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Epoxidation of alkenes using dioxygen in the presence of an alcohol catalyzed by *N*-hydroxyphthalimide and hexafluoroacetone without any metal catalyst

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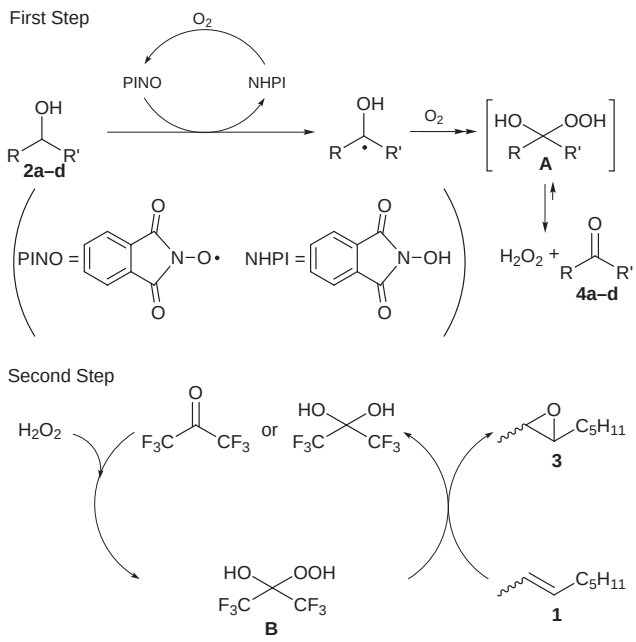
A new approach for the epoxidation of alkenes using O_2 without any metal catalyst was developed; a variety of alkenes were epoxidized in a regio- and stereoselective manner with O_2 in the presence of benzhydrol catalyzed by *N*-hydroxyphthalimide and hexafluoroacetone.

From an economic and environmental viewpoint, the epoxidation of olefins with O_2 is valuable and particularly attractive. Therefore, much effort has been made to utilize O_2 for the epoxidation of olefins, especially using transition metals as catalysts.[1] However, few efficient catalytic aerobic oxidation systems are known that proceed under mild conditions and are amenable to the production of bulk and fine chemicals.[2] We have recently found a novel aerobic oxidation system of hydrocarbons *via* a radical process which employs *N*-hydroxyphthalimide (NHPI) as the catalyst under mild conditions.[3,4] Using this method, alcohols are also able to be oxidized with O_2 to ketones or carboxylic acids *via* the formation of α-hydroxy hydroperoxides.[5] To highlight the importance of this radical catalyst for aerobic oxidation, our efforts are now directed to a new approach for the epoxidation of alkenes using O_2 without any metal catalyst.

Our epoxidation involves a new strategy consisting of radical and ionic processes as key reactions, *i.e.* (i) *in situ* generation of H_2O_2 *via* α-hydroxy hydroperoxide **A** from an alcohol and O_2 assisted by NHPI, and (ii) the epoxidation of olefins by 2-hydroperoxyhexafluoropropan-2-ol **B** derived from the formed H_2O_2 and hexafluoroacetone (HFA) (Scheme 1).†

To optimize reaction conditions for the epoxidation of alkenes, oct-2-ene **1** was chosen as a model substrate and allowed to react under O_2 (1 atm) in the presence of alcohol **2** under the influence of catalytic amounts of NHPI and HFA (Table 1).‡



Scheme 1

The first variable examined was the alcohol used as the source of hydroperoxide (entries 1–4). It was proved that benzhydrol **2b** is the best source of hydroperoxide in the present epoxidation system. The use of propan-2-ol **2c** reduced the conversion and selectivity of **1** to **3**. It is believed that abstraction of the α-hydrogen from **2c** by phthalimide-*N*-oxyl (PINO), generated from NHPI and O_2, takes place in competition with abstraction of the allylic hydrogen of the olefin **1**.§ In an electrochemical oxidation using NHPI as the mediator, Masui *et al.* reported that the allylic oxidation of olefins occurs more easily than the dehydrogenation of alcohols, such as propan-2-ol and cyclohexanol, to ketones.[6] Hence, in epoxidations using an alcohol whose α-hydrogen is more easily abstracted than the allylic hydrogen of **1**, the epoxidation was expected to proceed more easily. Thus, the reaction of **1** using benzyl alcohol **2d** led to **3** with higher selectivity and conversion. HFA was also important to complete the epoxidation (entries 1, 5 and 6). An α-hydroxy hydroperoxide derived from 1,1,1-trifluoroacetone was inadequate to epoxidize **1** in satisfactory yield.

On the basis of these results, the aerobic epoxidation of various olefins using **2b** in the presence of catalytic amounts of NHPI and HFA was examined under selected reaction conditions (Table 2).

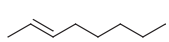
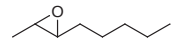
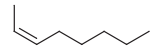
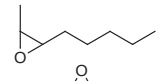
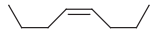
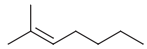
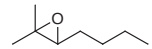
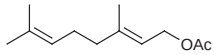
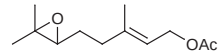
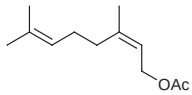
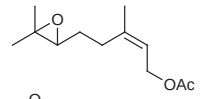
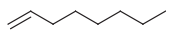
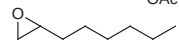
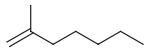
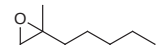
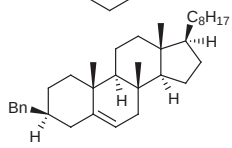
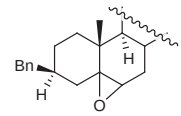
The epoxidation of *cis*- and *trans*-oct-2-enes proceeded smoothly in a stereospecific manner to form *cis*- and *trans*-2,3-epoxyoctanes, respectively, in high yields. It is noteworthy that the present system provides a stereospecific epoxidation route with O_2, since in the epoxidation of *cis* olefins using O_2 no such selectivity has been previously observed. Geranyl acetate and neryl acetate afforded the corresponding epoxides in which the double bonds remote from their acetoxy groups were epoxidized with high regioselectivities. Even terminal olefins, which are difficult to epoxidize compared with internal olefins, could be epoxidized by the present method. However, the epoxidation of cyclohexene led to cyclohexene oxide in

Table 1 Epoxidation of oct-2-ene **1** to 2,3-epoxyoctane **3** with O_2 in the presence of alcohols **2a–d** by NHPI and HFA[a]

		Conversion (%)		Yield (%)[b]	
Run	Alcohol	**1**	**2a–d**	**3**	**4a–d**
1	MePhCHOH **2a**	90	30	66 (73)	29 (97)
2[c]	Ph_2CHOH **2b**	94	36	85 (90)	33 (92)
3[d]	Pr^iOH **2c**	58	—	24 (42)	—
4	BnOH **2d**	84	27	60 (71)	20 (74)
5[e]	**2a**	7	34	3	32 (94)
6[f]	**2a**	8	34	4	33 (98)

[a] **1** (3 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol%), HFA (HFA•$3H_2O$) (10 mol%) and **2** (15 mmol) in PhCN (6 ml) for 24 h. [b] Product yields were determined by GC analysis. Selectivity is in parentheses. [c] 18 h. [d] Conversion of **2c** and yield of **4c** were not determined. [e] In the absence of HFA. [f] 1,1,1-Trifluoroacetone was used instead of HFA.

Table 2 Epoxidation of various alkenes with O_2 catalyzed by NPHI and HFA in the presence of benzhydrol **2b**[a]

Entry	Substrate	*t*/h	Conversion (%)	Product	Yield (%)	Selectivity (%) (*trans* : *cis*)
1		18	93		87	93 (>99:<1)
2 [b]		24	90		72	80 (>99:<1)
3		16	94		81	86 (98:2)
4		16	96		80	83 (99:1)
5		15	90		74	82
6		20	88		71	81
7		20	89		74	83
8 [c,d]		24	80		72	90
9 [d,e]		24	83		70	84
10 [d,f]		24	78		63	80
11 [d,e]		20	72		60	83 (75:25)

[a] Substrate (3 mmol) was allowed to react under dioxygen (1 atm) in the presence of NHPI (0.3 mmol), HFA (0.3 mmol) and **2b** (15 mmol) in PhCN (6 ml) at 80 °C. [b] **2a** was used in place of **2b**. [c] Reaction was carried out at 90 °C. [d] α,α,α-Trifluorotoluene was used as solvent. [e] NHPI (0.6 mmol) was used. [f] Cyclohex-2-en-1-one (8%), cyclohex-2-en-1-ol (2%) and cyclohexane-1,2-diol (1%) were obtained. [g] Ratio α : β.

somewhat lower yield because of concomitant formation of allylic oxidation products such as cyclohexenone (8%) and cyclohexenol (2%). Cholesteryl benzoate produced the 5,6-α-epoxide in preference to the 5,6-β-epoxide (α : β = 75 : 25), which is comparable to epoxidation by MCPBA.[7] In contrast, the same epoxidation using the aldehyde–O_2 system with an Ni complex is reported to give α : β = 31 : 69.[8]

We believe that the actual epoxidizing reagent **B** arises from HFA and H_2O_2 liberated from α-hydroxy hydroperoxides **A**.[9] In fact, ^{1}H NMR experiments show that treatment of **2a** with O_2 in the presence of NHPI in CD_3CN at 70 °C produced H_2O_2, but not α-hydroxy hydroperoxide.¶

In conclusion, we have developed the epoxidation of olefins by *in situ* generation of H_2O_2 from alcohols and O_2 under the influence of NHPI and HFA without any metal catalyst. This method provides an alternative route to the epoxidation of olefins by molecular oxygen in a stereospecific manner.

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Notes and references

† 2-Hydroperoxyhexafluoropropan-2-ol is reported to be easily derived from HFA (or HFA hydrate) and H_2O_2: see R. P. Heggs and B. Ganem, *J. Am. Chem. Soc.*, 1979, **101**, 2484.

‡ *Typical procedure* for the epoxidation of **1**: A PhCN (6 ml) solution of **1** (3 mmol), NHPI (49 mg, 10 mol%), HFA•$3H_2O$ (66 mg, 10 mol%) and **2b** (15 mmol) was placed in a two–necked flask equipped with a balloon filled with O_2. The mixture was stirred at 80 °C for 18 h, and then extracted with Et_2O. The organic layer was dried over $MgSO_4$ and analyzed by GLC with an internal standard. The products were separated from the solvent under reduced pressure and purified by column chromatography on silica gel (*n*-hexane–AcOEt = 20 : 1) to give the corresponding epoxides.

§ In a previous paper, we reported that phthalimide-*N*-oxyl (PINO) is produced by exposing NHPI to O_2 at 80 °C in PhCN, see ref. 4.

¶ ^{1}H NMR analysis of the resulting reaction mixture indicates a broad peak at δ 8.8 attributed to the proton of H_2O_2 and protons assigned to the methyl groups of alcohol **2a** and ketone at δ 1.4 and δ 2.6, respectively, but no peaks corresponding to the α-hydroxy hydroperoxide were observed. In addition, an independent reaction of **2a** (5 mmol) with O_2 (1 atm) in the presence of NHPI (10 mol%) at 70 °C in MeCN (5 ml) gave H_2O_2 (1.6 mmol) and acetophenone (**4a**) (1.8 mmol).

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9 It is well-known that the α-hydroxy hydroperoxide easily gives H_2O_2 and a ketone, see W. T. Hess, *Kirk-Othmer Encyclopedia of Industrial Chemistry*, ed. J. I. Kroschwitz and M. Howe-Grant, 4th edn., Wiley, New York, 1995, vol. 13, pp. 976–977 and references cited therein.

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