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Furan Synthesis

Metal-Catalyzed [1,2]-Alkyl Shift in Allenyl Ketones: Synthesis of Multisubstituted Furans**

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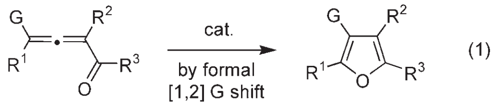
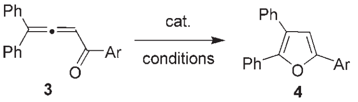
Cycloisomerization of allenyl ketones is an efficient approach for the assembly of the furan ring, an important heterocyclic unit.[1] This transformation in the presence of transition-metal catalysts was first reported by Marshall et al.[2] and later by Hashmi et al.[3] for the synthesis of furans [G = H, Eq. (1)]. Recently, we have developed a set of transition-metal-catalyzed cascade transformations of allenyl ketones involving 1,2-migration of various groups (G = SR,[4] Hal,[5] $OP(O)(OR)_2$, OC(O)R, OSO_2R[6]) to produce up to tetrasubstituted furans [Eq. (1)]. Herein, we wish to report a novel metal-catalyzed [1,2]-alkyl shift in allenyl ketones as a key step in the formation of up to fully carbon-substituted furans [Eq. (1)].



Marshall (G = H, cat. = Ag)
Hashmi (G = H, cat. = Pd, Au)
Gevorgyan (G = SR, Hal, $OP(O)(OR)_2$, OC(O)R, OSO_2R',
cat. = Cu, Ag, Au)
this work (G = Alk, Ar)

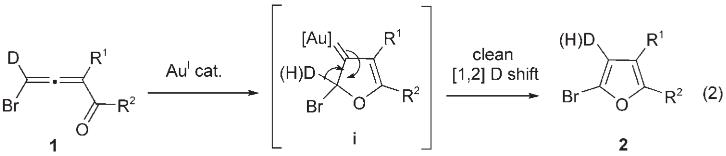
Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst[b]	mol %	Solvent	T [°C]	Yield [%][c]
1	$AuBr_3$	5	toluene[d]	100	23
2	AuI	5	toluene[d]	100	traces
3	$[Au(PPh_3)]OTf$	1	toluene[d]	100	100 (89)
4	$[Au(PPh_3)]OTf$	5	CH_2Cl_2[e]	RT	99
5	$PtCl_2$	5	toluene[f]	100	21
6	$PtCl_4$	5	toluene[f]	100	21
7	$[PdCl_2(PhCN)_2]$	5	toluene[f]	100	35
8	CuX (X = Cl, Br, I)	5	toluene[f]	100	0
9	CuOTf·PhH	5	toluene[f]	100	42
10	$Cu(OTf)_2$	5	toluene[g]	100	95
11	$AgPF_6$	5	toluene[g]	100	47
12	AgOTf	5	toluene[g]	100	(80)
13	AgOTf	20	CH_2Cl_2[e]	RT	70 (62)
14	$Al(OTf)_3$	5	toluene[g]	100	64
15	$Zn(OTf)_2$	5	toluene[g]	100	39
16	TMSOTf	20	CH_2Cl_2[e]	RT	82 (62)
17	$In(OTf)_3$	5	toluene[g]	100	91 (81)
18	$Sn(OTf)_2$	5	toluene[g]	100	97 (81)
19	TIPSOTf	5	toluene[g]	100	100 (81)
20	$TMSNTf_2$	5	toluene[g]	100	72

[a] Entries 1–4: Ar = p-Br-C_6H_4; entries 5–20: Ar = Ph. [b] Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl. [c] Yield determined from NMR spectrum; yield of isolated product in parentheses. [d] 0.05 M solution of **3**. [e] 0.02 M solution of **3**. [f] 1 M solution of **3**. [g] 0.1 M solution of **3**.

Recently, we reported the Au-catalyzed regiodivergent synthesis of halofurans.[5] It was found that in the presence of Au^I catalysts clean hydrogen migration from **1** occurs to form **2** [Eq. (2)]. The absence of H/D-scrambling, in contrast to that observed in the Cu/base-assisted synthesis of pyrroles,[7] supported the clean [1,2]-hydrogen shift to the carbenoid center in intermediate **i**.[5]



It occurred to us that 1,2-migration of an alkyl/aryl group by this mechanism is also feasible,[8–11] which may allow for the assembly of fully carbon-substituted furans. To this end, we have tested the possible cycloisomerization of allene **3** to give furan **4** in the presence of different catalysts (Table 1). We have found that employment of Au^I and Au^{III} halides gave low yields of furan **4** (Table 1, entries 1 and 2). Gratifyingly, switching to cationic Au^I complexes led to formation of **4k** in nearly quantitative yield (Table 1, entries 3 and 4). In analogy to gold halides, Pt^{II}, Pt^{IV}, and Pd^{II} salts were inefficient in this reaction (Table 1, entries 5–7). Use of Cu^I halides resulted in no reaction (Table 1, entry 8), while employment of cationic Ag^I, Cu^I, and Cu^{II} salts produced **4** in moderate to high yields (Table 1, entries 9–13). Encouraged by these results, we also tested main-group metals in this reaction. Surprisingly, Al, Si, Sn, and In triflates provided moderate to excellent yields of desired furan **4** (Table 1,

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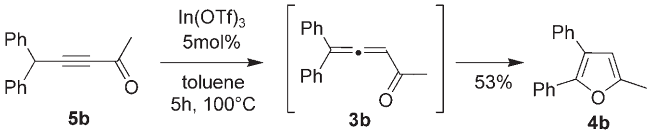
entries 14, 16–19). Although [Au(PPh$_3$)]OTf, AgOTf, In(OTf)$_3$, Sn(OTf)$_2$, and TIPSOTf were nearly equally efficient in the cascade cycloisomerization of **3** to give **4**, In(OTf)$_3$ appeared to be a more general catalyst with respect to the substrate scope.[12]

Next, cycloisomerization of differently substituted allenyl ketones **3a**–**m** was examined under the optimized conditions (Table 2). Thus, cycloisomerization of 4,4-diphenyl-substituted allenyl ketones **3b**–**d** proceeded smoothly to provide good to high yields of furans **4b**–**d** (Table 2, entries 2–4). Selective migration of the phenyl over the methyl group occurred in allenyl ketone **3e** to give **4e** in 72% yield (Table 2, entry 5). Not surprisingly, cycloisomerization of allenyl ketone **3i**, possessing two methyl groups, provided the corresponding furan **4i** in low yield only (Table 2, entry 8). In contrast to the disfavored methyl-group migration in Table 2, entry 5, migration of the ethyl group competed with the phenyl group in **3f**, which resulted in formation of a 2.3:1 mixture of regioisomeric furans **4f** and **4g**, respectively (Table 2, entry 6). Cyclopentylidene allenyl ketone **3h** underwent smooth cyclization with ring expansion[13] to give fused furan **4h** in 75% yield (Table 2, entry 7). It was also demonstrated that a variety of functional groups such as methoxy (Table 2, entry 9), bromo (Table 2, entry 10), nitro (Table 2, entry 11), and cyano (Table 2, entry 12) were perfectly tolerated under these reaction conditions.

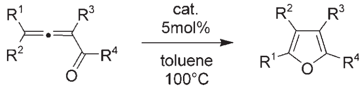
In addition, we have shown that trisubstituted furan **4b** can be obtained directly from alkynyl ketone **5b** [Eq. (3)]. However, the yield for this one-pot transformation was somewhat lower than that for cycloisomerization of allene **3b** (Table 2, entry 2).

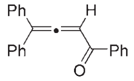
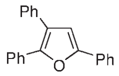
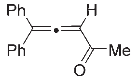
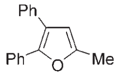
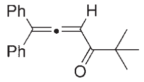
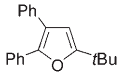
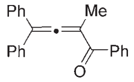
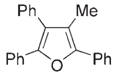
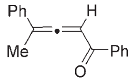
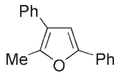
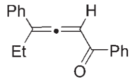
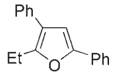
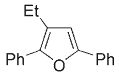
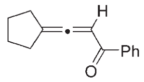
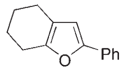
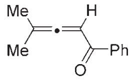
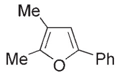
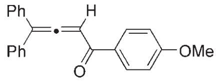
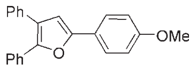
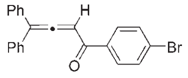
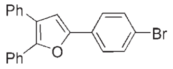
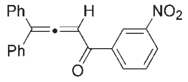
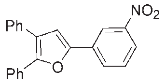
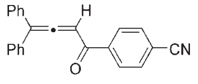
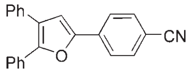


5b **3b** **4b** (3)

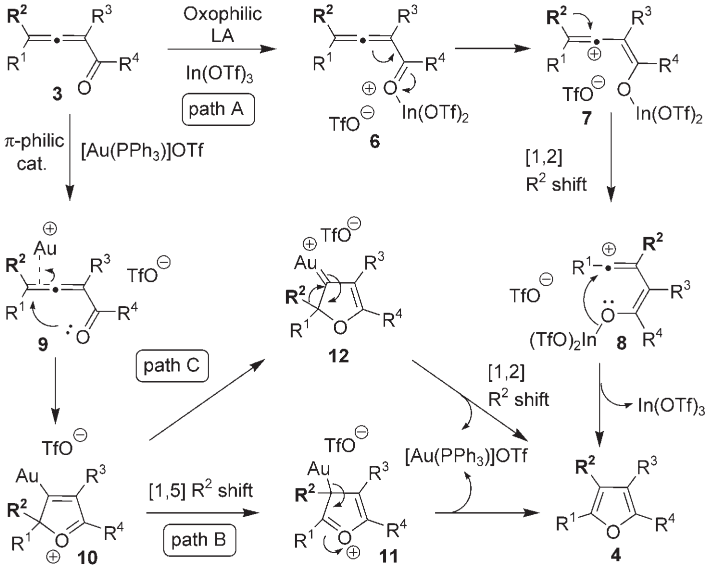
We propose the following mechanism for the cascade transformation of allenyl ketone **3** into furan **4** (Scheme 1). Cycloisomerization in the presence of oxophilic Lewis acids, such as In, Sn, and Si triflates, follows path A, according to which, the Lewis acid activates the enone moiety (see **6**) to form vinyl cation **7**.[14] [1,2]-Alkyl shift in **7** produces the regioisomeric vinyl cation **8**,[15] which, upon cyclization, transforms into furan **4** and regenerates the Lewis acid catalyst. Alternatively, π-philic catalysts, such as $\mathrm{Ag^I}$, $\mathrm{Cu^I}$, and $\mathrm{Au^I}$ salts, activate the carbon–carbon double bond of allene (see **9**) and trigger nucleophilic attack of a carbonyl oxygen lone pair at the terminal carbon of the allene moiety to form cyclic oxonium intermediate **10**.[2c,5] [1,5]-Alkyl shift[16] (Scheme 1, path B) to form **11** with subsequent elimination of metal gives **4**. The involvement of an electro-

Table 2: Lewis acid catalyzed synthesis of furans.



Entry	Allenyl ketone		Furan		Yield [%][a]
1		**3a**		**4a**	81[b]
2		**3b**		**4b**	64[c]
3		**3c**		**4c**	90
4		**3d**		**4d**	79[d]
5		**3e**		**4e**	72 (52)[e,f]
6		**3f**	 	**4f** **4g**	88[g] (76)[h,f,i]
7		**3h**		**4h**	75
8		**3i**		**4i**	10[f]
9		**3j**		**4j**	62
10		**3k**		**4k**	93 (89)[h]
11		**3l**		**4l**	85[b]
12		**3m**		**4m**	94[b]

[a] Yield of isolated product; 0.25–0.8-mmol scale, In(OTf)$_3$ was used unless otherwise mentioned. [b] 5 mol% Sn(OTf)$_2$ was used. [c] 10 mol% In(OTf)$_3$ was used. [d] 20 mol% AgOTf/*p*-xylene, 140°C, 1 h. [e] 2 mol% [Au(PPh$_3$)]OTf was used. [f] Yield determined from NMR spectrum. [g] 2.3:1 mixture of **4f**:**4g** by ^{1}H NMR spectroscopy. [h] 1 mol% [Au(PPh$_3$)]OTf was used. [i] 2.2:1 mixture of **4f**:**4g** by ^{1}H NMR spectroscopy.



Scheme 1. Proposed mechanisms for the synthesis of furans **4**.

philic mechanism (Scheme 1, paths A and B) is supported by the data presented in Table 2. Thus, the migratory aptitude of a phenyl vs. that of a methyl group (> 100:1) is in good agreement with that reported in the literature for rearrangements of cations.[17] Although a mechanism involving [1,2]-alkyl shift in the carbenoid intermediate **12**[5,8] (Scheme 1, path C) cannot be completely ruled out at this point, it is considered to be less likely.[18,19]

In summary, we have developed a novel metal-catalyzed method for the synthesis of furans, which proceeds by an unprecedented [1,2]-alkyl shift in allenyl ketones. This method allows for efficient synthesis of up to fully carbon-substituted and fused furans.

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Keywords: allenyl ketones · furans · gold · Lewis acids · rearrangment

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[11] For a synthesis of dehydrofuranones by [1,2]-alkyl shift, analogous to a formal ketol rearrangement, see: S. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem.* **2006**, *118*, 6010; *Angew. Chem. Int. Ed.* **2006**, *45*, 5878, and references therein.
[12] See the Supporting Information for details.
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[19] No cyclopropanation product was observed in the cycloisomerization of dimethylallenyl ketone **3i**; however, this transformation was reported as a major process in the cycloisomerization of a carbocyclic analogue of **12**. See Ref. [9a].