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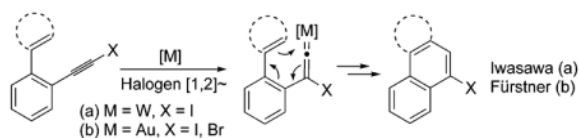
1,2-Halogen Migration in Haloallenyl Ketones: Regiodivergent Synthesis of Halofurans

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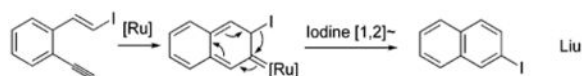
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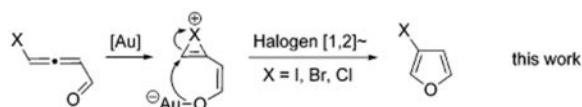
Transformations involving selective 1,2-halogen migration have not been reported until recently,¹ when Iwasawa and then Fürstner disclosed 1,2-iodine,² and 1,2-iodine and -bromine migration,³ respectively, in alkynyl halides to produce fused haloarenes (eq 1). Furthermore, Liu showed a 1,2-iodine shift in a Ru alkylidene complex (eq 2).⁴ Both transformations involved metal carbenoid intermediates and were used in the synthesis of carbocycles. To the best of our knowledge, no syntheses of halogenated heterocycles involving halogen migration have been reported to date. Herein, we wish to report Au-catalyzed selective 1,2-migration of iodine, bromine, and chlorine, proceeding via a halirenium intermediate, leading to 3-halofurans in good to excellent yields (eq 3).



(1)



(2)



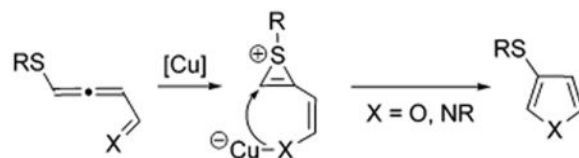
(3)

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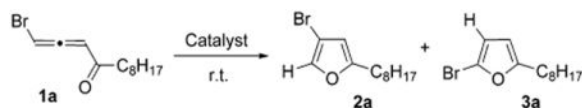
Supporting Information **Available:** Preparative procedures, analytical and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Halofurans, important building blocks, are traditionally obtained by electrophilic halogenation of furans,⁵ via halogen-induced cyclizations⁶ or cyclocondensations of halogenated precursors.⁷ Most of these approaches require employment of strongly electrophilic reagents, thus limiting their application to substrates lacking acid-sensitive functionalities. We have recently reported the Cu-catalyzed synthesis of 3-thiofurans, which involved selective 1,2-migration of a thio group in thioallenyl ketones, proceeding via a thiirenium intermediate (eq 4).⁸



(4)

We hypothesized that replacement of sulfur with halogen might provide convenient access to 3-halofurans. Inspired by this idea, we subjected bromoallenyl ketone **1a**⁹ to a Cu-catalyzed cycloisomerization (eq 5),¹⁰ which indeed led to formation of 3-bromofuran **2a**, albeit in poor yield (20–30%). In contrast, AgBF₄, which proved to be efficient in the cycloisomerization of different allenyl ketones,¹¹ did not catalyze this reaction at all. Employment of PtCl₂, however, produced 3-bromofuran **2a** in 50% yield along with small amounts of 2-bromofuran **3a**. To our delight, employment of AuCl₃ afforded 3-bromofuran **2a** in 86% yield with high selectivity (Table 1, entry 1),¹² which was further improved by elevation of reaction temperature (entries 4 and 5). Surprisingly, switching solvent to THF caused a dramatic change in selectivity, affording 2-bromofuran **3a** as a major product (entry 6). The latter was also exclusively obtained in the presence of Au(PEt₃)Cl (entry 8).

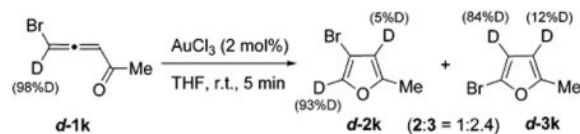


(5)

We propose two complementary pathways for selective formation of **2** and **3** (Scheme 1). According to path A, oxophilic Au(III) species coordinates to oxygen (**a**) provoking intramolecular Michael addition of Br to the enone moiety, leading to bromoirenium zwitterion **b**,¹³ which, via subsequent addition–elimination, furnishes 3-bromofuran **2** (path A). Alternatively, the rather more π -philic Au(I) species coordinates to the distal double bond of allene (**c**), activating it toward intramolecular attack of oxygen followed by tautomerization to form gold carbenoid species **d**. The latter, after 1,2-hydride shift,¹⁴ furnishes 2-bromofuran **3** (path B).

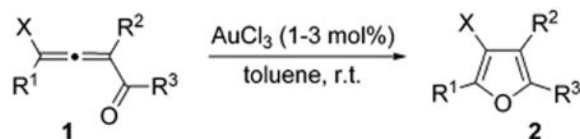
To gain additional support for path A, we tested Brønsted and Lewis acids as potential catalysts for this transformation. It was found that this reaction proceeds selectively in the presence of AlCl₃ and even silica gel, affording 3-bromofuran **2a**, albeit in low yield.¹⁰ The reversal of regioselectivity observed in the AuCl₃-catalyzed reaction in THF (Table 1, entry 6) can be attributed to a decrease of oxophilicity of the Au(III) complex in ethereal solvent. To verify whether selective formation of 2-bromofuran **3** proceeds via 1,2-hydride shift (path B), we subjected deuterated allenyl ketone **d-1k** to the cycloisomerization conditions

(eq 6). This reaction produced a mixture of 2- and 3-bromofurans in a ratio of 2.4:1 without detectable loss of deuterium,¹⁵ thus strongly supporting path B.^{16,17}



(6)

Next, we investigated the scope of this cascade transformation. Thus, differently substituted haloallenylic ketones were subjected to Au(III)-catalyzed cycloisomerization (eq 7, Table 2). It was found that a variety of alkyl- and aryl-substituted bromoallenylic ketones and aldehydes underwent smooth cycloisomerization, affording 3-bromofurans in good to excellent yields (entries 1–5). Remarkably, this method allowed for efficient synthesis of halofurans possessing hydroxymethyl (**2e**) and alkene (**2f**) functionalities, which are incompatible with known methods employing electro-philic reagents. It was found that fully substituted iodoallenylic ketones reacted more slowly than their bromo analogues, producing corresponding furans in good yield (entry 6). Gratifyingly, ambident disubstituted allenylic iodides underwent exclusive iodine migration to afford 2-alkyl- and -aryl-substituted iodofurans in 97 and 71% yields, respectively (entries 7 and 8). Chloroallene **1j** also underwent this transformation to produce 3-chlorofuran **2j**.¹⁸



(7)

In summary, we have demonstrated Au(III)-catalyzed 1,2-iodine, -bromine, and -chlorine migration in haloallenylic ketones, proceeding via a halirenium intermediate. This chemistry is interesting not only as a novel cascade transformation but also as a mild, selective, and efficient approach to different types of 3-halofurans, some of which are not available via existing methodologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

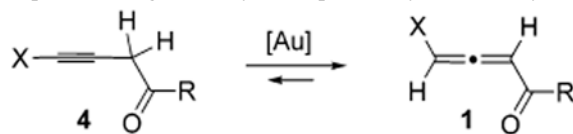
Acknowledgments

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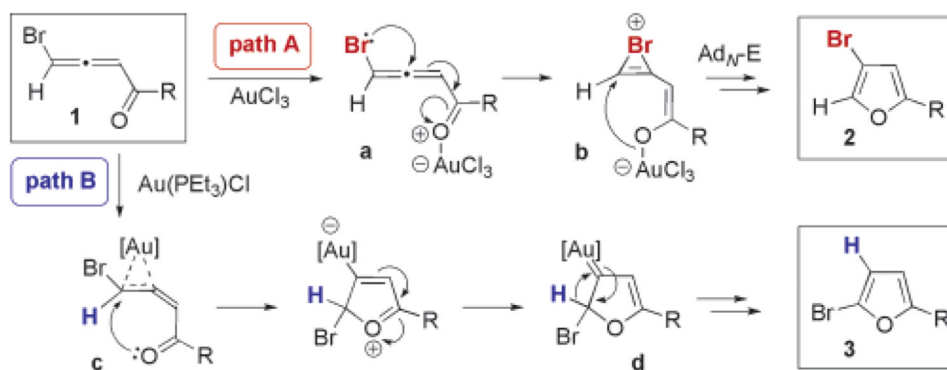
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9. Bromoallene **1a** contained trace to notable amounts of bromopropargyl ketone **4a**, from which it was obtained. Under reaction conditions, **4** underwent rapid isomerization to **1**. The same applies to iodoallene **1i** (see Table 2). Facile propargyl–allenyl isomerization of propargyl ketones in the presence of gold catalyst was previously observed by Hashmi; see ref 12c.



10. See Supporting Information for details.
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16. Decrease in regioselectivity of deuterium versus bromine migration is explained by the isotope effect analogous to that observed by Hashmi in the Pd-catalyzed cycloisomerization of allenyl ketones. See: Hashmi ASK, Ruppert TL, Knöfel T, Bats JW. *J Org Chem.* 1997; 62:7295. [PubMed: 11671843]
17. Apparently, rapid AuCl₃-catalyzed propargyl–allenyl isomerization (see ref 9) is responsible for partial incorporation of deuterium in position 3 of **d-2k** (4 for **d-3k**).

18. Much more sluggish reaction of **1j** is in accordance with decreased ability of the Cl atom to form halirenium species **b** (Scheme 1).



Scheme 1. Proposed Pathways for the Synthesis of Halofurans 2 and 3

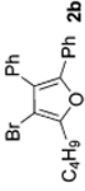
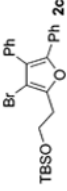
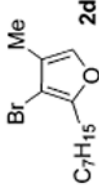
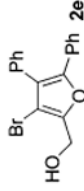
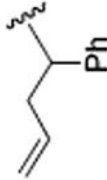
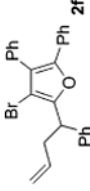
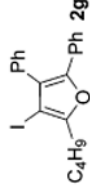
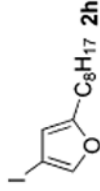
Table 1
Optimization of Au-Catalyzed Synthesis of Halofurans

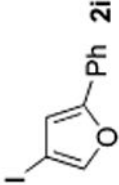
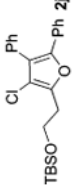
entry	catalyst (1–2 mol %)	solvent (1 M)	<i>T</i> (°C)	2:3 ^a
1	AuCl ₃	toluene	rt	95:5
2	AuCl ₃	toluene	0	88:12
3	AuCl ₃	toluene	40	97:3
4	AuCl ₃	toluene	50	98:2
5	AuCl ₃	toluene	70	98:2
6	AuCl ₃	THF	rt	5:95
7	Au(PPh ₃)Cl	toluene	rt	16:84
8	Au(PEt ₃)Cl	toluene	rt	<1:99

^aGC ratios.

Table 2

Au-Catalyzed Synthesis of Halofurans

#	R ¹	R ²	R ³	X	Time	Product	Yield, % ^a
1	C ₄ H ₉	Ph	Ph	Br	1 day		75%
2	(CH ₂) ₂ OTBS	Ph	Ph	Br	1 day		73%
3	C ₇ H ₁₅	Me	H	Br	1 hr		73%
4	CH ₂ OH	Ph	Ph	Br	1 day		61%
5		Ph	Ph	Br	0.5 hr		88%
6	C ₄ H ₉	Ph	Ph	I	3 days		73%
7	H	H	C ₈ H ₁₇	I	5 min		97%

#	R ¹	R ²	R ³	X	Time	Product	Yield, % ^a
8 ^b	H	H	Ph	I	1 hr		71%
9	(CH ₂) ₂ OTBS	Ph	Ph	Cl	3 days		48%

^a Isolated yield.

^b A 7:1 mixture of **1i** and **4i** was employed.⁹