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Nazarov Reactions

Silver and Brønsted Acid Catalyzed Nazarov-Type Cyclizations To Generate Benzofulvenes[**]

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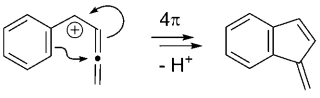
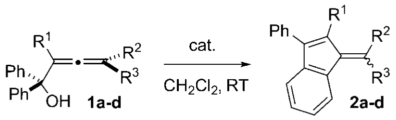
Benzofulvenes are valuable compounds that have found various applications in organometallic chemistry as precursors of indenyl ligands,[1] and in materials science.[2] Their preparations traditionally rely on the transformation of indane[1a] or indanone derivatives.[2c] Nevertheless, a few methods based on the direct formation of the benzofulvene framework from mono or acyclic precursors have been described.[3] The exocyclic double bond of benzofulvenes may also be introduced directly using allenes or higher cumulenes.[4]

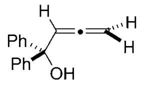
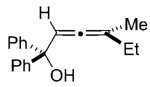
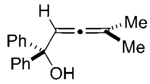
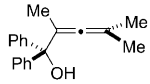
The allenic version of the 4π electrocyclization of arylprop-2-ene-1-yl cations by a Nazarov-type reaction,[5] that is, the transformation of arylbuta-2,3-dienyl cations, would provide a direct route to benzofulvenes (Scheme 1).[6] Early attempts to generate the latter from α-allenyl benzyl alcohols using stoichiometric $HgBr_2$ showed the feasibility of this approach,[7] although competitive allene activation toward nucleophilic attack of the alcohol functionality to give 2,5-dihydrofurans could not be avoided.[8] More recently, specific examples of a domino 4π electrocyclization/Friedel–Crafts reaction using stoichiometric TsOH at elevated temperatures were reported.[9] We describe herein the first catalytic version of the title transformation.



Scheme 1. Nazarov pathway to benzo-fused products.

Table 1: Optimization of the reaction conditions.



Entry	Allene	Cat., mol%	Product	*t* [h]	Yield [%][a]
1	 **1a**	$ZnCl_2$, 200[b]	**2a**	24	77
2	 **1b**	$ZnCl_2$, 200[b]	**2b**	2	42 (45)[c]
3	**1b**	$Zn(OTf)_2$, 3	**2b**	6	65 (45)[c]
4	**1b**	$Cu(OTf)_2$, 4	**2b**	6	50 (45)[c]
5	**1b**	AgOTf, 2	**2b**	1	72 (45)[c]
6	**1b**	TfOH, 10	**2b**	6	74 (15)[c]
7	 **1c**	$ZnCl_2$, 200[b]	**2c**	2	37[d]
8	**1c**	AgOTf, 0.5	**2c**	3	92
9	**1c**	AgOTf, 1	**2c**	0.5	92
10	**1c**	TfOH, 10	**2c**	1	80
11	**1c**	$H_3PMo_{12}O_{40}$, 1	**2c**	1	90
12	**1c**	$AuClPPh_3$, $AgSbF_6$, 2	**2c**	1	85
13	**1c**	$AuCl_3$, 3	**2c**	12	38[e]
14	 **1d**	AgOTf, 1	**2d**	1	92

[a] Yields of isolated products. [b] Et_2O used instead of CH_2Cl_2. [c] Diastereomeric excess given in parentheses (*E*/*Z* isomers not determined). [d] The oxa-cyclized furan was isolated in 18% yield. [e] The oxa-cyclized furan was isolated in 8% yield.

We started our investigation on a substrate of type **1** exhibiting a monosubstituted allene framework (Table 1, **1a**).[10] Complex reaction mixtures or decomposition ensued when using AgOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, or TfOH. Nevertheless the desired product **2a** was isolated from a reaction employing two equivalents of zinc chloride for 24 hours at room temperature in diethyl ether (Table 1, entry 1). The reaction was much faster when the substituents R^2 and R^3 were not hydrogen atoms. Whereas an excess of $ZnCl_2$ delivered the expected benzofulvene in moderate yield after two hours (Table 1, entry 2), $Zn(OTf)_2$ (3 mol%) afforded the product in 65% yield upon isolation (Table 1, entry 3).[11] The use of $Cu(OTf)_2$ was also suitable, but less efficient (Table 1, entry 4). Excellent results were obtained with AgOTf (Table 1, entries 5, 8, and 9)[12] and TfOH (Table 1, entries 6 and 10).

Triflic acid could advantageously be replaced by phosphomolybdic acid (PMA),[13] with a reduced loading of 1 mol% (Table 1, entry 11). Gold(I) proved slightly less efficient (Table 1, entry 12) than AgOTf or PMA, whereas

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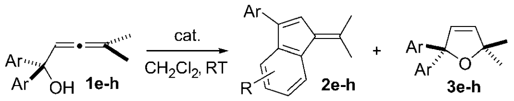
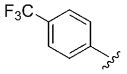
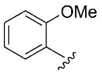
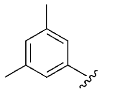
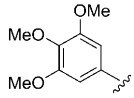
gold(III) worked sluggishly and also generated the oxacyclized by-product (Table 1, entry 13). Lastly, by using AgOTf, a substrate displaying a tetrasubstituted allene moiety could also be selectively and efficiently transformed into the desired product despite considerable steric strain (Table 1, entry 14).

We noticed that the replacement of one phenyl group by a methyl group at the carbon atom (C1) bearing an OH group led to a mixture of products. Therefore we decided to use quaternary alcohols having two aryl groups at C1 and to focus on AgOTf, TfOH, and PMA for the study of the substrate scope (Table 2). The reaction leads to aryl-substituted benzofulvenes which could potentially feature atropisomerism.

Table 2: α-Hydroxyallenes displaying two identical aryl groups at C1.



Entry	Allene	Ar	Cat., mol%	t [h]	Desired product	**2/3**[a]	Yield [%][b]
1	**1e**		AgOTf, 1	1	**2e**	1:1.21[c]	77
2	**1e**		$H_3PMo_{12}O_{40}$, 1	1	**2e**	–	84
3	**1f** (R = OMe)		AgOTf, 10	48	**2f** (R = OMe)	2.4:1[c]	57
4	**1f** (R = OMe)		$H_3PMo_{12}O_{40}$, 4	24	**2f** (R = OMe)	–	46
5	**1f** (R = OMe)		TfOH, 50	0.16	**2f** (R = OMe)	–	72
6[d]	**1f′** (R = OEt)		AgOTf, 40	48	**2f′** (R = OEt)	–	55
7	**1g**		AgOTf, 1	1	**2g**	–	90
8	**1h**		AgOTf, 3	1	**2h**	–	80

[a] Ratio determined by NMR spectroscopy. For cases in which no ratio is reported, product **3** was not observed. [b] Yields of isolated product. Except for entries 1 and 3 where the yield is given for the combined mixture. [c] The products were separated by flash chromatography on silica gel. [d] The ethoxy ether was used instead of the alcohol.

The introduction of *para*-trifluoromethyl substituents to the aryl groups resulted in the formation of the corresponding 2,5-dihydrofuran **3e** in addition to **2e** when using AgOTf (Table 2, entry 1).[14] The formation of the 2,5-dihydrofuran was suppressed by carrying out the reaction using PMA, wherein **2e** was isolated in 84% yield after a reaction time of one hour at room temperature (Table 2, entry 2). The same feature was observed with *ortho*-methoxy groups (Table 2, entries 3 and 4), although a prolonged reaction time (48 and 24 hours, respectively) and a higher catalyst loading (10 and 4 mol%, respectively) were required. Only the use of 50 mol% of TfOH allowed a decrease in the reaction time to 10 minutes (Table 2, entry 5). Notably, the substitution of the OH group by OEt also prevented the formation of the furan, even when using the more carbophilic AgOTf (Table 2, entry 6). Lastly, fast and efficient reactions took place when 3,5-dimethyl (Table 2, entry 7) and 3,4,5-dimethoxy substituents (Table 2, entry 8) were present on the aryl rings.

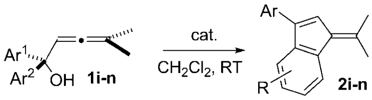
Overall, these results suggest that the electronic properties of the aryl groups have little impact on the formation of the intermediate dienyl cation and its electrocyclization. However, steric demand at the *ortho* position delays the reaction unless a higher concentration of dissociated protons is involved (excess TfOH). Therefore, *ortho* substituents might impede the approach of the large Lewis or undissociated Brønsted acids and therefore the dealkoxylation step. This slowing of the reaction was additionally ascertained while studying the cyclization of α-hydroxyallenes bearing two different aryl groups (Table 3).

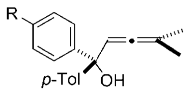
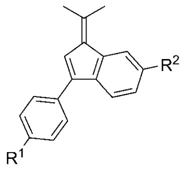
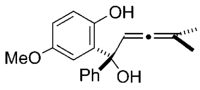
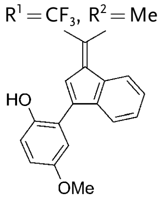
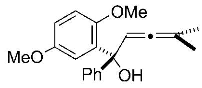
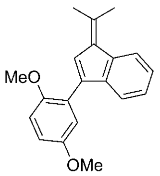
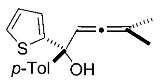
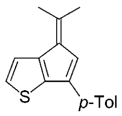
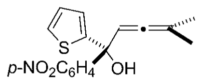
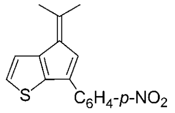
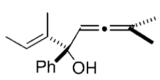
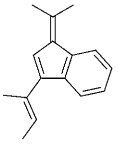
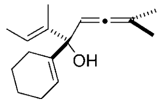
A clear trend could not be observed with *para*-substituted aryl groups displaying donor or acceptor substituents, thereby confirming that electronic effects were not very important (Table 3, entries 1 and 2). The conversion was complete within one hour by using 1 mol% of AgOTf in both cases; no furan was formed and products **2i** and **2j** were isolated in high yields as a regioisomeric mixture. In the next series, unsubstituted and *ortho*-substituted benzenes were investigated (Table 3, entries 3–6). As noted earlier, the reaction rate was dramatically lowered, unless excess TfOH was employed. The formation of benzofulvenes proved regioselective at the unsubstituted benzene ring in each case. Therefore, it appears that *ortho* substituents also slow down the electrocyclization, resulting in a highly regioselective cyclization.

In the next step of our investigation, thiophene was used as an aryl group along with an electron-rich (Table 3, entry 7) and electron-poor (Table 3, entry 9) *para*-substituted benzene ring. As expected, fast reactions took place with both AgOTf and PMA, regardless of the substitution pattern. The electrocyclization proceeded regioselectively at the 3-thienyl position.[15] This result is in good agreement with a conrotatory 4π electrocyclization pathway. Indeed, computations at the MP2/6-31G(d) level of theory[16] revealed that the corresponding transition state involving a phenyl group lies 1.6 kcal mol^{-1} higher in free energy than the one in which the 3-thienyl moiety is implicated (see the Supporting Information for details).

Lastly, we introduced alkenyl groups into the substrates to investigate if simple fulvenes could be formed. The (*Z*)-2-butenyl substituent was first used along with a phenyl substituent (Table 3, entry 10). The reaction was found to be completely regioselective at the phenyl group. The (*Z*)-2-

Table 3: α-Hydroxyallenes displaying two different groups at C1.



Entry	Allene	Cat., mol%	*t* [h]	Product	Yield [%][b]
					
1	**1i**: R = OMe	AgOTf, 1	1	**2i**: R^1 = Me, R^2 = OMe and R^1 = OMe, R^2 = Me (1.4:1)[a]	90[c]
2	**1j**: R = CF_3	AgOTf, 1	1	**2j**: R^1 = Me, R^2 = CF_3 and R^1 = CF_3, R^2 = Me (1.3:1)[a]	88[c]
3					
	1k	AgOTf, 2	30	**2k**	79[d]
4	**1k**	TfOH, 50	0.16	**2k**	61
					
5	**1l**	AgOTf, 5	48	**2l**	62
6	**1l**	$H_3PMo_{12}O_{40}$, 4	24	**2l**	66
					
7	**1m**	AgOTf, 1	2	**2m**	66
8	**1m**	$H_3PMo_{12}O_{40}$, 1	1	**2m**	62
					
9	**1n**	AgOTf, 1	2	**2n**	50
10					
	1o	AgOTf, 1	1	**2o**	82
					
11	**1p**	AgOTf, 1	1	degradation	
12	**1p**	$H_3PMo_{12}O_{40}$, 1	1	degradation	

[a] Ratio of the isomeric products that were isolated. [b] Yields of isolated products. [c] Isomers were not separable so the yield represents the combined yields of the isolated isomers. [d] Product was contaminated by 38% of furan as determined by NMR spectroscopy.

butenyl substituent was then used along with a cyclohexenyl substituent (Table 3, entries 11 and 12). However, in these cases, only complex mixtures of unidentified products were obtained.

In conclusion we have developed a general method for the preparation of benzofulvenes from diaryl α-hydroxyallenes under catalytic reaction conditions. When using a monosubstituted allene framework, $ZnCl_2$ proved to be a superior catalyst, whereas in the other cases (di- or tetrasubstituted allenes), AgOTf, TfOH, and PMA gave the best results. When two phenyl groups were present, the regioselectivity could be controlled by *ortho* substituents. The thienyl group also proved more reactive than phenyl groups. These results are consistent with a catalytic 4π electrocyclization pathway, potentially delivering benzofulvene-based ligands. Of particular interest will be the preparation of axially chiral aryl benzofulvene derivatives.

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