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Cationic iron-catalyzed intramolecular hydroalkoxylation of unactivated olefins

Kimihiro Komeyama,* Takayuki Morimoto, Yuushou Nakayama and Ken Takaki*

Department of Chemistry and Chemical Engineering, Graduate School of Engineering, Hiroshima University, Kagamiyama, Higashi-Hiroshima 739-8527, Japan

Abstract—Cationic iron complexes are effective catalysts for intramolecular hydroalkoxylation for unactivated olefins under mild conditions to form the corresponding cyclic ethers in excellent yield.
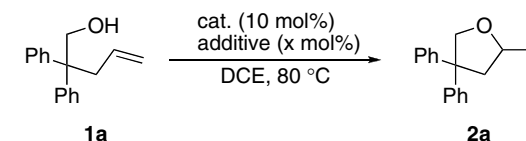© 2007 Elsevier Ltd. All rights reserved.

The importance of heterofunctionalization of unactivated olefins has been widely recognized in the field of synthesis of natural products and much effort has been made towards the exploitation of this methodology.[1] Of the recently developed processes, metal-catalyzed heteroatom–carbon bond construction is a powerful tool in this area; for instance, expensive Au, Ag, Pt, Ir, and Ru catalysts, efficiently coordinate carbon–carbon multiple bonds like alkynes,[2] diene,[3] and allenes,[4] to lead to the corresponding adducts in good yields. However, their reactivity for the olefin moiety is low; thus, high temperature and long reaction time are necessary for the transformation to proceed.[5] On the other hand, we have recently demonstrated that iron salts were good catalysts for intramolecular hydroamination of unactivated olefins to provide *N*-heterocyclic compounds in excellent yield under mild conditions.[6] With regard to the actual role of the iron in the reaction, there was a possibility to generate Brønsted acid, particular HCl, from the iron salt. Although, the reaction did not proceed by means of the acid, the possibility has not been completely ruled out so far. Therefore, the present system was tried out for intramolecular hydroalkoxylation of unactivated olefins to elucidate this point. Consequently, iron salts were found to exhibit a catalyst activity that was superior to the activity of Brønsted acids. We report herein these details.

Treatment of γ-hydroxyolefin **1a** with 10 mol % of FeCl$_3$·6H$_2$O in DCE (0.1 M) for 70 min at 80 °C under

nitrogen afforded 2-methyl-4,4-diphenyltetrahydrofuran (**2a**) in 91% yield, whereas several dehydrated products[7] were also given in the reaction (Table 1, entry 1). Similar dehydration was observed using other iron (II) and (III) chlorides (entries 2 and 3) and Brønsted acids (entries 11 and 12). In strong contrast, a cationic iron complex Fe(OTf)$_3$, which was conveniently prepared from the treatment of FeCl$_3$ and AgOTf with separating out AgCl,[8] could completely depress the formation of the

Table 1. Screening of catalysts for intramolecular hydroalkoxylation of **1a**

Entry	Catalyst	Additive (x)	Time	Yield[a] (%)
1[b]	FeCl$_3$·6H$_2$O	None	70 min	91
2[b]	FeCl$_3$	None	70 min	96
3[b]	FeCl$_2$·4H$_2$O	None	70 min	50
4	FeCl$_3$	AgOTf (30)	30 min	Quant
5	FeCl$_3$	AgClO$_4$ (30)	70 min	93
6	FeCl$_3$	AgBF$_4$ (30)	13 h	70
7	FeCl$_2$·4H$_2$O	AgOTf (20)	30 min	94
8	FeCl$_2$·4H$_2$O	AgClO$_4$ (20)	70 min	Quant
9	FeCl$_2$·4H$_2$O	AgBF$_4$ (20)	18 h	0
10	AgOTf[c]	None	30 min	8
11[b]	HCl	None	70 min	56
12[b]	TfOH	None	30 min	90

[a] Determined by ^{1}H NMR.
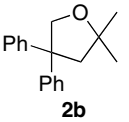[b] Small amounts (ca. 5%) of dehydrated byproducts were obtained.
[c] 30 mol % of catalyst was used.
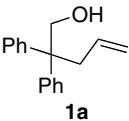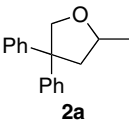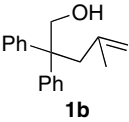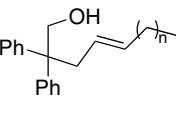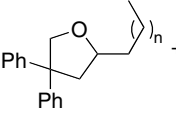
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* Corresponding authors. E-mail: kkome@hiroshima-u.ac.jp

dehydrated products to give **2a** in quantitative yield (entry 4). Moreover, the cationic complex was greatly superior to iron chloride in the reaction without the formation of dehydrate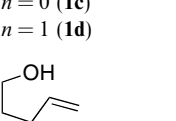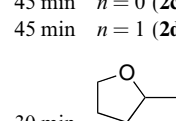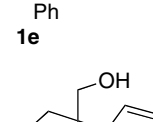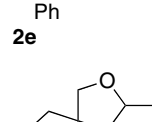s. In this context, the reactivity of the cationic iron complexes increased in the order: $^-BF_4 < {}^-ClO_4 < {}^-OTf$ as counter anions. The same trend was observed in the case of divalent iron species (entries 7–9). AgOTf was of low activity in comparison to the present catalyst system (entry 10).[5b] Favorable solvents were non-polar ones like DCM, hexane, and toluene, whereas polar solvents such as 2-propanol, DMF, DMSO, and acetonitrile were disfavored in this reaction.

Next, the catalyst system could be extended to be the synthesis of a diverse set of cyclic ethers (Table 2).[9] In the present system, it was easy for the hydroxy group to take part in the heterofunctionalization of internal olefins, leading to tetrahydrofuran derivatives as major product in good yields (entries 3 and 4). Moreover, the presence of useful functions: acetate, pivaloate, and benzoate, was permitted in the reaction, but the addition led to low stereoselectivity (entries 5–9).

**Table 2.** Intramolecular hydroalkoxylation of unactivated olefins[a]

Entry	Substrate	Time	Product	Yield[b] (%)
1	**1a**	30 min	**2a**	97
2	**1b**	30 min	**2b**	94
3	$n = 0$ (**1c**)	45 min	$n = 0$ (**2c**)	94 [11:1]
4	$n = 1$ (**1d**)	45 min	$n = 1$ (**2d**)	95 [10:1]
5	**1e**	30 min	**2e**	95 (3:1)
6	R = H (**1f**)	4 h	R = H (**2f**)	97 (1.2:1)
7	R = Ac (**1g**)	2 h	R = Ac (**2g**)	94 (1.4:1)
8	R = Piv (**1h**)	4 h	R = Piv (**2h**)	97 (1.1:1)
9	R = Bz (**1i**)	3 h	R = Bz (**2i**)	96 (1.2:1)

[a] Reaction conditions: hydroxyolefin (0.5 mmol), FeCl₃ (10 mol %), AgOTf (30 mol %), DCE (5 mL), 80 °C.

[b] Isolated yield. The value in parenthesis indicated [regioisomeric] and (stereoisomeric) ratios, respectively.

To evaluate the actual role of the cationic iron species for the heterofunctionalization, especially, whether the iron participated in olefin activation or not, we compared the present reaction with a Brønsted acid-catalyzed reaction (Scheme 1). Reaction of 2,2,5-triphenylpent-4-en-1-ol (**1j**) with 10 mol % of the cationic iron complex at 80 °C for 45 min gave only 6-*endo*-trig cyclized product **3j** in 76% yield.[10] In strong contrast, exposure of **1j** to a solution of triflic acid (10 mol %) in DCE effected the dehydrative isomerization and the subsequent Friedel–Crafts cyclization to produce bicyclic compound **4** in quantitative yield.[11] These results could indicate that the reaction processes of the present catalyst and that of Brønsted acid were different. Thus, in the former case the iron metal center might not only coordinate with the hydroxy group but also the olefinic orbital, as shown in **A**. In contrast, in the latter case proton should initially interact with only the electron-rich hydroxy group, as depicted in **B**, to induce the dehydration. On the other hand, the participation of a radical process in this media was tested using AIBN (10 mol %) as radical initiator at 80 °C, but no reaction was observed. In addition, the heterofunctionalization of **1a** could complete in the presence of 2,6-di-*tert*-butyl-4-methylphenol (50 mol %), leading to **2a** in 91% yield within 70 min.

Based on these results described above, the reaction process would be explained as depicted in Scheme 2. Coordination of the cationic iron center with both the hydroxy and the olefin moiety would yield a key intermediate **C**. In this step, if the metal center was weakly electron-deficient like FeCl₃, dehydration might proceed to provide by-products due to the inadequate coordination to the olefin. Then, the hydroxy group would attack to iron-activated olefinic carbon to produce intermedi-
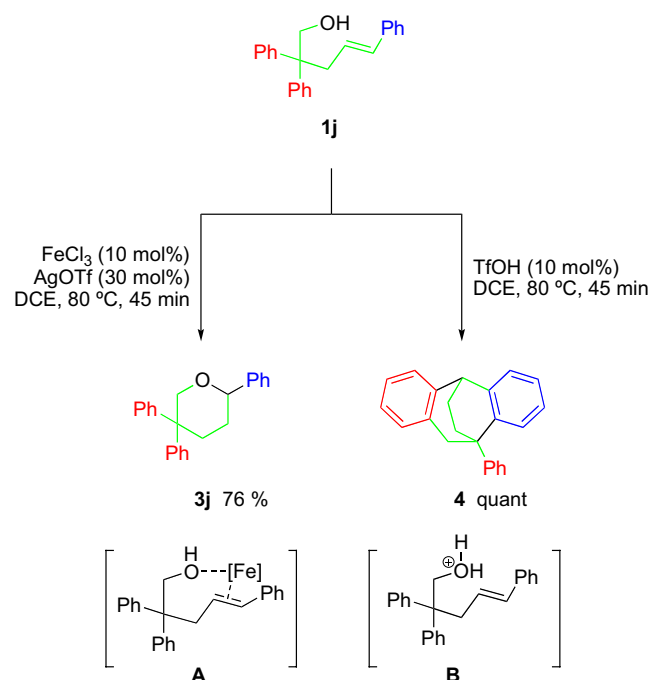
Scheme 1.
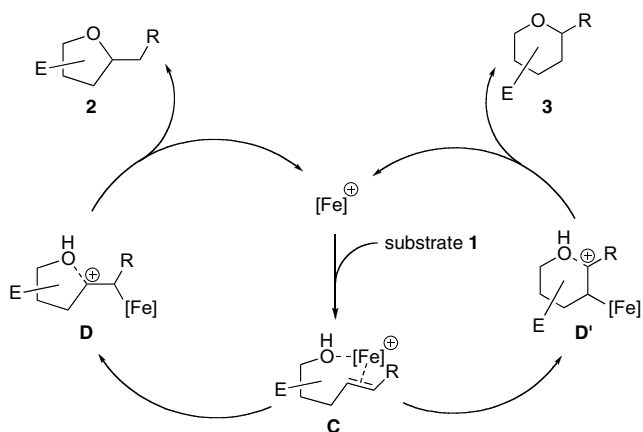
Scheme 2. Plausible reaction mechanism.

ate **D** or **D′** and the subsequent protonation could intramolecularly occur to afford cyclic ether **2** or **3**.

In summary, we have demonstrated a catalytic activity of the cationic iron complexes for intramolecular hydroalkoxylation of unactivated olefins under mild conditions. The reaction system is compatible with many functional groups, giving rise to various types of cyclic ethers. The role of the cationic iron catalysts might be a dual activation of both the hydroxy group and the olefin moiety. The most striking feature is that the environmentally friendly catalysis enables us to readily induce hydroalkoxylation of unactivated olefins, that is hardly attainable under mild conditions. Studies on improvement of the selectivity of products and on details of the reaction mechanism as well as on expansion of the reaction scope are in progress.

Acknowledgement

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7. The dehydrated products were not identified, but we firmly confirmed them by GC–MS analysis and TLC monitoring of the reaction mixture, wherein their Rf values were judged as hydrocarbon.

8. All cationic iron complexes were prepared in situ from the stirring of FeCl$_{2\,or\,3}$ to AgX (X = OTf, ClO$_4$, BF$_4$; 2 or 3 equiv) in DCE for 2 h at room temperature. Similar cationic iron complexes were synthesized in the following report: Britovsek, G. J. P.; England, J.; Spintzmesser, S. K.; White, A. J. P.; Williamson, D. A. *Dalton Trans.* **2005**, 945.

9. *General procedure for hydroalkoxylation* **1**. To cationic iron complex, which was prepared in situ from iron chloride (0.05 mmol) and AgOTf (0.15 mmol) in DCE (2.5 mL) for 2 h at room temperature, was added the solution of hydroxyolefins **1** (0.5 mol) in DCE (2.5 mL) under N$_2$ atmosphere. After heating during suitable time, the reaction mixture was cooled, filtered through a short silica-gel column using hexane/ethyl acetate as an eluent. Separation by column chromatography (silica-gel 60 N, 63–200 μm) using hexane/ethyl acetate solvent afforded products **2**.

10. Similar 6-*endo*-trig cyclization was observed in our previous report; see Ref. 6.

11. **4**: Isolated as a white solid; mp: 120–121 °C; ^{1}H NMR (CDCl$_3$) δ 2.21–2.33 (2H, m), 2.39–2.49 (2H, m), 3.53 (1H, dd, J = 16.7, 2.4 Hz), 3.68 (1H, d, J = 16.7 Hz), 3.97 (1H, t, J = 2.4 Hz), 6.56 (1H, J = 7.7 Hz), 6.98–7.56 (12H, m); ^{13}C NMR (CDCl$_3$) δ 30.5, 35.7, 44.9, 46.0, 47.6, 125.4, 126.0, 126.3, 126.4, 126.5, 126.8, 127.9, 128.1, 131.6, 125.5, 142.2, 143.6, 143.7, 147.9, aromatic two carbons were overlapped; MS *m/s* 296 (M$^+$, 88), 265 (18), 218 (19), 203 (40), 191 (100). Anal. Calcd for C$_{23}$H$_{20}$: C, 93.20; H, 6.80. Found: C, 93.20; H, 6.68.