Dual Functionalization of Allene: Facile Construction of Heteropolycycles Mediated by Brønsted Acid

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A facile construction of a heteropolycyclic framework is developed by exploiting the dual functionalization of allene. On treatment of phenethyl alcohol or amine bearing a terminal allene with the Brønsted acid, two consecutive reactions to allene, nucleophilic addition of heteroatom and the Friedel–Crafts reaction, occurred to give 2-oxa- or azabicyclo[2.2.2]octane skeleton.

Tetrahydrofuran and pyrrolidine are ubiquitous skeletons found in many naturally occurring and biologically active compounds. Because of this, considerable effort has been directed toward the construction of these structures.¹ The intramolecular addition of an X-H bond to a C=C bond, namely, hydroalkoxylation and hydroamination, is the most straightforward and atom-economical method. Although scattered examples of the transition metal-catalyzed hydroalkoxylation and hydroamination of alkene have been reported recently,² the addition reaction with unactivated alkene is difficult to accomplish due to the low reactivity of the alkene. In contrast, allene is more reactive than alkene due to the strained nature of the cumulated C=C bond.³ For this reason, the transition metal-catalyzed hydrofunctionalization of allenes has been investigated as a means to circumvent some of the difficulties associated with catalytic alkene functionalization.⁴ The Brønsted acid-catalyzed version, however, remains elusive.⁵ In this communication, we wish to report the functionalization of allenes induced by a Brønsted acid. Interestingly, in this process, hydrofunctionalization and the Friedel-Crafts reaction occurred successively to afford heteropolycycles (dual functionalization of allene).

Phenethyl alcohol **2** was chosen as the substrate for cyclization for two reasons (eq 1): 1) easy preparation from commercially available **1** in three steps^{4d} and 2) high propensity for cyclization due to the "Thorpe–Ingold Effect."⁶



With the requisite substrate in hand, the cyclization was performed: a solution of **2** in toluene was exposed to several strong Brønsted acids (20 mol %, Table 1). On treatment with CSA, no other products were obtained even in refluxing toluene (Entry 1). TFA was also ineffective (Entry 2). In the case of TsOH+H₂O, the starting material was almost completely consumed. Surprisingly, the resulting product was not tetrahydrofuran **3** but unexpected polycyclic product **4** (39%, Entry 3), whose structure was confirmed by single-crystal X-ray analysis (Figure 1).⁷ In this case, a small amount of naphthalene **5** was also obtained (14%). After several experiments, we found that TfOH was the

Table 1. Examination of reaction conditions

Ph Ph 2 Acid (20 conditional conditional c		mol%) Ph Ph + Ph - 3		0 + Ph 4		Ĺ	5	
Entry	Acid	Solvent	Temp/°C	Time/h	<u>}</u>	ield	/%	
					3	4	5	
1	CSA	toluene	reflux	4		—	—	
2	TFA	toluene	reflux	9	—		—	
3	TsOH•H ₂ O	toluene	reflux	5		39	14	
4	TfOH	toluene	60	3		56	trace	
5	TfOH	CH_2Cl_2	reflux	5		80	trace	
6 ^a	TfOH	$CH_2Cl_2 \\$	reflux	4		64	trace	

^a10 mol % acid was employed.



Figure 1. X-ray structure of 4. Hydrogen atoms are omitted for clarity.



Scheme 1. Plausible mechanism.

most effective, giving **4** exclusively (56%). Gratifyingly, when CH_2Cl_2 was used instead of toluene, the chemical yield of **3** was dramatically improved (80%). Decreasing the catalyst load to 10 mol % lowered the chemical yield (64%, Entry 6).

Scheme 1 illustrates a plausible mechanism of this reaction. At first, the nucleophilic addition of oxygen atom to vinyl cation

 Table 2. Examination of reaction conditions using phenethylamine derivative as starting material

Ph Ph TiOH (x mol%) Ph Ph Ph TiOH (x mol%) CH ₂ Cl ₂ conditions									
8a			9a	10					
Entry	$x/\mathrm{mol}\%$	Temn/°C	Time/h -	Yield/%					
Linu y		remp/ c		9a	10	8 a			
1	20	reflux	18	17	52	23			
2	50	reflux	3	30	35				
3	150	reflux	2	58	5	—			
4	150	0°C	3	68	8	6			

A,⁸ generated by the protonation of terminal allene, occurred to give vinyl ether **B**. The generation of oxonium cation **C** and the subsequent the Friedel–Crafts reaction of the internal phenyl group furnished polycycle **4** (path I). Thus, two reactions (nucle-ophilic addition of heteroatom and the Friedel–Crafts reaction) to allene occurred successively in one reaction vessel (dual functionalization of allene). Another reaction pathway, the Friedel–Crafts reaction sequence (path II), may be operative.

To confirm the actual reaction pathway, we conducted the following reaction: a solution of corresponding methyl ether **6** in CH₂Cl₂ was exposed to TfOH (20 mol %). The Friedel–Crafts product (dihydronaphthalene) **7** was obtained in 24% yield. However, starting material **6** was not consumed completely (61% recovery) even over prolonged reaction time (21 h, cf. 5 h, Entry 5, Table 1). These data suggest that both pathways (I and II) are operative in this reaction, with path I being predominant.⁹

Next, we examined the formation of isoquinoline polycycle **9** from phenethylamine **8** (Table 2), which was prepared in a manner similar to that using alcohol **2**.^{4e} First, the reaction was conducted with the above optimized conditions (20 mol % TfOH in refluxing CH₂Cl₂). Desired product **9a** was obtained in a low yield (17%), accompanied by a substantial amount of by-product (the Friedel–Crafts product) **10** (52%, Entry 1). The large catalyst load was crucial to this reaction, i.e., the employment of 50 mol % catalyst afforded **9a** in 30% yield (Entry 2). In the case of 150 mol % catalyst load, the chemical yield was raised to 58% (Entry 3). Gratifyingly, when the reaction was conducted at 0 °C, **9a** was obtained in good yield (68%, Entry 4).

The electron density of the internal phenyl group had a remarkable influence on the chemical yield of **9** (Scheme 2).^{10,11} Tolyl-substituted **8b** gave **9b** in moderate yield (61%). On the other hand, 7-chloro-substituted isoquinoline **9c** was obtained in only 26% yield. Due to the poor nucleophilicity of the chlorosubstituted phenyl group, active iminium species **H**, generated by the nucleophilic addition of nitrogen atom to allene followed by protonation, presumably reacted with some other nucleophile (the most likely one was H₂O in CH₂Cl₂), giving several byproducts.¹¹

In summary, we have developed a new method for the construction of a polycyclic framework via the dual functionalization of allene. This method is applicable to both oxygen- and



Scheme 2. Substituent effect of internal phenyl group.

nitrogen-containing heterocycles. Further study on related reactions is underway.

References and Notes

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- 8 In a formal sense, the formation of allylic carbocation intermediate by protonation of the center carbon overwhelms that of vinyl cation. However, kinetically favored protonation furnishes the vinyl cation intermediate. This result could be explained by stereoelectronic factors. Because the allene structure is nonplanar, an initial protonation of the center carbon leads to a twisted structure that avoids allylic conjugation. See: a) K. B. Wiberg, C. M. Breneman, T. J. LePage, J. Am. Chem. Soc. 1990, 112, 61. b) A. Gobbi, G. Frenking, J. Am. Chem. Soc. 1994, 116, 9275.
- 9 Naphthalene 5 was formed by olefin isomerization from intermediate F followed by dehydrative 1,2-phenyl migration.
- 10 The preparation of corresponding starting materials (**8b** and **8c**) is described in Supporting Information.
- 11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.