Synthetic Methods

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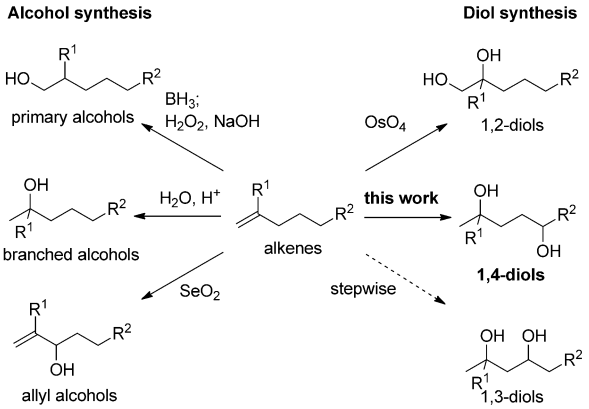
Direct Synthesis of 1,4-Diols from Alkenes by Iron-Catalyzed Aerobic Hydration and C–H Hydroxylation**

*Takuma Hashimoto, Daisuke Hirose, and Tsuyoshi Taniguchi**

Abstract: *Various 1,4-diols are easily accessible from alkenes through iron-catalyzed aerobic hydration. The reaction system consists of a user-friendly iron phthalocyanine complex, sodium borohydride, and molecular oxygen. Furthermore, the effect of additional ligands on the iron complex was examined for a model reaction. The second hydroxy group is installed by direct C(sp^3)–H oxygenation, which is based on a [1,5] hydrogen shift process of a transient alkoxy radical that is formed by formal hydration of the olefin.*

The development of synthetic methods for introducing hydroxy groups into organic molecules is a fundamental task in organic chemistry because hydroxy groups exist in many useful organic compounds, such as biologically active products and industrial materials.[1] In general, alkenes are chosen as precursors for alcohols because numerous reliable methods for introducing hydroxy groups into alkenes have been established (Scheme 1).[1] For instance, hydroboration and hydration of alkenes are powerful transformations for the preparation of monoalcohols, and these methods complement each other in terms of regioselectivity.[1,2] A hydroformulation–reduction process of alkenes is a new concept for the synthesis of terminal alcohols.[3] Selenium dioxide is often used for selective allylic hydroxylation.[2,4] An osmium tetroxide mediated 1,2-dihydroxylation reaction of alkenes is a reliable method to obtain *cis*-configured 1,2-diols.[1,5,6] In connection with this reaction, epoxidation of alkenes followed by hydration is used to prepare *trans*-1,2-diols.[1] 1,3- or 1,4-diols are compounds that are synthetically as important as 1,2-diols.[7] Although methods for the direct synthesis of 1,3-diols from alkenes have not been established,[8] they can be easily prepared by stepwise methods, for example, by combining an aldol reaction with a reduction process. In contrast, efficient methods that provide short synthetic routes to 1,4-diols have hardly been reported.[9] Therefore, direct dihydroxylation methods for the synthesis of 1,4-diols from simple alkenes are valuable.[10] Herein, we describe the direct 1,4-dihydroxylation of aliphatic alkenes by an iron-catalyzed aerobic formal hydration of olefins and C(sp^3)–H oxidation.



Scheme 1. Methods for the hydroxylation of alkenes.

Oxygenation of unactivated C–H bonds has been one of the main subjects in organic chemistry over the past century.[11] The direct hydroxylation of unactivated C(sp^3)–H bonds is a synthetically attractive method.[12] A number of stoichiometric or catalytic methods for the hydroxylation of hydrocarbons using oxygen sources such as peroxides or hypervalent iodine compounds have been reported, and secondary or tertiary C–H bonds are predominantly oxidized to produce secondary or tertiary alcohols via cationic or radical intermediates.[11] In contrast, the direct hydroxylation of methyl C–H bonds is rare, but transition-metal catalysts that can activate the methyl group enable this transformation with the aid of effective directing groups.[11,12d,e] Some remote functionalization reactions with free radicals can also be described as directed C–H functionalizations because they often involve an intramolecular hydrogen shift of a highly reactive radical species; in a C(sp^3)–H functionalization, this is typically a [1,5] hydrogen shift.[13]

Iron-catalyzed redox hydration reactions of alkenes with hydride reagents and molecular oxygen represent a mild method to introduce a hydroxy group.[14] Radical species presumably participate in the mechanism, and extensions of this reaction to advanced chemical transformations were recently reported.[14c–f] In the course of another investigation of these types of reactions, we noticed that remote C(sp^3)–H oxygenation can occur alongside hydration of an olefin. This observation has been overlooked thus far, and therefore, we designed an experiment using simple alkene **1a** to reveal the

[*] T. Hashimoto, Dr. T. Taniguchi
School of Pharmaceutical Sciences
Institute of Medical, Pharmaceutical and Health Sciences
Kanazawa University
Kakuma-machi, Kanazawa 920-1192 (Japan)
E-mail: tsuyoshi@p.kanazawa-u.ac.jp
D. Hirose
Graduate School of Natural Science and Technology
Kanazawa University
Kakuma-machi, Kanazawa 920-1192 (Japan)

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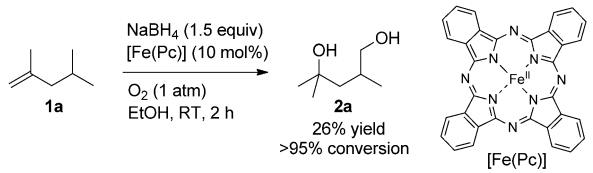
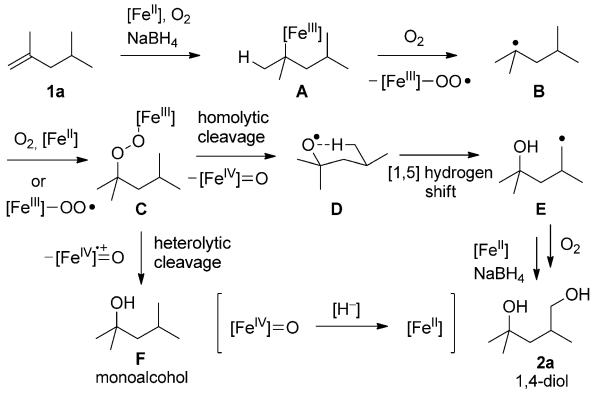
details of this reaction. Treatment of alkene **1a** with a catalytic amount (10 mol%) of iron phthalocyanine [Fe(Pc)] and sodium borohydride ($NaBH_4$; 1.5 equiv) under an oxygen atmosphere in ethanol (0.1M) gave 1,4-diol **2a** in 26% yield (Scheme 2).[15] Although the yield of 1,4-diol **2a** was not adequate at that point, it was clear that this reaction had the following unique and advantageous characteristics: 1) This



Scheme 2. A preliminary experiment on 1,4-dihydroxylation. Yield based on isolated product.

reaction is the first example of a synthesis of 1,4-diols from a simple alkene in one step. 2) Reagents such as iron phthalocyanine and sodium borohydride are inexpensive and convenient, and the use of molecular oxygen as the oxygen source is ideal from economic and environmental viewpoints.[16]

We intended to determine how the yield for the synthesis of 1,4-diol **2a** could be improved by elucidating the reaction mechanism. A putative iron(III) hydride complex, which is generated from iron phthalocyanine and sodium borohydride in the presence of oxygen, might set off the reaction with **1a** to give adduct **A** (Scheme 3).[14] The reaction of organoiron complex **A** with oxygen would generate tertiary-carbon-centered radical **B**, which is followed by formation of iron



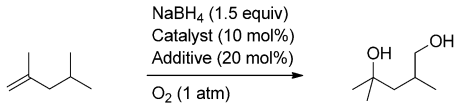
Scheme 3. Mechanistic proposal.

peroxide complex **C**. The formation of radical **B** was supported by mechanistic experiments, which included cyclization reactions of 1,6-dienes[14d] and trapping with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).[18] Alkoxy radical intermediate **D** would be formed by cleavage of the weak O–O bond of complex **C**.[15] If the reaction was terminated at intermediate **C** by heterolytic bond cleavage or reduction, monoalcohol **F** should be formed as the hydration product. Indeed, **F** was detected by GC-MS analysis as the main by-product of the reaction shown in Scheme 2.[17] On the other hand, highly reactive alkoxy radical **D** would undergo a [1,5] hydrogen shift to provide alkyl radical intermediate **E**. This process was supported by a ring-opening reaction of the radical clock substrate 2-methyl-5-(*trans*-2-phenylcyclopropyl)-2-pentene.[18] Finally, 1,4-diol **2a** would be obtained through a pathway that is similar to that for the formation of complex **C** from alkyl radical **B**.[18]

As described above, competitive formation of monoalcohol **F** was likely to result in a diminished yield of diol **2a**. We examined various reaction conditions (catalysts, hydride sources, amount of reagents, solvents, temperature, etc.) to improve the yield of diol **2a**, but none of the attempts led to any improvements.[18] Next, we focused on the pathway to generate alkoxy radical **D** and compound **F** from iron peroxide intermediate **C**. Nam and co-workers reported that the destiny of iron porphyrin peroxide complexes is strongly influenced by the axial ligands on the iron center.[19] In the presence of weak electron donors, such as triflate or perchlorate ions, heterolytic cleavage of the O–O bond of the iron peroxide complex is preferred over homolytic cleavage and leads to the corresponding alkoxide and an oxoiron(IV) cation radical intermediate. On the other hand, strong electron donors, such as alkoxides or a chloride ion, promote the homolytic cleavage of the O–O bond to provide the corresponding alkoxy radical and the oxoiron(IV) complex. Therefore, we hypothesized that the addition of a strongly electron-donating ligand to the reaction system might increase the amount of alkoxy radical **D**, which may then undergo a [1,5] hydrogen shift.

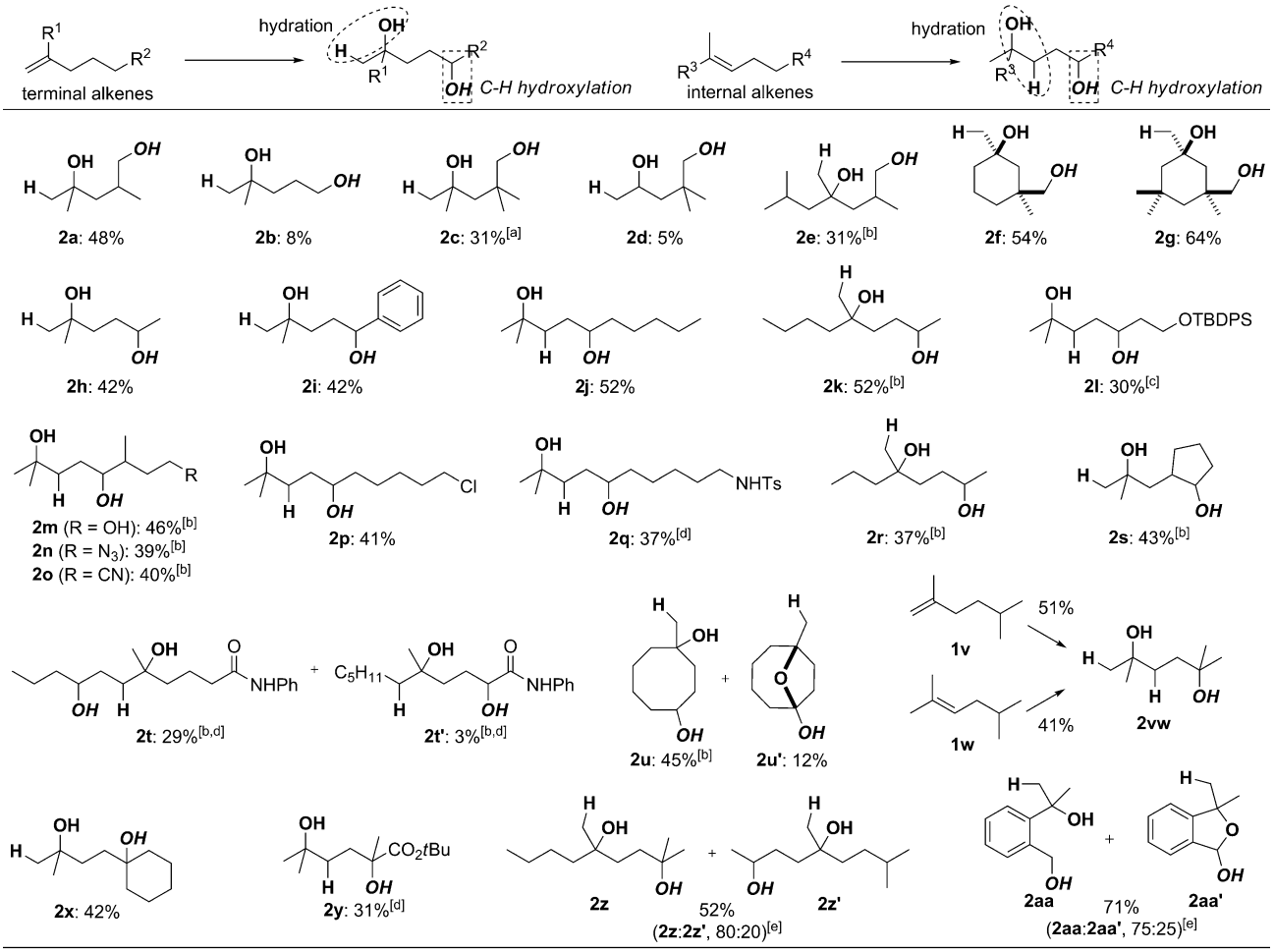
The results of reactions with various additives are shown in Table 1.[18] As the chloride anion is a strong electron donor, a modest, but clear improvement of the yield of diol **2a** was observed when the reaction was conducted in the presence of lithium chloride (20 mol%; entry 2). In contrast, the addition

Table 1: The effect of additives on the transformation.[a]



Entry	Catalyst	Additive	Yield[b] [%]
1	[Fe(Pc)]	–	26
2	[Fe(Pc)]	LiCl	44
3	[Fe(Pc)]	$LiClO_4$	20
4	[Fe(Pc)]	NaOMe	41
5	[Fe(Pc)]	KOAc	38
6	[Fe(Pc)]	imidazole	29
7	[Fe(Pc)]	1-methylimidazole	38
8	[Fe(Pc)]	DMSO	45
9	[Fe(Pc)]	Me_2S	48 (43)[c]
10	[Mn(Pc)]	Me_2S	48
11	[Fe(Tpp)Cl]	Me_2S	51

[a] Reaction conditions: **1a** (0.8 mmol), catalyst (0.08 mmol), $NaBH_4$ (1.2 mmol), additive (0.16 mmol), EtOH (8 mL), O_2 atmosphere (1 atm), 2 h, room temperature. [b] Yield of isolated **2a**. [c] [Fe(Pc)] (5 mol%). DMSO = dimethylsulfoxide, Tpp = tetraphenylporphyrin.



Scheme 4. Synthesis of 1,4-diols from various alkenes. Reaction conditions: Alkene (0.8 mmol), $NaBH_4$ (1.2 mmol), [Fe(Pc)] (0.08 mmol), Me_2S (0.16 mmol), EtOH (8 mL), O_2 atmosphere (1 atm), 2–7 h, room temperature. Yields are based on isolated products. [a] $NaBH_4$ was added in six portions of 0.2 mmol (0.25 equiv) with intervals of 30 min, and the mixture was stirred for further 11 h. [b] A mixture of two diastereomers was obtained. Ratios were estimated by ^{1}H NMR analysis: **2e** (60:40), **2k** (50:50), **2m** (50:50), **2n** (50:50), **2o** (50:50), **2r** (50:50), **2s** (70:30), **2t** (50:50), **2t'** (50:50), **2u** (50:50). [c] 0.2 mmol scale. [d] $NaBH_4$ (2.0 equiv; 1.6 mmol). [e] Estimated by ^{1}H NMR analysis. TBDPS = *tert*-butyldiphenylsilyl, Ts = *p*-toluenesulfonyl.

of lithium perchlorate did not improve the yield of **2a**, as the perchlorate anion only weakly coordinates to the iron complex (entry 3). Similarly, an alkoxy or an acetate ligand worked favorably in the present reaction (entries 4 and 5). This trend is consistent with a report by Nam and co-workers. Encouraged by these results, we examined the use of imidazole and 1-methylimidazole, which are strongly donating amine ligands, but the yields did not improve (entries 6 and 7). On the other hand, sulfur compounds, such as dimethyl sulfoxide and dimethyl sulfide, worked very well, and good yields and reproducibility were observed.[20] Dimethyl sulfide provided the best yield, and its removal is easy because of its volatility. After we tested further additives, such as other halogen, nitrogen, sulfur, phosphine, and carbene compounds,[18] we concluded that the conditions shown in entry 9 are the most suitable for the present reaction, despite the foul smell of the small amount of dimethyl sulfide. Manganese phthalocyanine or iron tetraphenylporphyrin chloride were similarly effective catalysts as iron phthalocyanine (entries 10 and 11), but iron phthalocyanine seemed to be the most suitable catalyst in terms of practicality.[21] These results confirmed the previously suggested effects that axial ligands exert on the iron peroxide complex.

Subsequently, we applied the optimized reaction conditions to several alkenes (Scheme 4). A significant difference in yield was observed for the reactions of branched alkene **1a** and linear alkene **1b** to yield 1,4-diols **2a** and **2b**, respectively. This observation clearly indicates that an entropic effect is predominant in the C–H oxygenation process. On the other hand, the reaction of the more substituted alkene **1c** was somewhat sluggish, and a different procedure was needed to drive the reaction to completion. Furthermore, diol **2c** was isolated in a lower yield than the product of the reaction with **1a**. This result suggests that the C–H oxygenation process passes through a six-membered transition state **D**; an unfavorable 1,3-diaxial repulsion exists between the two axial methyl groups in the transition state from alkene **1c**. Another limitation of the present reaction was revealed by the reaction of the simple terminal alkene **1d**, as diol **2d** was isolated in

low yield. As the corresponding monoalcohol was formed as the major product of this reaction, tertiary peroxide intermediate **C** is likely to be an intermediate for the formation of alkoxy radical **D**. Other 1,4-diols (**2e–g**) were obtained in moderate to good yields by C–H oxygenation of the methyl groups of alkenes **1e–g**. For alkenes **1h–u**, C–H oxygenation occurred on methylene carbon atoms to give diols **2h–u**, which entail secondary hydroxy groups. Interestingly, linear alkenes, such as **1h** and **1i**, were suitable substrates and provided the corresponding diols (**2h** and **2i**) in reasonable yields, whereas alkene **1b** did not. Internal alkene **1j** also underwent aerobic hydration and C–H oxygenation to afford the corresponding diol **2j**.

Many functional groups were tolerated under the present reaction conditions. For instance, when the reaction of **1a** was performed in the presence of 3-iodoanisole, 1-bromododecane, ethyl benzoate, or nitrobenzene, these additives remained intact.[18] The recovery (>90%) of the organohalides might indicate that the reaction does not proceed through an electron transfer process.[14g] Furthermore, the 1,4-diols **2l–q** were obtained from the reactions of the corresponding alkenes **1l–q**, which bear various functional groups. Whereas carbon–carbon double bonds generally reacted with the hydride, carbon–heteroatom multiple bonds, such as an azide or a nitrile, remained intact. In the reaction of **1r**, which bears propyl and butyl groups, methylene C–H oxygenation exclusively yielded the secondary alcohol **2r**, and a primary alcohol was not detected in the crude reaction mixture. The reaction of alkene **1s** to give diol **2s** demonstrated that C–H oxygenation may also occur on a carbon atom that is part of a five-membered ring. Interestingly, during the reaction of internal alkene **1t** (as a ca. 70:30 mixture of geometric isomers) with a simple alkyl chain and an amide moiety, the second hydroxy group was predominantly introduced on the alkyl chain to give 1,4-diol **2t**. This is probably due to the electrophilic nature of the alkoxy radical, which prefers not to abstract a hydrogen atom from the electron-deficient α-position of a carbonyl moiety, so that **2t′** was obtained in low yield. In the reaction of methylenecyclooctane (**1u**), 1,4-diol **2u** and a small amount of hemiacetal **2u′** were obtained, which indicates that C–H oxygenation proceeded in good yield (overall yield: 57%). The formation of **2u′** implies that a minor pathway exists that leads to the formation of a ketone intermediate.[18]

C–H oxygenation of the tertiary carbon atoms in alkenes **1v–y** proceeded to afford 1,4-diols **2vw** (from **1v** and **1w**), **2x**, and **2y**, which bear two tertiary hydroxy groups. The somewhat lower yield of **2y** may be rationalized in the same terms as the diminished yield of the reaction with **1t**. Alkene **1z**, which bears butyl and isopentyl groups, predominantly afforded tertiary alcohol **2z**, along with a small amount of secondary alcohol **2z'** (tentatively identified). Generally, the bond dissociation energies (BDEs) for the homolytic cleavage of C–H bonds tend to decrease with an increase in the number of substituents (primary > secondary > tertiary),[13,22] and the results of the reactions with **1r** and **1z** are consistent with this trend. Therefore, the rate of C–H oxygenation in the present reaction seems to be greatly influenced by the BDE, as is the case for many known C–H functionalization reactions. When 2-(2-methylphenyl)propene (**1aa**) was employed as the substrate, the expected diol **2aa** was isolated along with a small amount of hemiacetal derivative **2aa′** (a similar derivative was also observed for the reaction of **1u**), but the combined yield of the C–H oxygenation products was high. Thus, we succeeded in demonstrating that this reaction is a simple and reliable method to obtain various 1,4-diols from alkenes. As mentioned above (Scheme 3), the corresponding monoalcohols were the main by-products (ca. 20–50%) of the present reaction. Furthermore, the formation of small amounts of other by-products revealed that β-scission reactions of the tertiary alkoxy radicals occurred for several substrates.[23] It is difficult to avoid these side reactions at present. As a tentative solution, we showed that a representative monoalcohol could be easily recycled by its transformation into the corresponding alkene by acid-catalyzed elimination.[18]

In conclusion, we have developed a unique 1,4-hydroxylation reaction of aliphatic alkenes that involves C(sp^3)–H oxygenation. This reaction enabled oxidation of all types of C(sp^3)–H bonds (methyl/primary, methylene/secondary, and tertiary carbon centers) and allowed us to obtain various 1,4-diols from simple alkenes using nontoxic and inexpensive reagents under mild conditions. Molecular oxygen is the source for the two oxygen atoms of the 1,4-diols. Experimental results suggest that a [1,5] hydrogen shift of a radical species occurs as part of the reaction mechanism, and the addition of ligands that strongly coordinate to the iron peroxide intermediate seems to be important to improve the yields for many substrates. This transformation of aliphatic alkenes may be compared to the oxidative metabolism of hydrocarbons by heme iron complexes and molecular oxygen.[24] Our novel approach for the transformation of simple molecules into functionalized compounds shows that an advanced chemical transformation can be realized with a convenient and common reaction system.

Experimental Section

Typical procedure for the synthesis of 1,4-diols from alkenes: Iron phthalocyanine (45.5 mg, 0.08 mmol), dimethylsulfide (10.0 mg, 0.16 mmol), and sodium borohydride (45.4 mg, 1.2 mmol) were added to a solution of 2,4-dimethyl-1-pentene (**1a**; 78.5 mg, 0.8 mmol) in ethanol (8 mL) at room temperature; the mixture was stirred at the same temperature for 2 h under an oxygen atmosphere (balloon). The reaction mixture was filtered, and the solvent was removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1) to give 2,4-dimethylpentane-1,4-diol (**2a**; 50.2 mg, 48%) as a colorless oil. For details, see the Supporting Information.

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[17] The quantity of monoalcohol **F** could not be accurately determined by GC analysis of the reaction mixture because the peak of **F** partially overlapped with peaks of impurities that result from the use of $NaBH_4$. Analysis of the reaction mixture after quenching (with water or acids) gave peaks with poor quality (broad or tailing).

[18] See the Supporting Information for details.

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[20] The reproducibility of the present reaction was tentatively confirmed by running some selected reactions twice; see the Supporting Information.

[21] [Fe(Pc)] [$26.50/1 g (Aldrich), ¥7500/25 g (TCI)] was less expensive than [Fe(Tpp)Cl] [$69.30/500 mg (Aldrich), ¥22 500/500 mg (Wako)] in 2013. Furthermore, impurities of [Fe(Tpp)Cl] often contaminated the product.

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[23] For instance, 1,8-nonanediol (7%) was isolated along with **2u** and **2u′** in the reaction of **1u**. This compound was certainly produced by a β-scission process of the alkoxy radical followed by reduction of the resultant ketone.

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