b** in the presence of NIS but in the absence of gold catalyst.[9] Under these conditions, **2b** did not react, a result in line with the deactivating effect of the *gem*-difluoro group. An additional control experiment revealed that ynone **1d** remained unchanged upon treatment with NIS in the absence of gold catalyst. Therefore, the iodination event likely involves the capture of an in situ generated vinylgold intermediate. When vinyl iodides are formed, an additional site of functionalization through cross-coupling reactions is available.[9,11]

Table 3: Gold(I)-catalyzed alkoxyiodination and alkoxybromination.



A: 5 mol% AuCl, 1.2 equiv NIS, acetone
B: 5 mol% AuCl, 1.2 equiv NBS, CH_2Cl_2
C: 5 mol% AuCl, 1.2 equiv NCS, CH_2Cl_2

3 X = I
4 X = Br
5 X = Cl

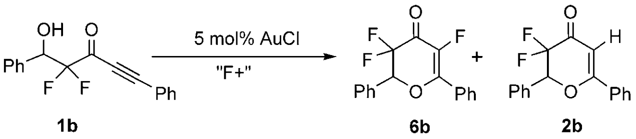
Entry	Ynone	Conditions	Product	Yield **3, 4**, or **5** [%][a]
1	**1a**	**A**	**3a**	65
2	**1b**	**A**	**3b**	76
3	**1d**	**A**	**3d**	92
4	**1e**	**A**	**3e**	65
5	**1f**	**A**	**3f**	68
6	**1b**	**B**	**4b**	82
7	**1d**	**B**	**4d**	70
8	**1d**	**C**	**5d**	0[b]

[a] Yields of isolated products. [b] 32% **2d** and 37% **1d**. NIS = *N*-iodosuccinimide, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

The alkoxybromination[6e] and alkoxychlorination[6f,g] were attempted using *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS). The gold(I)-catalyzed alkoxybromination delivered the brominated pyranones **4b** and **4d** in 82 and 70% yield, respectively.[9,12] Control experiments similar to those conducted with NIS suggested that the bromination event involved a vinylgold species.[9] The alkoxychlorination of **1d** was unsuccessful; the protodeaurated dihydropyranone **2d** was formed as the sole product in 32% yield.

The scarce information available on transition-metal-catalyzed methods for C–F bond construction prompted us to investigate the feasibility of a cascade alkoxylation–fluorination.[13] This study raised several important questions such as the compatibility of the gold catalyst with electrophilic fluorinating reagents as well as the ability of the vinylgold intermediate to undergo oxidative fluorination. This reaction was attempted with ynone **1b** to determine the optimal combination of solvent, catalyst, and fluorinating reagent for the alkoxyfluorination (Table 4).

Table 4: Optimization of the gold(I)-catalyzed alkoxyfluorination of **1b**.



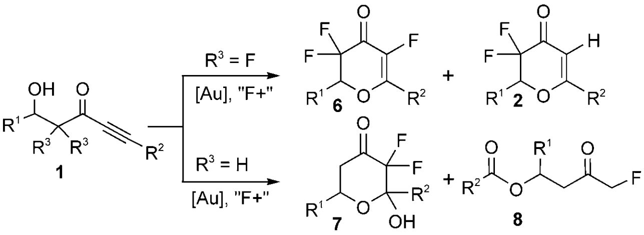
Entry	F^+ Reagent (equiv)	Conditions	**1b**:**6b**:**2b**[a]
1	NFSI (2.5)	CH_2Cl_2, RT, 18 h	73:0:27
2	NFSI (1.5)	CH_2Cl_2, reflux, 24 h	93:0:7
3[b]	pyridinium (2)[c]	MeCN, RT, 6 d	68:0:32
4	selectfluor (1.5)	MeCN, RT, 55 h	0:40:60
5	selectfluor (2.5)	MeCN, RT, 48 h	0:45:55
6	selectfluor (2.5)	CH_2Cl_2, $NaHCO_3$, RT, 66 h	100:0:0

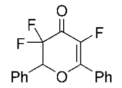
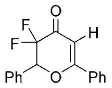
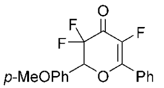
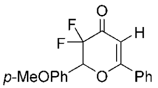
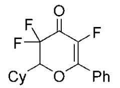
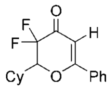
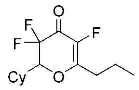
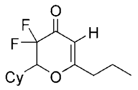
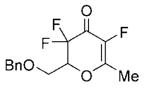
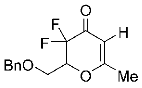
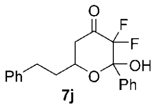
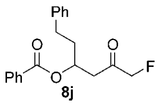
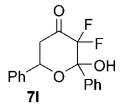
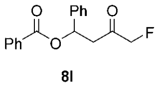
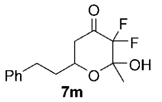
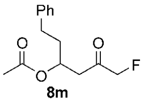
[a] Ratios determined by ^{19}F NMR spectroscopy of crude material. [b] AuCl 10 mol%. [c] *N*-fluoro-2,3,6-trimethylpyridinium tetrafluoroborate. NFSI = *N*-fluorobenzenesulfonimide.

The best results were obtained upon treatment of **1b** with 5 mol% AuCl in the presence of 2.5 equivalents selectfluor in MeCN. Analysis of the crude reaction mixture by ^{19}F NMR spectroscopy revealed the formation of two products, the trifluorinated dihydropyranone **6b** and the protodeaurated difluorinated dihydropyranone **2b** in a ratio of 2:3. Attempts to eradicate the protodeauration by starting from *O*-silylated β-hydroxyynones, adding coreagents such as various bases, or modulating the stoichiometry of the fluorinating reagent were unsuccessful.[9]

Investigations into the scope and limitations of this gold(I)-catalyzed cyclization–fluorination were carried out, probing the reactivity of both difluorinated and unfluorinated β-hydroxyynones (Table 5). The difluorinated ynones delivered the trifluorodihydropyranones along with difluorinated pyranones resulting from a competing protodeauration (entries 1–5, Table 5). The ratios of these two products were in the range of approximately 1:1 to 2:3, as determined by ^{19}F NMR spectroscopy of crude material. Since the starting material was completely consumed, the low yields of isolated fluorodeaurated pyranones **6** may be due to the instability of these products upon isolation. The structures of **6b** and **6e** were unambiguously characterized by X-ray analysis.[9] Upon treatment with 2.5 equivalents selectfluor in the presence of 5 mol% AuCl, the unfluorinated ynones **1j**,**l**,**m** delivered two products identified as the difluorinated tetrahydropyranones **7j**,**l**,**m** and the ring-opened monofluorinated ketones **8j**,**l**,**m** (entries 6–8, Table 5). The best yields for the ring closure of these unfluorinated β-hydroxyynones were obtained when the reactions were performed in MeCN/water.

Table 5: Gold(I)-catalyzed alkoxyfluorination of β-hydroxyynones.

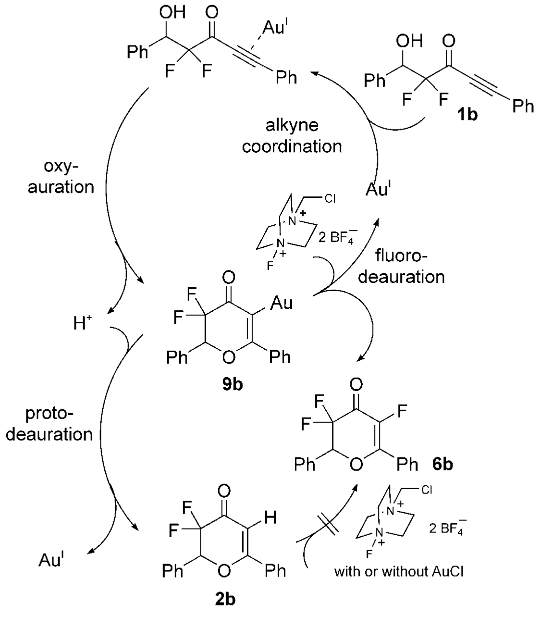


Entry	Ynone	Products		Yield [%]
1[a]	**1b**	 **6b**	 **2b**	20/33
2[a]	**1d**	 **6d**	 **2d**	26/33
3[a]	**1e**	 **6e**	 **2e**	20/15
4[a]	**1f**	 **6f**	 **2f**	27/37
5[a]	**1h**	 **6h**	 **2h**	24/43
6[b]	**1j**	 **7j**	 **8j**	59/39
7[b]	**1l**	 **7l**	 **8l**	50/13
8[b]	**1m**	 **7m**	 **8m**	41/32

[a] AuCl 5–10 mol%, selectfluor 2.5 equiv, MeCN, RT, 72–96 h; [b] AuCl 5 mol% selectfluor 2.5 equiv, MeCN/H$_2$O 1:1, RT, 18 h.

Several control experiments were conducted to gain insight into the mechanism of these gold(I)-catalyzed alkoxyfluorinations. No reaction occurred when the difluorinated ynone **1b** was treated with selectfluor in the absence of gold catalyst. We found that the reaction of the difluorinated dihydropyranone **2b** and selectfluor with or without AuCl delivered unreacted starting material with no trace of **6b** detectable by ^{19}F NMR spectroscopy. The *gem*-difluoro group in **2b** therefore strongly deactivates the alkoxyenone group towards electrophilic fluorination. These control experiments suggest that **2b** is not a plausible intermediate of the reaction pathway leading to **6b**, reinforcing the hypothesis that the transient vinylgold species **9b** undergoes fluorination (Scheme 2). This reaction constitutes the first example of oxidative fluorination of an organogold intermediate, possibly by electrophilic attack of selectfluor on the Au−C bond. However, the exact mechanistic pathway leading to trifluorinated pyranones will require further investigation.

The control experiments carried out on the unfluorinated hydroxyynones were less conclusive, as the ring-closed dihydropyranones underwent double fluorination when treated with selectfluor in the absence of gold catalyst.[9] For



Scheme 2. Proposed mechanism for the catalytic formation of **6b**.

these substrates, several mechanisms are plausible, such as protodeauration and subsequent double fluorination or fluorodeauration and subsequent single fluorination.[14] The formation of the ring-opened monofluorinated products **8** may be rationalized with a competitive ring opening of a hemiacetal intermediate formed upon addition of water.

In conclusion, we have developed a new method for the preparation of 5-iodo, 5-bromo- and 5-fluoro-3,3′-difluorodihydropyranones from β-hydroxy-α,α-difluoroynones. The gold-catalyzed 6-*endo-dig* cyclization of these substrates is not possible using alternative catalytic systems owing to the reduced nucleophilicity of the hydroxy group proximal to the *gem*-difluoro group. For the first time, it has been shown that gold catalysis is compatible with electrophilic fluorinating reagents. Significantly, the data reported herein also suggest that the oxidative fluorination of a vinylgold species is possible. Ongoing efforts seek to expand the scope of the proposed fluorodeauration and to probe its mechanism.

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Keywords: cyclization · fluorine · gold · homogeneous catalysis · ynones

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