## Effects of haloniums on gold-catalyzed ring expansion of 1-oxiranyl-1-alkynylcyclopropanes<sup>†</sup>

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We observed distinct chemoselectivities for the gold-catalyzed transformation of *cis*-1-oxiranyl-1-alkynylcyclopropanes 1 into various halogenated products in the presence of suitable Au(III) catalysts and *N*-halosuccinimide (halo = chloro, bromo and iodo).

Formation of a carbo- or heterocyclic ring is an important topic in organic synthesis. Among various ring sizes, four-membered<sup>1,2</sup> and medium ring sizes<sup>3</sup> (seven to nine members) are particularly notable because many natural products possess these structural units. However, few practical methods are available for these cyclic rings; among them, ring closure metathesis is a powerful tool for medium-sized rings.<sup>4</sup>

We reported a gold-catalyzed hydrative ring-expansion of *cis*-1-oxiranyl-1-alkynylcyclopropanes **1**, giving 3-oxabicyclo-[4.2.0]oct-4-en-6-ols **2** stereoselectively (dr > 10 : 1) *via* a hypothetic tertiary cation **A**.<sup>5</sup> Notably, their *trans* analogues failed to undergo stereoselective ring expansions because of a staggered orientation between the alkyne and epoxide groups. In the presence of PPh<sub>3</sub>AuSbF<sub>6</sub> (5 mol%),<sup>5</sup> alcohols **2** form 1-oxyallyl cations that undergo [4+2]-cycloaddition with butadienes or enones to give polycyclic products **3** and **4** with excellent diastereoselectivities.<sup>3</sup> Alkenyl halides are important functionalities for various metal-catalyzed carbon–carbon coupling reactions.<sup>6</sup> We sought to prepare halogen-containing bicyclic derivatives **5** *via* this hydrative ring expansion, in which X<sup>+</sup> replaces the gold fragment in intermediate **A**.<sup>7</sup>

Table 1 shows our catalyst screening using common  $\pi$ -alkyne activators,<sup>8</sup> with which starting *cis*-epoxide **1a** was completely consumed for all cases. In a standard operation, cis-epoxide 1a was treated with PPh<sub>3</sub>AuCl/AgSbF<sub>6</sub> (5 mol%) in wet CH<sub>2</sub>Cl<sub>2</sub> (DCM, 25 °C) for a short period (2-3 min), followed by an addition of N-chlorosuccinimide (NCS, 1.0 equiv.), giving a complex mixture of products (entry 1). Although AuCl<sub>3</sub> (10 mol%) enabled a hydrative cyclization of intermediate A derived from 1a (Scheme 1), its subsequent treatment with NCS (1 equiv.) gave 3-chloro-4,5-dihydro-2Hoxocin-6(3H)-one 6a, an eight-membered ether bearing a cis-configuration, albeit in 15% yield (entry 2); the cis-geometry was determined by <sup>1</sup>H NOE spectra. PtCl<sub>2</sub>/CO and AuBr<sub>3</sub> failed to give 6a in a tractable amount (entries 3 and 4). Stable Au(III) species such as AuCl<sub>2</sub>Pic (Pic = picolate, 10 mol%) greatly improved the yield of the desired 6a to 49% (entry 5), and further to 61% in the presence of PPh<sub>3</sub>PO (10 mol%, entry 6)

	H, O, H nC <sub>5</sub> H	(1) cata solvent/ additive (2) NCS	lyst H <sub>2</sub> O (2 e e, 25 °C S ( 1 equ		CI $rc_5H_{11}$ $rc_7H_{11}$
	<b>1a</b> (Ar = 4-MeC <sub>6</sub> H <sub>4</sub> )			<b>6a</b> (Ar = 4	1-MeC <sub>6</sub> H <sub>4</sub> )
Entry	Catalyst <sup>a</sup> /mol%	Solvent	t/h	Additive/ mol%	<b>6a</b> (yield [%]) <sup>b</sup>
1	PPh <sub>3</sub> AuCl (5)/ AgSbF <sub>6</sub> (5)	DCM	7		Complex mixture
2	AuCl <sub>3</sub> (10)	DCM	0.5	_	15%
3	AuBr <sub>3</sub> (10)	DCM	7	_	Complex mixture
4	$PtCl_2/CO$ (10)	DCM	7	_	Complex mixture
5	AuClPic (10)	DCM	0.16	_	49%
6	$AuCl_2Pic$ (10)	DCM	0.16	PPh <sub>3</sub> O (10)	61%
7	$AuCl_2Pic$ (5)	DCM	0.16	PPh <sub>3</sub> O (10)	60%
8	$AuCl_2Pic$ (5)	MeCN	0.5	PPh <sub>3</sub> O (10)	25%
9	AuCl <sub>2</sub> Pic $(5)$	MeCN	0.5	PPh <sub>3</sub> O (10)	35%

 Table 1
 Gold-catalyzed oxacyclization/ring expansions using NCS

<sup>*a*</sup> [Substrate] = 0.1 M. <sup>*b*</sup> Yields are reported after elution from a silica column.



Scheme 1 Reaction pathways for gold-catalyzed cyclizations.

that could inhibit the protodeauration.<sup>7a</sup> The yield of **6a** was kept at 60% even with a small loading (5 mol%) of AuCl<sub>2</sub>Pic. This catalysis is greatly affected by solvents in that THF and nitromethane gave poor yields (25–35%) of the desired ether **6a** (entries 8 and 9). Interestingly, naturally occurring compounds such as laurencin<sup>3a-c</sup> and laurenyne<sup>3d,e</sup> have similar structural skeletons.



Stereoselective formation of the eight-membered ether **6a** from starting *cis*-epoxide **1a** is mechanistically appealing because this process involves two consecutive openings of a starting cyclopropyl ring. We prepared *cis*-epoxides **1b–1j** to

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 Table 2
 Scope for the synthesis of eight-membered ring ethers

	H, Q,	(1) PicA R <sup>2</sup> H <sub>2</sub> C R <sup>1</sup> PPh <sub>3</sub> DCM	uCl <sub>2</sub> (3 mc) (2 equiv) O (5 mol% I, rt, 1 min	) )	
	1b-1j A	· (2) NCS	(1.0 eq), 1	0 min	<b>6b-6j</b> Ar
Entry	Epoxide <sup>a</sup>	Ar	$\mathbf{R}^1$	$\mathbb{R}^2$	Product (yield [%]) <sup>b</sup>
1	1b	C <sub>6</sub> H <sub>5</sub>	<i>n</i> -Pentyl	Н	<b>6b</b> (81%)
2	1c	p-MeOC <sub>6</sub> H <sub>4</sub>	n-Pentyl	Н	<b>6c</b> (56%)
3	1d	p-CNC <sub>6</sub> H <sub>4</sub>	n-Pentyl	Н	6d (69%)
4	1e	p-FC <sub>6</sub> H <sub>4</sub>	n-Pentyl	Н	<b>6e</b> (58%)
5	1f	p-ClC <sub>6</sub> H <sub>4</sub>	n-Pentyl	Н	<b>6f</b> (53%)
6	1g	-re- S	<i>n</i> -Pentyl	Н	<b>6g</b> (79%)
7	1h	ĩ \ĭ	n-Pentyl	Н	<b>6h</b> (77%)
8	1i	The second second	<i>n</i> -Pentyl	Н	<b>6i</b> (82%)
9	1j		<i>n</i> -Pentyl	Н	<b>6j</b> (47%)
10	1k	C <sub>6</sub> H <sub>5</sub>	Methvl	Н	<b>6k</b> (83%)
11	11	35 S	Methyl	Н	<b>61</b> (80%)
12	1m	$C_6H_5$	Methyl	Methyl	6m (57%)
<sup><i>a</i></sup> [Ep metha	oxide] = 0. ane. <sup>b</sup> Yield	1  M, NCS = 1 s are reported	N-chlorosi after elut	accinimic ion from	le, DCM = dichloro- a silica column.

assess the generality of this catalysis. For 1.2-disubstituted epoxides 1b-f bearing variable para-substituents at the alkynylphenyl (Ar =  $4-XC_6H_4$ ) positions, we obtained good yields (>69%) of compounds 62b (X = H) and 6d (X = CN) and moderate yields (53-58%) of compounds **6c** (X = MeO), **6e** (X = F) and **6f** (X = CI). This new catalysis is particularly suitable for epoxides 1g-i bearing Ar = 2-, 3-thienyl and 2-benzothienyl; resulting ether products 6g-i were obtained in 77-82% yields (entries 6-8) (Table 2). The same reaction appears to be less efficient for the 2-furanyl derivative 1j that gave the expected product 6j in 47% yield (entry 9). This ether synthesis is also applicable for distinct 1,2-disubstituted epoxides **1k** and **1l** bearing  $\mathbf{R}^1 = \mathbf{M}\mathbf{e}$ , giving resulting products 6k and 6l in 80-83% yields (entries 10-11). We obtained a similar ether 6m in 57% yield from the trisubstituted epoxide substrate 1m (entry 12). Among these cases, low product yields of ethers **6c** and **6j**, bearing an electron-rich 4-MeOC<sub>6</sub>H<sub>4</sub> and 2-furanyl, respectively, were presumably due to the occurrence of side products such as 2 and 5 (Scheme 1).

We examined this gold catalysis using a brominum source, *N*-bromosuccinimide (NBS); the results appear in Table 3. In a standard operation, epoxide **1a** was treated with a gold catalyst,  $H_2O$  (2 equiv.) and NBS (1.2 equiv.) in DCM simultaneously. Among three Au(III) catalysts, AuCl<sub>3</sub> gave the best yield (68%) for the resulting 5-bromo-3-oxabicyclo-[4.2.0]oct-4-en-6-ol **5b** whereas PicAuCl<sub>2</sub> produced 2,2-dibromo-1-phenylethanone **7** in 45% yield (entry 1). Compound **5b** was the target in our original proposal (Scheme 1).

We find an intriguing observation that NCS and NBS exhibited distinct behaviors in the ring expansions of the same epoxide **1b**. We examined the generality of the 3-oxabicyclo-[4.2.0]oct-4-en-6-ol synthesis using AuCl<sub>3</sub> (5 mol%), NBS and





 Table 4
 Product yields for ring expansions with NBS and NIS

	$Ar = \frac{1}{R_1}$	AuCl <sub>3</sub> (5 mo H <sub>2</sub> O(2 eq. PPh <sub>3</sub> O(5 mo NBS or NIS (1.2 eqiv.) DCM rt	1%) ) ) 6 5	x Ar	H R1	5 (X = Br) 5' (X = I)	
Entry	Epoxide <sup>a</sup>	Ar	R <sup>1</sup>	<b>R</b> <sup>2</sup>	Product	(yield [%]) <sup>b</sup>	
1	1a	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Pentyl	Н	5a (X =	Br, 56%)	
2	1g	$\mathcal{F}_{\mathcal{S}}$	Pentyl	Н	<b>5</b> g (X =	Br, 63%)	
3	1i	r KS	Pentyl	Н	5i (X =	Br, 70%)	
4	1k	$C_6H_5$	Methyl	Н	5k (X =	Br, 63%)	
5	1m	$C_6H_5$	Methyl	Pethyl	5m (X =	Br, 61%)	
6	1a	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Pentyl	Н	5a' (X =	= I, 60%)	
7	1b	$C_6H_5$	Pentyl	Н	5b' (X =	= I, 75%)	
8	1g	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Pentyl	Н	5g' (X =	= I, 72%)	
9	1h	7 S	Pentyl	Н	5h'(X =	= I, 70%)	
10	1i	rt S	Pentyl	Н	5i' (X =	I, 73%)	
11	1k	C <sub>6</sub> H <sub>5</sub>	Methyl	Н	5k'(X =	= I, 72%)	
12	1m	$C_6H_5$	Methyl	Methyl	5m' (X =	= Í, 70%)	
a reub	stratal -	01 M NIS	- N	-	inimida b	Vialda ana	
[Substrate] = 0.1  M,  MIS = N-1000  succinimide. Yields are							
reported after elution from a silica column.							

NIS (N-iodosuccinimide) for several *cis*-epoxides, as depicted in Table 4. This synthesis is extensible for *cis*-epoxides **1a**, **1g**, **1i**, and **1k** bearing alterable alkynylaryl (Ar = 4MePh, 2-thienyl, 2-benzothienyl) and epoxyalkyl (R = *n*-pentyl, methyl) groups; their resulting products **5a**, **5g**, **5i** and **5k** were obtained in 56–70% yields (entries 1–4). The reaction works also for the trisubstituted epoxide **1m** that gave the expected product **5m** in 61% yield (entry 5). The use of NIS for the same epoxides **1a,b**, **1g–i**, **1k** and **1m** not only gave products of the same type, including **5a',b'**, **5g'–I'**, **5k'** and **5m'** with high diastereoselectivity, but also produced them in yields (60–75%, entries 6–12) greater than those cases from the NBS sources.

Shown in Scheme 2 are control experiments to clarify the possible intermediacy of alcohol 2b in the gold-catalyzed transformation of the starting epoxide 1b into desired halogenated products 6b, 5b and 5b', as depicted in Tables 2–4. Treatment



Scheme 2 Control experiments and the use of chiral epoxide.

of **2b** with 5% AuCl<sub>2</sub>(Pic) and NCS (1.2 equiv.) in  $CH_2Cl_2$  led only to its recovery; good recovery yields were also obtained for treatment of **2b** with AuCl<sub>3</sub> with NBS or NIS. We also prepared chiral epoxide **1m** with 67% ee, but its gold-catalyzed reaction with NCS gave the resulting product **6m** with a complete loss of chirality.

As alcohol **2b** is not the intermediate for the generation of halogenated products 6b, 5b and 5b' using epoxide 1a, we propose a mechanism involving metal-containing 3-oxabicyclo-[4.2.0]oct-4-en-6-ol **B** via hydrolysis of the initial carbocation **A**. In the presence of PPh<sub>3</sub>PO and NCS, we believe that protodeauration of cation A to form alcohol 2b appears to be slow due to the presence of PPh<sub>3</sub>O such that the gold fragment of intermediate B activates the proximate hydroxyl group toward the attack of NCS. This process causes the opening of a cyclobutanol ring to give an eight-membered ether 6b; the proton released from the hydrolysis of cation A, in the form of PPh<sub>3</sub>PO-H<sup>+</sup>, assists the liberation of Cl<sup>+</sup> from NCS.<sup>9,10</sup> We observed a change in the chemoselectivity for NBS and NIS because soft " $Br^+$ " and " $I^+$ " have a high affinity toward the gold fragment to produce a direct replacement (Scheme 3).<sup>7</sup>

In summary, we observed distinct chemoselectivities<sup>11</sup> for the gold-catalyzed transformation of *cis*-1-epoxy-1-alkynylcyclopropanes **1** into various halogenated products in the presence of suitable Au(III) catalysts and *N*-halosuccinimide (halo = chloro, bromo and iodo). In the presence of NCS and



Scheme 3 Proposed mechanisms for various haloniums.

AuCl<sub>2</sub>(Pic) catalysts, we obtained 3-chloro-4,5-dihydro-2Hoxocin-6(3H)-one **6**, an eight-membered ether, *via* two consecutive ring openings of a starting cyclopropane ring. In the presence of NXS (X = Br and I) and AuCl<sub>3</sub> catalysts, we obtained 5-halo-3-oxabicyclo[4.2.0]oct-4-en-6-ols **5** and **5'** efficiently, *via* a single cyclopropane opening. Both reactions gave one diastereomeric product.

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