

Catalytic Cyclization of Alkenyl *N,O*-Acetals by Fe(OTf)₃

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(Received May 13, 2009; CL-090470; E-mail: kkome@hiroshima-u.ac.jp)

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).



We first investigated catalytic activities of various transition-metal complexes and Brønsted acid in the cyclization of 2-(but-3-enyl)-3-hydroxyisindolin-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 AlCl₃ and BF₃·OEt₂ 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). PdCl₂ afforded a complex mixture (Entry 6). Use of PtCl₂ caused olefin isomerization of **1a** to give a mixture of (*E*)- and (*Z*)-2-(but-2-enyl)-3-hydroxyisindolin-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)₂-OTf 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	(Cu(OTf) ₂ ·C ₆ H 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) ₂ OTf	27	71 [80/20]	100
11	Bi(OTf) ₃	3	70 [76/24]	100

^aDetermined by NMR. ^bOlefin isomerization occurred.

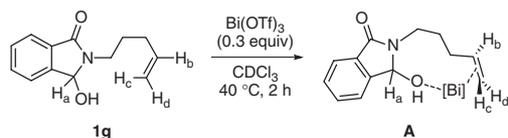
With optimal conditions in hand, the cyclization of several alkenyl *N,O*-acetals was investigated as summarized in Table 2.⁴ 2,2-Disubstituted olefin was a good coupling partner for the *N,O*-acetal moiety, giving rise to heterocycles **2b** as a mixture of three regioisomers in 94% yield, even at room 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 BF₃·OEt₂, 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 ¹H NMR (Scheme 1 and Figure S1¹⁰). 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 OH, 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		2		94
2 ^b		1		94
3 ^b		1		97
4 ^c		6		84
5 ^b		15		90
6 ^c		20		84
7 ^b		3		79

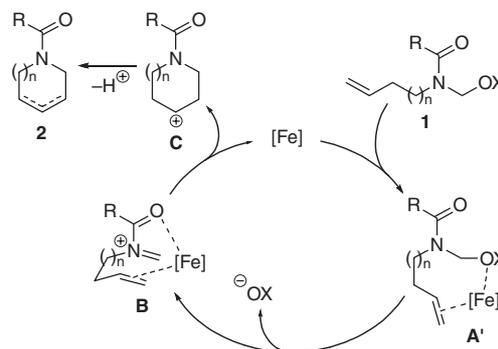
^aIsolated yield. ^b25 °C. ^c70 °C.

**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 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, pre-

**Scheme 2.** Plausible reaction mechanism.

venting side-reactions. Synthetic application of the cyclization is under investigation.

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. K.K. acknowledges financial support from Electronic Technology Research Foundation of Chugoku.

References and Notes

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- 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).
- 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 N₂. 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**.
- A ratio of the three isomers **2b** was 60:24:16, judged by ¹H, ¹³C 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**.
- 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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