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Metal-Free, NHPI Catalyzed Oxidative Cleavage of C–C Double Bond Using Molecular Oxygen as Oxidant

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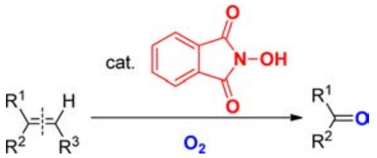
ABSTRACT



A metal-free *N*-hydroxyphthalimide (NHPI) catalyzed aerobic oxidative cleavage of olefins has been developed. Molecular oxygen is used as the oxidant and reagent for this oxygenation reaction. This methodology has prevented the use of toxic metals or overstoichiometric amounts of traditional oxidants, showing good economical and environmental advantages. Based on the experimental observations, a plausible mechanism is proposed.

The oxidative cleavage of a C–C double bond represents a broad class of fundamental transformations in organic chemistry.[1] According to the literature, there are mainly four kinds of methodologies for the oxygenation of olefins (Scheme 1): (1) Traditional methods carried out by ozonolysis[2] or using the Lemieux–Johnson Protocol (OsO_4 followed by $NaIO_4$),[3] although their utility is often limited by safety concerns; (2) Using transition metals as catalysts, such as Mn,[4] Mo,[5] Ru,[6] Pd,[7] Re,[8] Fe,[9] Au,[10] Os,[11] and Ce[12] in combination with peroxides, peracids,

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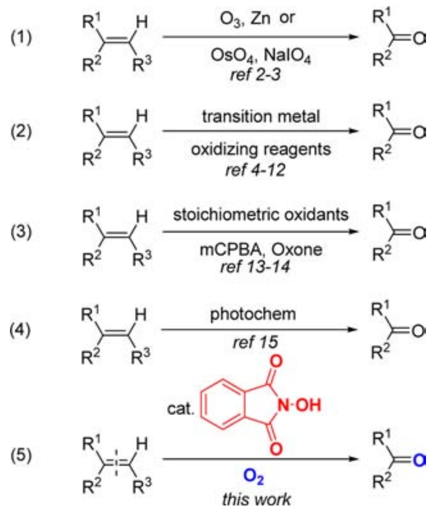
and other oxidizing reagents; (3) Nonmetal reactions that include using equivalent oxidants,[13] such as *m*CPBA, PCC, and the recently developed aryl-γ^3-iodane-based methods for C−C double bond cleavage;[14] (4) Through photochemical methods, which need additional photosensitizers and special implements.[15] Despite great progress having been made in the field of olefin oxidative cleavage, these processes generally suffer from safety concerns, the use of expensive and toxic metals, or the use of overstoichiometric amounts of oxidants, which also have high expenses and would produce a large amount of byproduct. Therefore, development of a safe and metal-free method is still desirable for these synthetic transformations.

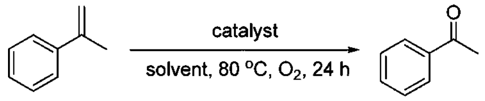
In contrast, on behalf of green and sustainable chemistry, molecular oxygen is considered as an ideal oxidant due to its natural, inexpensive, and environmentally friendly characteristics and, therefore, offers attractive academic and industrial prospects.[16] However, the oxygenation methods using O_2 as the oxidant are limited by high oxygen pressure[17a] or low yields.[17b] Based on our previous work related to dioxygen activation and using molecular oxygen as the terminal oxidant,[18] we also think about using the molecular oxygen as the oxidant for the cleavage of olefins. Herein, we report a facile and operationally convenient oxygenation for the oxidative cleavage of olefins catalyzed by NHPI (*N*-hydroxyphthalimide) with O_2 as the oxidant and reagent.

Scheme 1. Traditional Methods for Cleavage of Alkenes



The α-methylstyrene (**1a**) was first investigated using NHPI as the catalyst, which has attracted much attention for aerobic oxidation in recent years.[19,20] To our surprise, α-methylstyrene (**1a**) could be converted to acetophenone (**2a**) in 58% yield by only using 20 mol % NHPI in MeCN under an O_2 atmosphere, without any other additives. Subsequently, various parameters were screened to improve the reaction efficiency (Table 1). The experiments showed that the solvent (entries 1−9, Table 1) had great influence on the reaction yield and DMA (*N,N*-dimethylacetamide) was proven to be the most suitable candidate for this transformation (80% yield, entry 5, Table 1). As previous literature revealed,[21] NHPI had very low solubility in a nonpolar organic medium, and this is consistent with our experiment results: a polar solvent generally provided better results (see Supporting Information (SI)). Then

Table 1. Oxidative Cleavage of α-Methylstyrene (**1a**)[a]



1a **2a**

entry	catalyst (mol %)	metal salt (5 mol %)	solvent	yield (%)[b]
1	NHPI (20)	–	MeCN	58
2	NHPI (20)	–	toluene	25
3	NHPI (20)	–	HOAc	61
4	NHPI (20)	–	EA	58
5	NHPI (20)	–	DMA	80
6	NHPI (20)	–	DME	62
7	NHPI (20)	–	PhCN	<10
8	NHPI (20)	–	EtOH	28
9	NHPI (20)	–	DMF	<10
10	**NHPI (10)**	–	**DMA**	**80**
11[c]	NAPI (10)	–	DMA	68
12	Tempo (20)	–	DMA	trace
13	4-MeOTempo (20)	–	DMA	trace
14	NHPI (10)	$FeCl_2$	DMA	55
15	NHPI (10)	$CoCl_2$	DMA	79
16	NHPI (10)	CuBr	DMA	14
17	NHPI (10)	$Mn(OAc)_2\cdot 2H_2O$	DMA	25
18[d]	NHPI (10)	–	DMA	29
19[e]	NHPI (10)	–	DMA	trace

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10−20 mol %), and solvent (1 mL) reacted at 80 °C under an O_2 (1 atm) atmosphere for 24 h. [b] GC yield using *n*-dodecane as an internal standard. [c] NAPI: *N*-acetylphthalimide. [d] Under an air atmosphere. [e] Under an Ar atmosphere.

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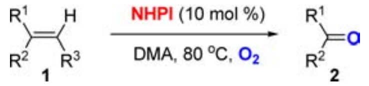
the catalyst loading was decreased from 20 to 10 mol %, and a comparable reaction efficiency was shown (entry 10, Table 1). Compared with the previous result[17b] from Hayashi's group which used molecular oxygen and gave 41% **2a**, we achieved a higher yield (80%, entry 10) by this present NHPI catalysis. A lower yield of **2a** was obtained when an analogue of NHPI, NAPI (*N*-acetylphthalimide), was used (entry 11, Table 1). The other commonly used O_2 activators, such as Tempo and 4-MeOTempo,[22] just gave trace results (entries 12–13, Table 1). According to literature, plenty of NHPI catalytic systems were coupled with metals, such as the well-known "Ishii catalytic system".[19] In order to confirm whether an ultratrace amount of metal has an effect on our catalytic system, several commonly used metals were added, but the reaction did not proceed well except for the $CoCl_2$, which gave similar results (entries 14–17, Table 1). These results might exclude the effect of metal. When the reaction was carried out under air or an Ar atmosphere, the reaction yield was dramatically reduced, which addressed the importance of O_2 (entries 18–19, Table 1).

A range of substrates were investigated as listed in Table 2. When α-alkyl aryl ethylenes were used as substrates, the reactions ran smoothly, and corresponding products were produced in moderate to good yields. With either electron-donating or -withdrawing groups at the para position of the aryl group R^1, oxidative reactions ran efficiently (entries 1–3, Table 2). The reaction was slower with substrates bearing substituted groups at the ortho position of the phenyl group and the reaction yield also decreased (cf. entries 9 and 10, Table 2), and when 1-methyl-2-(prop-1-en-2-yl)benzene was used as the substrate, the reaction yield was < 10%. These results indicated that steric hindrance plays a significant role in affecting the efficiency of oxidation. When the alkyl group of R^2 was prolonged, we were pleased to find that the desired product even with a nonyl group could also be obtained in moderate yield (entry 7, Table 2). The reactivity of substituted geminal biaryl ethylenes was also demonstrated, and they were smoothly cleaved to the corresponding biaryl methanone (entries 8–13, Table 2). A heteroaryl group was compatible in this catalytic system as well (entry 13, Table 2). Substituted styrene was converted into the benzaldehyde in low yield (entry 14, Table 2); it seems that the styrene would aggregate in this catalytic system. And the 1,2-substituted alkene could also be converted into the corresponding aldehyde **2n** (40%, entry 15) in the presence of acetone oxime (10 mol %) which could promote the generation of the PINO radical from NHPI,[20b] although in moderate yield (entry 15, Table 2).

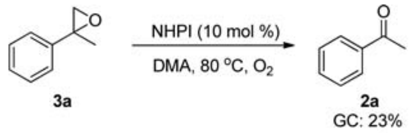
Table 2. Oxidative Cleavage of Substituted Styrenes[a]



entry	R^1	R^2	R^3	yield (%)[b]
1	C_6H_5	CH_3	H	**2a** (80)
2	4-FC_6H_5	CH_3	H	**2b** (85)
3	4-$CH_3C_6H_5$	CH_3	H	**2c** (52)
4	1-naphthyl	CH_3	H	**2d** (75)
5	C_6H_5	CH_2CH_3	H	**2e** (57)
6[c]	C_6H_5	$(CH_2)_3CH_3$	H	**2f** (60)
7[e]	C_6H_5	$(CH_2)_8CH_3$	H	**2g** (48)[d]
8	C_6H_5	C_6H_5	H	**2h** (74)[d]
9	C_6H_5	4-$CH_3C_6H_5$	H	**2i** (67)[d]
10[f]	C_6H_5	2-$CH_3C_6H_5$	H	**2j** (36)[d]
11[g]	C_6H_5	4-$CH_3OC_6H_5$	H	**2k** (74)[d]
12	C_6H_5	4-FC_6H_5	H	**2l** (78)[d]
13	C_6H_5	2-Thienyl	H	**2m** (40)[d]
14[e]	4-$CH_3OC_6H_5$	H	H	**2n** (26)
15[g]	4-$CH_3OC_6H_5$	H	CH_3	**2n** (40)

[a] Reaction conditions: **1** (0.2 mmol), NHPI (10 mol %), and DMA (1 mL) reacted at 80 °C under an O_2 (1 atm) atmosphere. [b] GC yield using *n*-dodecane as an internal standard. [c] NHPI (20 mol %); temperature: 100 °C. [d] Isolated yields. [e] **1** (0.5 mmol), NHPI (10 mol %), acetone oxime (10 mol %), and DMA (0.5 mL). [f] Isolated as a mixture, phenyl (*o*-tolyl)methanone/2-phenyl-2-(*o*-tolyl)oxirane = 3:2.43. For the mechanism, see Supporting Information. [g] **1** (0.5 mmol), NHPI (20 mol %), acetone oxime (10 mol %), and DMA (0.5 mL).

To shed light on the mechanism of the above reactions, we designed the following experiments (eqs 6 and 7). The reaction was carried out with 2-methyl-2-phenyloxirane **3a**, which was prepared from α-methyl styrene **1a**.[23] However, only 23% of acetophenone **2a** was observed.



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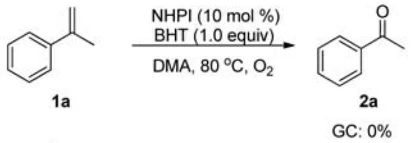

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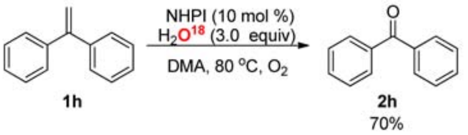

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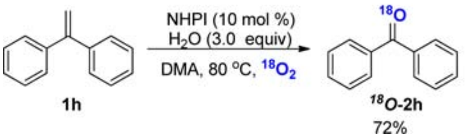

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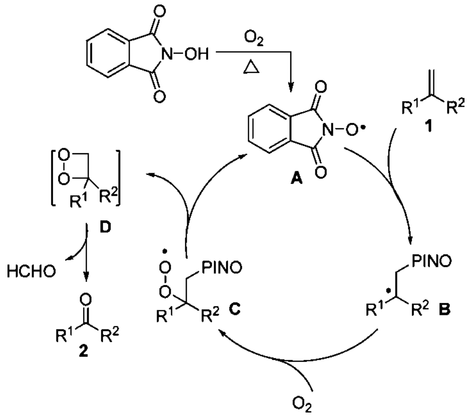
Scheme 2. Proposed Mechanism for Cleavage of Alkenes



This result indicates the epoxide might not be the intermediate of this transformation. We also found that this oxidation was completely inhibited by BHT (2,6-di-*tert*-butyl-4-methylphenol) (eq 7),[24] which was a traditional radical scavenger, and this might suggest a radical initiation pathway. Furthermore, we designed two ^{18}O labeled experiments and the reaction of **1h** in the presence of $^{18}O_2$ (1 atm) generated the ^{18}O labeled product **^{18}O-2 h** in 72% yield (eqs 8 and 9). This result shows that the oxygen atom originated from molecular dioxygen.

On the basis of the above results and previous studies,[9d,25] the mechanism of this transformation is proposed (Scheme 2). PINO radical **A** is initially generated from NHPI through homolysis.[25b] Then the PINO radical **A** will add electrophilically to the C–C double bond to generate a carbon radical **B**,[9d] which could be further trapped by molecular oxygen to give a peroxyl radical **C**. Subsequently, dioxetane intermediate **D** is produced with the formation of PINO radical **A** to complete the catalytic circle. The dioxetane **D** readily cleaves thermally into the corresponding carbonyl products.[25a]

In summary, we have developed a facile and operationally convenient method for the oxidative cleavage of alkenes. Molecular oxygen is used as the oxidant and reagent for this oxygenation reaction employing NHPI as the catalyst. This methodology has prevented the use of toxic metals or overstoichiometric amounts oxidants, showing good economical and environmental advantages. Further studies to probe the mechanism of these transformations, and the application of this reaction, are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.