Catalytic Cyclization of Alkenyl *N*,*O*-Acetals by $Fe(OTf)_3$

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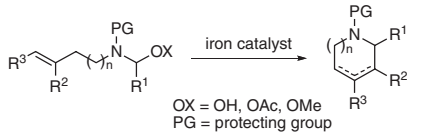
$Fe(OTf)_3$, was found to be a good catalyst for the cyclization of alkenyl *N*,*O*-acetals to give various nitrogen-containing heterocycles in high yields.

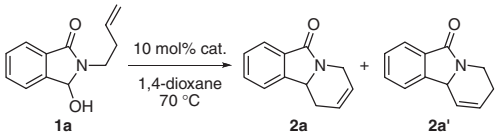
Nitrogen-containing heterocycles are widely distributed in nature and a lot of these compounds display important biological and pharmaceutical activities. Although the heterocycles have been prepared by various methods,[1] development of more efficient and convenient approaches to the synthesis of the functionalized heterocycles under mild conditions is still desired. For the sophisticated procedure, *N*-acyliminium ion is a useful synthetic intermediate due to its highly electrophilic character, which allows the intramolecular addition of various σ- and π-nucleophiles to afford numerous heterocycles.[2] However, there is no catalytic example of iminium ion cyclization. Herein, we would like to report a catalytic cyclization of alkenyl *N*,*O*-acetals by $Fe(OTf)_3$ to provide an easy access to nitrogen-containing heterocycles (eq 1).



(1)

We first investigated catalytic activities of various transition-metal complexes and Brønsted acid in the cyclization of 2-(but-3-enyl)-3-hydroxyisoindolin-1-one (**1a**) as a model substrate (Table 1). Treatment of **1a** with 10 mol % of $Sc(OTf)_3$ afforded the azacyclohexene **2a** and its isomer **2a′** in 24 and 8% yields, respectively (Entry 1). Although $Sc(OTf)_3$ showed a good mass balance, the reaction was not catalytic even with additional stirring due to a loss of activity. Similar phenomena were observed with $AlCl_3$ and $BF_3 \cdot OEt_2$ catalysts. With TfOH, CuOTf, and $Cu(OTf)_2$ catalysts, most of **1a** was consumed without decreasing the catalyst activity, but a low mass balance was found because of oligomerization of **1a** (Entries 2–4). In strong contrast, AgOTf did not initiate the reaction (Entry 5). $PdCl_2$ afforded a complex mixture (Entry 6). Use of $PtCl_2$ caused olefin isomerization of **1a** to give a mixture of (*E*)-and (*Z*)-2-(but-2-enyl)-3-hydroxyisoindolin-1-one in 28% yield without cyclization (Entry 7). Further screening revealed that employment of $Fe(OTf)_3$ catalyst improved the product yield to 73% NMR yield (Entry 8), from which the pure product was obtained by column chromatography in 63% yield with the same isomer ratio (**2a**:**2a′** = 76:24). Other iron triflates, $Fe(OTf)_2$, and $CpFe(CO)_2OTf$ were also effective for the cyclization, but they needed longer reaction time to complete the reaction (Entries 9 and 10). Similar catalytic activity was observed by $Bi(OTf)_3$ (Entry 11). 1,4-Dioxane, 1,2-dichloroethane, and 1,2-dimethoxyethane were suitable solvents, whereas toluene decreased the reaction rate.[3]

Table 1. Screening of catalyst



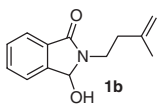
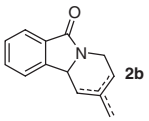
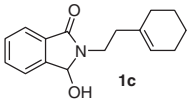
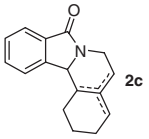
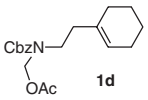
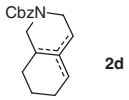
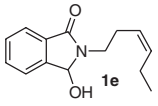
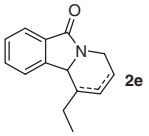
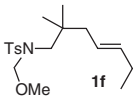
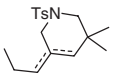
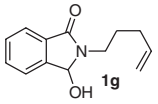
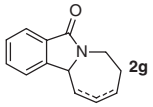
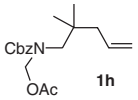
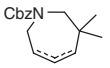
Entry	Catalyst	Time/h	Total yield/%[a] [**2a**/**2a′**][a]	Conv./%[a]
1	$Sc(OTf)_3$	3	32 [75/25]	34
2	TfOH	3	46 [72/28]	96
3	$Cu(OTf)_2$	3	36 [86/14]	62
4	$(CuOTf)_2 \cdot C_6H_6$	48	35 [77/23]	79
5	AgOTf	3	0 [—]	3
6	$PdCl_2$	3	0 [—]	96
7	$PtCl_2$	8	0 [—]	92[b]
8	$Fe(OTf)_3$	3	73 [77/23]	100
9	$Fe(OTf)_2$	27	68 [81/19]	92
10	$CpFe(CO)_2OTf$	27	71 [80/20]	100
11	$Bi(OTf)_3$	3	70 [76/24]	100

[a]Determined by NMR. [b]Olefin isomerization occured.

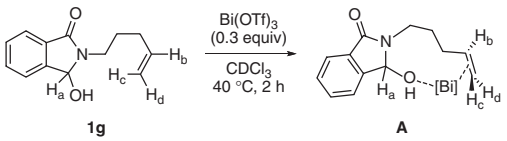
With optimal conditions in hand, the cyclization of several alkenyl *N*,*O*-acetals was investigated as summarized in Table 2.[4] 2,2-Disubstituted olefin was a good coupling partner for the *N*,*O*-acetal moiety, giving rise to heterocycles **2b** as a mixture of three regioisomers in 94% yield, even at room temperature (Entry 1).[5] Similarly, high reactivity was observed in the case of 1,2,2-trisubstituted substrates, **1c** and **1d** (Entries 2 and 3). Acyclic *N*,*O*-acetal function also participated in the cyclization (Entry 3). The cyclization of internal olefins such as **1e** and **1f** favored the formation of azacyclohexenes, and thus, neither the 5-membered ring from **1e** nor the 7-membered one from **1f** was detected (Entries 4 and 5). In contrast, cyclization of *N*,*O*-acetal with a terminal 4-pentenyl moiety such as **1g** and **1h** constructed only azacycloheptene skeletons in good yields (Entries 6 and 7).[6]

For several plausible mechanisms in the cyclization, the iminium ion could be a key intermediate because its generation has been well known to occur the α-fragmentation of *N*,*O*-acetal with typical Lewis acid other than iron.[7] However, useful iminium ion generators such as $BF_3 \cdot OEt_2$, $Sc(OTf)_3$, and TfOH did not display high catalytic performance in the present cyclization. To gain further information of the iron-catalyzed mechanism, a reaction of alkenyl *N*,*O*-acetals **1g** and $Bi(OTf)_3$ (0.3 equiv), which possesses similar catalytic activity to the iron and is diamagnetic, was monitored by ^{1}H NMR (Scheme 1 and Figure S1[10]). An acetal proton (H_a) of the alkenyl *N*,*O*-acetal **1g** appeared at 5.72 ppm as a doublet signal (J = 11.9 Hz) in the absence of the catalyst. In contrast, treatment of **1g** with $Bi(OTf)_3$ resulted in a disappearance of the coupling between H_a and O*H*, and low-field shifts of H_a as well as all olefinic protons

Table 2. $Fe(OTf)_3$-catalyzed cyclization of alkenyl *N*,*O*-acetals **1**

Entry	Substrate	Time/h	Product	Yield/%[a]
1[b]	 **1b**	2	 **2b**	94
2[b]	 **1c**	1	 **2c**	94
3[b]	 **1d**	1	 **2d**	97
4[c]	 **1e**	6	 **2e**	84
5[b]	 **1f**	15	 **2f**	90
6[c]	 **1g**	20	 **2g**	84
7[b]	 **1h**	3	 **2h**	79

[a]Isolated yield. [b]25 °C. [c]70 °C.

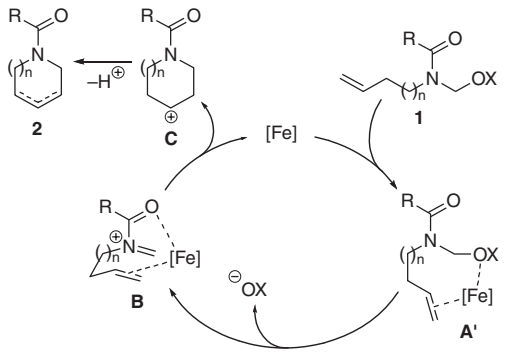


Scheme 1.

(H_b, H_c, and H_d),[8] in which **2g** was formed in 19% yield. The spectra may suggest the formation of σ- and π-chelated intermediate **A** during the present cyclization.[9]

Based on these results, we propose a mechanism for the iron-catalyzed cyclization of alkenyl *N*,*O*-acetals **1** in Scheme 2. First, cationic iron would dually coordinate to the hydroxy group and the olefin of **1**, leading to the intermediate **A′**, in which the two reaction-sites could be brought together as shown in Scheme 1. Subsequent cyclization of **A′** takes place readily through electron transfer from the olefin to the generated iminium ion function of **B** to afford the carbocation **C**. The species could spontaneously liberate a proton to yield the corresponding azacycloalkenes **2**.

In conclusion, we have demonstrated the first catalytic cyclization of alkenyl *N*,*O*-acetals by $Fe(OTf)_3$ to give azacycloalkenes in high yields. High catalyst activity of the iron could be caused by its dual coordination to both hydroxy group and olefin, which brings two reaction-sites together, and facilitates electron transfer from the olefin to the iminium ion moiety, preventing side-reactions. Synthetic application of the cyclization is under investigation.



Scheme 2. Plausible reaction mechanism.

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References and Notes

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3 Solvent effect in Entry 8 (Table I): 1,4-dioxane (73%, 3 h); 1,2-dichloroethane (67%, 7 h); 1,2-dimethoxyethane (52%, 3 h); toluene (42%, 48 h).

4 General procedure: Alkenyl *N*,*O*-acetal **1** (0.44 mmol) and $Fe(OTf)_3$ (10 mol %) in dry 1,4-dioxane (4.4 mL) were stirred at 25 or 70 °C under N_2. After completion of the reaction, the resulting mixture was passed through a short silica gel column with ether eluent, and then concentrated. The crude product was purified by column chromatography on silica gel with EtOAc–hexane (50/50) eluent to afford the azacycloalkene **2**.

5 A ratio of the three isomers **2b** was 60:24:16, judged by ^{1}H, ^{13}C NMR, and GC-MS. However, it was difficult to determine the exact position of the olefinic moiety, because they were not separable. A similar situation was encountered in other heterocycles **2c**–**2h**.

6 In the case of acyclic *N*,*O*-acetals with terminal olefin like **1h**, combination of *N*-protecting group and living one was important to avoid dealkylation providing secondary amine.[10]

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10 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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