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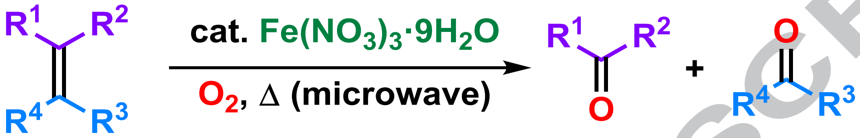

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Iron(III) nitrate-induced aerobic and catalytic oxidative cleavage of olefins

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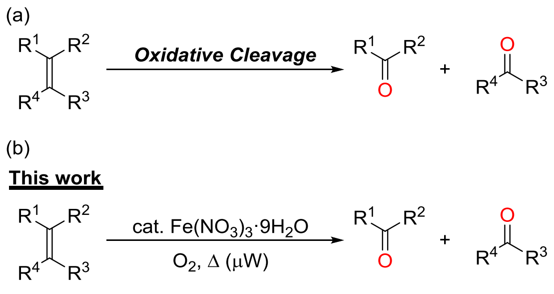
ABSTRACT

Microwave-assisted catalytic oxidative cleavage of olefins using $Fe(NO_3)_3{\cdot}9H_2O$ under O_2 is reported. This reaction system is particularly effective when 9-benzylidene-9*H*-fluorene derivatives are used as substrates even though they are tri- and tetra-substituted olefins.

The oxidative cleavage of olefins to produce carbonyl-containing compounds is a fundamental and important reaction in organic synthesis (Scheme 1a). Harries ozonolysis[2] represents one of the most common methods[1] for this conversion, although it also includes issues regarding explosive properties, toxicity, and the fact that it must be carried out the reaction at low temperatures using special equipment. Therefore, more convenient methods using easily available reagents are needed for this conversion. Catalytic oxidative cleavage using O_2 as a terminal oxidant has attracted interest from the environmental point of view and the fact that the reaction is more benign.[3] Catalysts or activators that have been explored for this purpose include NHPI,[4] TEMPO,[5] AIBN,[6] *t*-BuONO,[7] metal catalysts such as Co,[8] Mn,[8c,9] Pd,[10] Cu,[11] Ni[12] complexes, polyoxometallates (POM)-M-NO_2,[13] Fe(III) bearing a pyridine bisimidazoline ligand,[14] Au nanoparticles,[15] and CAN,[16] and photoredox catalysts or activators such as CBr_4,[17] I_2,[18] porphyrin derivatives,[19] $AcrH^+$,[20] eosin Y,[21] and aromatic disulfides.[22] It has also been reported that biocatalyst[23] undergoes oxidative cleavage using O_2 as a terminal oxidant. In most of these reports, terminal or less-substituted olefins have been used as typical substrates, but there are only limited examples of the aerobic and catalytic oxidative cleavage of tri- and tetra-substituted olefins. Among them, a catalytic system using POM-M-NO_2 is of interest,[13] since the more substituents the starting material contains, the more reactive it is. In this system, NO_2 is thought to play a key role. In this context, we hypothesized that metal nitrates could be used in this reaction, because NO_2 can be generated from them by heating. Here, we report on the catalytic oxidative cleavage of alkenes using $Fe(NO_3)_3{\cdot}9H_2O$ under an atmosphere of O_2 at a temperature of 150 °C (Scheme 1b).[24]

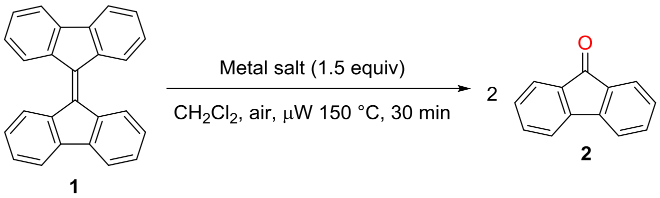
An initial investigation was carried out using 9,9'-bifluorenylidene (**1**) as a tetra-substituted olefin. Table 1 provides information on the screening of metal nitrates. In the presence of 1.5 equivalents of a metal nitrate, **1** was reacted in CH_2Cl_2 at 150 °C (microwave irradiation) under air for 30 min. When $Zn(NO_3)_2{\cdot}6H_2O$ and $Cu(NO_3)_2{\cdot}3H_2O$ were used, the corresponding oxidatively cleaved ketone **2** was obtained in 7 and 46%, respectively (entries 3 and 5) although the use of $NaNO_3$, $AgNO_3$, and $Co(NO_3)_2{\cdot}6H_2O$ did not afford **2** (entries 1, 2 and 4). In this screening, $Fe(NO_3)_3{\cdot}9H_2O$ was clearly the best metal nitrate, with the product **2** being obtained in quantitative yield (entry 6). Instead of microwave heating, a conventional heating condition (oil bath) was performed using toluene as a solvent in a sealed tube. Consequently, the reaction proceeded without any problems to give **2** in 98% yield (entry 7). To check the effect of water contained in $Fe(NO_3)_3{\cdot}9H_2O$, the reaction was carried out in the presence of MS4A. The yield decreased to 77% (entry 8), where the nitrated products of **2** were observed in GC-MS. Product **2** was not produced when other Fe salts such as $FeCl_3$ and $Fe(OAc)_2$ were used (entries 12 and 13). These results suggest that NO_2 is involved in the reaction, because $Fe(NO_3)_3$, when heated, is known to generate three molecules of NO_2.[25] In fact, reducing the amount of $Fe(NO_3)_3$ to 0.5 equivalents did not lower the yield (entry 9). On



Scheme 1. (a) Oxidative cleavage of olefins and (b) This work.

the other hand, decreasing the temperature to 100 °C gave rise to decreasing the yields (entries 10 and 11). These results suggest the involvement of thermally generated NO_2.

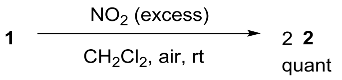
Table 1. Investigation of metal salts for the oxidative cleavage of **1**.



Entry	Metal salts	Yield/ % [a]
1	$NaNO_3$	0
2	$AgNO_3$	0
3	$Zn(NO_3)_2{\cdot}6H_2O$	7
4	$Co(NO_3)_2{\cdot}6H_2O$	0
5	$Cu(NO_3)_2{\cdot}3H_2O$	46
6	$Fe(NO_3)_3{\cdot}9H_2O$	>99
7	$Fe(NO_3)_3{\cdot}9H_2O$ (conventional heating)[b]	98
8	$Fe(NO_3)_3{\cdot}9H_2O$ with MS4A	77
9	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5 equiv)	>99
10	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5 equiv), 120 °C	39
11	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5 equiv), 100 °C	7
12	$FeCl_3$	0
13	$Fe(OAc)_2$	0

[a] Yield was determined by ^{1}H NMR analysis of the reaction mixture based on 1,3,5-tribromobenzene as an internal standard. [b] Toluene was used as a solvent. The reaction was performed in a sealed tube at 150 °C.

The generation of NO_2 was qualitatively confirmed by examining the reaction in the presence of 1,3,5-trimethoxybenzene, which is known to react with even a trace amounts of NO_2 to produce a deep blue solution.[13,26] In order to confirm the involvement of NO_2 in the oxidative cleavage, the substrate **1** was treated with an excess of NO_2 at room temperature (Scheme 2). The product **2** was obtained in quantitative yield, suggesting that NO_2 is active species in this reaction. The dependence of yield on the amount of $Fe(NO_3)_3$ used were investigated by running the reaction under an atmosphere of N_2 (Fig. 1). The relationship was linear, and the use of 80 mol% $Fe(NO_3)_3$ was found to cause a complete reaction. This amount of $Fe(NO_3)_3$ generates 2.4 equivalents of NO_2 to the substrate.



Scheme 2. Oxidative cleavage of **1** by NO_2.

A plausible reaction pathway is shown in the bottom half of Scheme 3a. Two molecules of NO_2 add to the olefin to give the dinitrite compound **3**. The elimination of NO together with carbon-carbon bond cleavage then takes place to result in the production of carbonyl compounds. Transformations of such dinitrite compound to carbonyl compounds at high temperature (260-280 °C) are reported in previous studies.[27] In this scheme, the involvement of an iron species cannot be excluded because other metal nitrates in Table 1 also generate NO_2 at the conditions used. It appears that the reduced NO is re-oxidized with a co-oxidant such as O_2 to regenerate NO_2 to complete the catalytic cycle, as shown in Scheme 3. Actually, this mechanism was confirmed by running the reaction in the presence of 10 mol% $Fe(NO_3)_3$ under O_2, in which the product **3** was obtained in 97% yield (Scheme 3b).

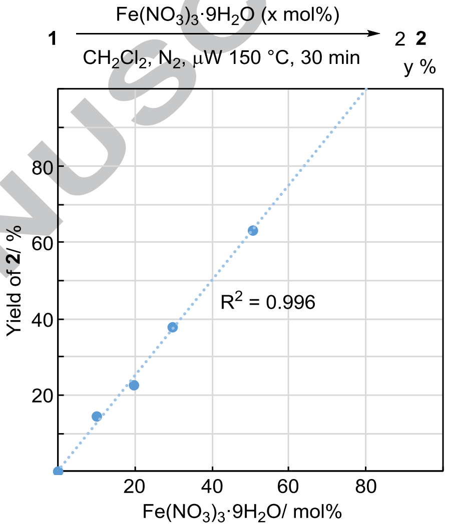
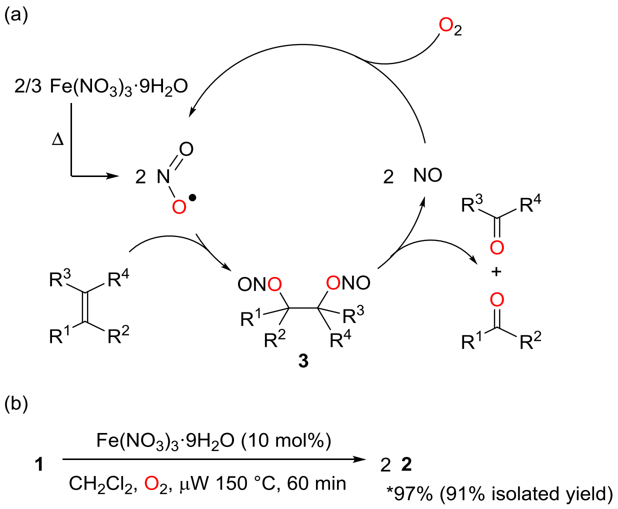


Fig. 1. Dependence of the yield of **2** on the amount of $Fe(NO_3)_3$ under a N_2 atmosphere for oxidative cleavage.

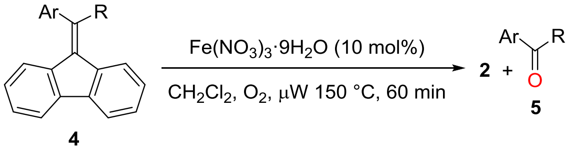


Scheme 3. (a) Plausible catalytic cycle. (b) Oxidative cleavage of **1** with a catalytic amount of $Fe(NO_3)_3{\cdot}9H_2O$ under O_2 at 150 °C. * Yield was determined by ^{1}H NMR analysis of the reaction mixture based on 1,3,5-tribromobenzene as an internal standard.

Table 2 provides information regarding the scope of this catalytic system. Some 9-benzylidene-9*H*-fluorene derivatives

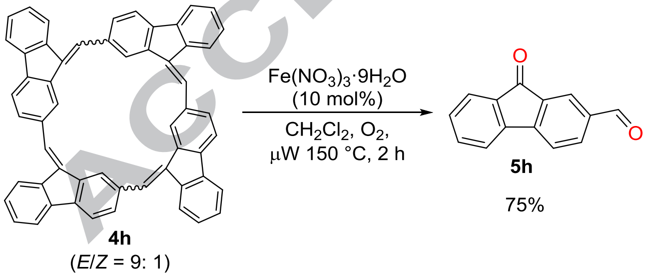
4a-g were initially investigated. The oxidative cleavage of the employed 7 derivatives **4a-g** proceeded to give fluorenone (**2**) in high yields (89-99%, entries 1-7). However, the yield of the simultaneously produced corresponding aldehyde **5** was moderate (**5a**: 50%, **5b**: 63%, **5c**: 78%, **5d**: 79%, **5e**: 78%, and **5f**: 86%, entries 1-6) due to overoxidation.[28] The yield of 1-naphthaldehyde **5g** was particularly low (entry 7). Only a trace amount of the oxidatively cleaved products was obtained from the reaction of diphenyl substituted derivative **4a'** (entry 8). Interestingly, our recently reported macrocycle **4h**[29] bearing four olefin moieties also reacted completely to give the corresponding ketoaldehyde **5h** in 75% yield (Scheme 4).

Table 2. Substrate scope for 9-benzylidene-9*H*-fluorene derivatives **4**



Entry	Ar, R **4**	Yields/ %	
		2	**5a-g**
1	Ph, H **4a**	89[a]	50[a]
2	4-MePh, H **4b**	96[b]	63[b]
3	4-ClPh, H **4c**	95[b]	78[b]
4	4-BrPh, H **4d**	99[b]	79[b]
5	4-MeOPh, H **4e**	97[b]	78[b]
6	4-CF_3Ph, H **4f**	97[b]	86[b]
7	1-naphthyl, H **4g**	98[a]	19[a]
8	Ph, Ph **4a'**	trace	trace

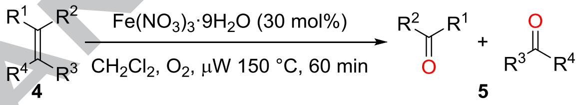
[a] Yields were determined by GC-MS analysis of the reaction mixture based on 1,3,5-tribromobenzene as an internal standard. [b] Yields were determined by ^{1}H NMR analysis of the reaction mixture based on 1,3,5-tribromobenzene as an internal standard.

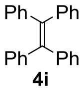
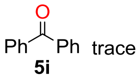
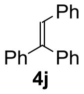
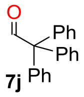
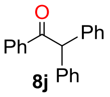
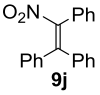
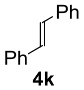
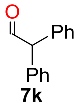
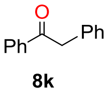
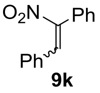
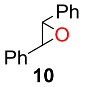
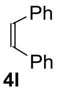
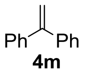
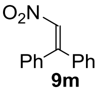
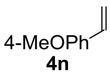
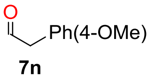
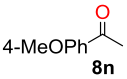


Scheme 4. Oxidative cleavage of macrocycle **4h**.

Phenyl-substituted ethylene compounds were next investigated (Table 3). Because these derivatives showed a lower reactivity compared to 9-benzylidene-9*H*-fluorene derivatives, 30 mol% of $Fe(NO_3)_3\cdot 9H_2O$ was used in these reactions. The use of tetraphenylethene (**4i**) as a tetra-substituted substrate gave only trace amounts of the benzophenone (**5i**) (entry 1). On the other hand, the tri-substituted triphenylethene (**4j**) reacted to give the corresponding product **5i** and benzaldehyde (**5a**) in 68% and 10% yields, respectively (entry 2). In the case of *trans*- and *cis*-stilbene (**4k** and **4l**), **5a** was produced in 32% and 30%, respectively (entries 3 and 6). When 1,1-diphenylethene (**4m**) was used, the yield of **5i** was 34% (entry 7). The use of 4-methoxystyrene (**4n**) gave only trace amounts of the corresponding aldehyde **5e** (entry 8). In the above series, rearranged carbonyl compounds **7** were observed (entries 1-8). A similar rearrangement was observed previously, as exemplified by the reaction of benzhydrylideneadamantane with NO_2 (Scheme S1). In this reaction, an epoxide is first formed, which then undergoes ring opening, followed by the migration of phenyl group to give the rearranged spiroketone (Scheme S1).[30] It is consistent with the results of entries 4 and 5, which are comparing the effect of epoxide. Therefore, such an epoxidation reaction would be expected to compete with the desired oxidative cleavage. In the case of less-hindered fluorenylidene derivatives due to their planar structures, the formation of the dinitrite compound **3** may be dominant rather than epoxidation. Other typical by-products were found to be non-rearranged oxidized products **8** and nitrated products **9** (entries 2-5). These side reactions all result in the yield of the main reaction being low.

Table 3. Substrate scope for phenyl-substituted ethylene compounds **4i-n**



Entry	Substrate	Yields/ %[a]		Observed by-products[b]		
1						
2		**5i** 68%	**5a** 10%			
3		**5a** 32%				
4[c]	**4k**	**5a** 8%		**7k** trace	**8k**	**9k**
5[c]		**5a** 20%		**7k** 67%	**8k**	**9k**
6		**5a** 30%		**7k**	**8k**	**9k**
7		**5i** 34%		**7m** (= **8k**)	**8m** (= **7k**)	
8		**5e** trace				

[a] Yields were determined by ^{1}H NMR analysis of the reaction mixture based on 1,3,5-tribromobenzene as an internal standard. [b] These compounds were suggested in ^{1}H NMR and GC-MS analyses. [c] 10 mol% of $Fe(NO_3)_3\cdot 9H_2O$ was used.

In conclusion, the catalytic oxidative cleavage of alkenes using $Fe(NO_3)_3 \cdot 9H_2O$ under O_2 was developed. This reaction system is particularly effective when 9-benzylidene-9*H*-fluorene derivatives are used as substrates even though they are tri- and tetra-substituted olefins.

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Supplementary Material

Supplementary data (Scheme S1 and experimental details associated with this article can be found, in the online version, at https://doi.org/xxx.

Iron(III) nitrate-induced aerobic and catalytic oxidative cleavage of olefins

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Highlight

- Catalytic oxidative cleavage of olefins under O_2
- Use of inexpensive $Fe(NO_3)_3 \cdot 9H_2O$
- Environmental benign method
- Particularly effective when 9-benzylidene-9*H*-fluorene derivatives are used as a substrate