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Radical addition of ethers to alkenes under dioxygen catalyzed by *N*-hydroxyphthalimide (NHPI)/$Co(OAc)_2$

Kazutaka Hirano, Satoshi Sakaguchi and Yasutaka Ishii*

Department of Applied Chemistry, Faculty of Engineering & High Technology Research Center, Kansai University, Suita, Osaka 564-8680, Japan

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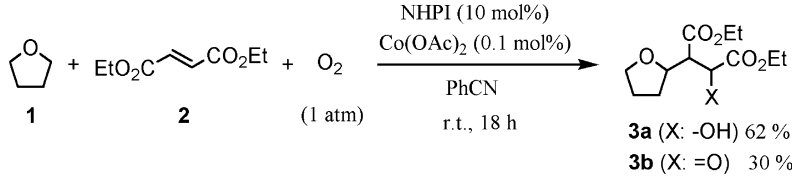
Abstract—The reaction of various ethers with alkenes bearing an electron-withdrawing substituent in the presence of *N*-hydroxyphthalimide combined with $Co(OAc)_2$ under dioxygen produced the corresponding adducts in which oxygen is incorporated to alkenes in good yields. Oxcetane, furan and pyrane smoothly added to ethyl fumarate even at room temperature to give coupling products in high yields. An acyclic ether like dibutyl ether also added to fumarate under mild conditions to give a hydroxylated adduct in satisfactory selectivity. © 2002 Published by Elsevier Science Ltd.

The formation of new C–C bonds by the addition of carbon radicals to C=C bonds is a powerful strategy in organic synthesis. A wide variety of methods have appeared for the generation of carbon radicals.[1] However, the generation of α-etheral carbon radicals from ethers is limited to peroxide and light induced methods, which are usually difficult to carry out selectively under mild conditions. To the best of our knowledge, the radical initiated addition of cyclic ethers to alkenes was first reported by Wallace and Gritter in 1961.[2] Treatment of tetrahydrofuran (THF) with a radical initiator like *t*-butyl peroxide at 150°C in the presence of 1-octene affords 4-dodecanone (40.6%), which suggests the rearrangement of the initially formed α-etheral radical to an acyl radical.[2] A similar treatment of THF with 1-octene is reported to form 4-dodecanone as a dominant product and 2-octyltetrahydrofuran.[3] Furthermore, the reaction of THF with maleic anhydride under the influence of benzoyl peroxide at refluxing temperature produced the corresponding 2-furyl adduct (70%).[4] On the other hand, the addition of ethers to haloalkenes initiated by peroxides and UV irradiation has also been examined by several authors.[5] In previous papers, we reported that carbon radicals can be generated through a catalytic process from alcohols and acetals by using *N*-hydroxyphthalimide (NHPI) under dioxygen. The reactions of alcohols and acetals in the presence of alkenes like methyl acrylate produced α-hydroxy-γ-butyrolactones[6] and β-hydroxy acetals,[7] respectively, in good yields. In this paper, we wish to report the introduction of α-etheral radicals and molecular oxygen to electron-deficient alkenes catalyzed by NHPI in the presence of a small amount of $Co(OAc)_2$ under mild conditions.

A typical reaction was carried out as follows: To a solution of THF (**1**) (15 mmol) and diethyl fumarate (**2**) (3 mmol) in PhCN (3 mL) was added NHPI (0.3 mmol) and $Co(OAc)_2$ (0.1×10^{-3} mmol), and the mixture was allowed to react under atmospheric dioxygen (1 atm) at room temperature for 18 h giving adducts diethyl 3-(2′-furyl)-2-hydroxysuccinate (**3a**) (62%) and diethyl 3-(2′-furyl)-2-oxasuccinate (**3b**) (30%) (Eq. (1)).



(1)

Among the reactions examined in several solvents, we found that benzonitrile (PhCN) led to adducts **3a** and **3b** in higher selectivity, as discussed later. Thus, **1** was reacted with **2** in PhCN under various conditions (Table 1). The reaction of **1** with **2** in the presence of

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* Corresponding author. Tel.: +81-6-6368-0793; fax: +81-6-6339-4026; e-mail: ishii@ipcku.kansai-u.ac.jp

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Table 1. Reaction of tetrahydrofuran (**1**) to diethyl fumarate (**2**) by NHPI-catalyst under various conditions[a]

Run	NHPI (mol%)	$Co(OAc)_2$ (mol%)	O_2/N_2 (1 atm)	Conv. (%)[b]	Yield (%)[c]	
					3a	**3b**
1	10	0.1	1.0	97	62	30
2	5	0.1	1.0	46	28	18
3	10	0.05	1.0	95	59	30
4	0	0.1	1.0	No reaction		
5	10	0	1.0	No reaction		
6	10	0.1	0.8/0.2	41	24	15
7	10	0.1	0.5/0.5	32	20	12
8[d]	10	0.1	1.0	90	44	29
9[e]	10	0.1	1.0	No reaction		

[a] **2** (3 mmol) was allowed to react with **1** (15 mmol) under dioxygen in the presence of NHPI (10 mol%) and $Co(OAc)_2$ (0.1 mol%) at rt for 18 h.
[b] Conversion of **2**.
[c] Yield based on **2** used.
[d] **1** (3 mL) was used without solvent.
[e] $Co(acac)_3$ was used instead of $Co(OAc)_2$.

NHPI (10 mol%) and $Co(OAc)_2$ (0.1 mol%) with respect to **2** took place even at room temperature to produce adduct **3a** and further oxidized product **3b** in 92% total yield (Table 1, run 1). When the amount of NHPI was halved from 10 to 5 mol%, the conversion of **1** to **3a** and **3b** markedly decreased (run 2). However, almost the same results were obtained by the reduction of $Co(OAc)_2$ by half (run 3). It is important to note that no reaction was induced by removing either NHPI or $Co(OAc)_2$ from the reaction system (runs 4 and 5). In a previous paper, we showed that a cobalt–dioxygen complex generated in situ from a Co(II) species and dioxygen abstracts the hydrogen atom from NHPI to form a phthalimide-*N*-oxyl (PINO) radical which reacts with alkanes to initiate the chain reaction.[7] It is difficult to abstract the hydrogen from the NHPI by dioxygen at room temperature. Therefore, no reaction was observed in the absence of either NHPI or $Co(OAc)_2$ in the reaction system. The yield of the adducts, **3a** and **3b**, was greatly influenced by the partial pressure of O_2 in a mixed gas of O_2 and N_2 (runs 6 and 7). The reaction of **1** with **2** without any solvent was approximately completed in 6 h even at room temperature to form **3a** (44%) and **3b** (29%) in 90% conversion (run 8). Fig. 1 shows the effect of various solvents on the reaction of **1** with **2** at 40°C for 6 h. The reaction in acetic acid, ethyl acetate and acetonitrile resulted in higher conversion of **2**, but the selectivity to **3a** and **3b** was relatively low. In contrast, the reaction in lipophilic solvents like $PhCF_3$, PhCl and $PhCH_3$ resulted in adducts, **3a** and **3b**, in higher selectivities. It is interesting to note that the present reaction in PhCN leads to adducts **3a** and **3b** in very high selectivities, although the conversion was moderate. This may be due to the fact that the resulting adduct radical is easily trapped by dioxygen dissolved in the solvent rather than the chain transfer to the alkene owing to the cage effect of the viscous PhCN solvent.

On the basis of these results, several cyclic ethers were allowed to react with alkenes bearing an electron-withdrawing substituent in the presence of NHPI and $Co(OAc)_2$ under selected reaction conditions (Table 2).

The reaction of **1** with ethyl malonate without a solvent at 50°C for 6 h afforded **3a** (39%) and **3b** (25%) (run 1). In general, the radical addition to ethyl malonate is found to proceed more slowly than that to the corresponding fumarate.[1] Similarly, **1** added to ethyl acrylate at 40°C to give ethyl 3-(2′-furyl)-2-hydroxypropionate (**4a**) (42%) and ethyl 3-(2′-furyl)-2- oxapropionate (**4b**) (22%) (run 2). It is noteworthy that **1** reacted with methacrolein (**5**) to afford 2-furyl acetone (**6**) (68%) as the sole adduct (run 3).

An outline of the formation of the adduct **6** from **1** and **5** is explained by the following reaction path (Scheme 1). A 2-furyl radical **A** generated from **1** and PINO adds to **5** to form an adduct radical **B** which is trapped by dioxygen giving a hydroperoxide **C**. Previously, we showed that this type of hydroperoxide **C** is easily subjected to redox decomposition by Co ions to form

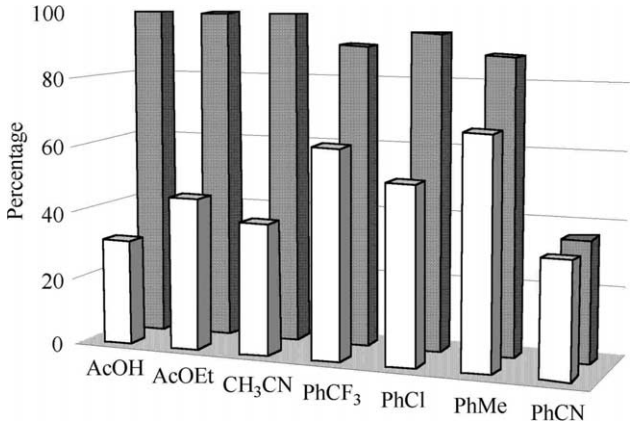
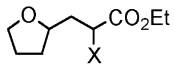
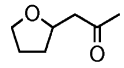
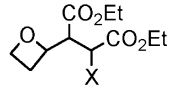
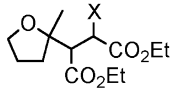
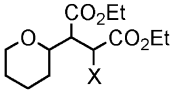


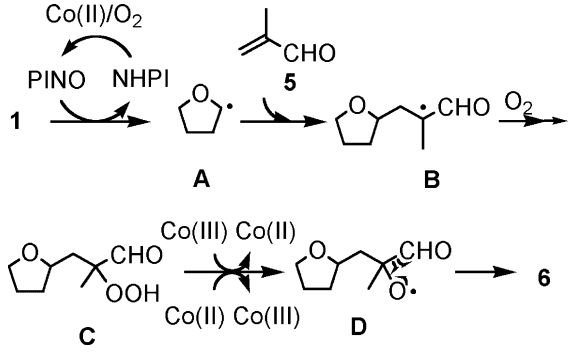
Figure 1. Solvent effect on the reaction of **1** with **2** to **3a** and **3b** (under O_2 (1 atm) in the presence of NHPI (10 mol%) and $Co(OAc)_2$ (0.1 mol%) at 40°C for 6 h in various solvents.) Conv. of **2** (■), yield of **3a**+**3b** (□).

Table 2. Reaction of various ethers with alkenes[a]

Run	Alkene	Ether	Temp. (°C)	Time (h)	Conv. (%)[b]	Product / Yield (%)[c] (**a** / **b**)
1[d]	EtO_2C CO_2Et	**1**	50	6	99	**3** 64 (61 / 39)
2[d]	CO_2Et	**1**	40	8	99	 **4** 64 (66 / 34)
3[d]	CHO **5**	**1**	40	6	84	 **6** 68
4	**2**		r.t.	20	83	 **7** 76 (74 / 26)
5[e]	**2**		40	1	99	 **8** 76 (63 / 37)
6[f]	**2**		40	5	71	 **9** 51 (84 / 16)

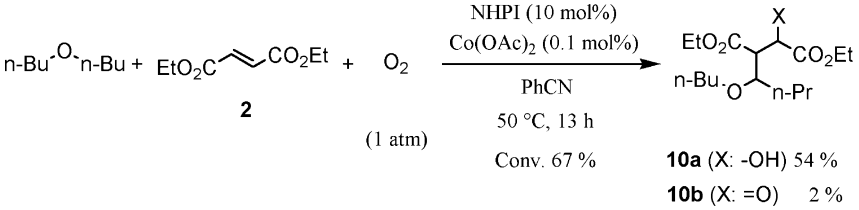
[a]Alkenes (3 mmol) was allowed to react with ethers (15 mmol) in the presence of NHPI (10 mol%) and $Co(OAc)_2$ (0.1 mol%) under O_2 (1 atm) in PhCN (3 mL). [b]Conversion of alkenes. [c]Based on alkenes. [d]**1** (3 mL) was used without solvent. [e]2-Methyl tetrahydrofuran (30 mmol) was used without solvent. [f]Without solvent.

an alkoxy radical **D** which readily liberates an aldehyde.[6] In the present reaction, it is likely that ketone **6** is formed through a similar reaction pathway as above. On the other hand, several cyclic ethers were reacted with ethyl fumarate **2** under selected reaction conditions. Trimethylene oxide added relatively slowly to **2** to give the corresponding adducts **7a** and **7b** in 76% total yield (run 4). The reaction of 2-methylfurane with **2** took place regioselectively to form adducts **8a** and **8b** in which the tertiary radical of the 2-methylfurane added to **2** (run 5). Tetrahydropyran reacted with **2** to form **9a** and **9b** in fair yields (51%) (run 6). In these reactions, ethers were converted into the corresponding lactones in 4–6% yields based on the ethers used.



Scheme 1.

Needless to say, the present reaction was extended to the addition of acyclic ethers to alkenes. For instance, the reaction of dibutyl ether with **2** under similar conditions as Table 1 (run 1) afforded adducts **10a** and **10b** in 56% yield in 67% conversion (Eq. (2)).



(2)

In conclusion, we have succeeded in the NHPI-catalyzed radical addition of ethers to alkenes bearing electron-withdrawing substituents under mild conditions. Unfortunately, these reactions gave diastereoisomeric mixtures of the products, but the present method

provides a useful synthetic tool for the preparation of various ether derivatives.

Spectral data. **3a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 4.66 (d, $J=2.6$ Hz, 1H), 4.34 (m, 1H), 4.16 (m, 4H), 3.94 (m, 2H), 2.91 (dd, $J=2.6$, 10.0 Hz, 1H), 2.24 (m, 1H), 1.94 (m, 2H), 1.64 (m, 1H), 1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=173.4$, 170.3, 75.8, 69.9, 67.9, 61.7, 60.9, 53.8, 31.0, 25.6, 14.1, 14.0; IR (NaCl) 3430, 2982, 1736, 1376, 1276, 1120, 1031 cm^{-1}. **3b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.39$ (m, 1H), 4.22 (m, 4H), 3.69 (m, 2H), 2.98 (d, $J=3.9$ Hz, 1H), 1.91 (m, 2H), 1.72 (m, 2H), 1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=193.4$, 172.8, 170.7, 75.5, 68.2, 61.9, 60.9, 52.6, 29.1, 25.5, 14.1, 14.0; IR (NaCl) 2982, 1732, 1372, 1189, 1067 cm^{-1}. **4a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.24$ (m, 2H), 4.07 (m, 1H), 3.81 (m, 2H), 3.55 (dd, $J=2.5$, 9.3 Hz, 1H), 1.90 (m, 2H), 1.87 (m, 4H), 1.29 (m, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=174.5$, 76.1, 69.4, 67.8, 61.4, 39.3, 31.6, 25.4, 14.1; IR (NaCl) 3419, 2932, 1732, 1203, 1129, 1067 cm^{-1}. **4b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.31$ (m, 2H), 4.16 (m, 1H), 3.87 (m, 2H), 3.74 (m, 2H), 2.01 (m, 4H), 1.37 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=192.7$, 160.9, 74.3, 67.9, 62.4, 45.1, 31.4, 25.4, 13.9; IR (NaCl) 2919, 1736, 1210, 1131, 1010 cm^{-1}. **6**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=3.87$ (m, 1H), 3.75 (t, $J=6.6$ Hz, 2H), 2.76 (dd, $J=7.3$, 15.6 Hz, 2H), 2.20 (s, 3H), 1.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=207.2$, 74.9, 67.4, 49.5, 29.5, 25.5, 23.8; IR (NaCl) 2957, 2352, 1715, 1356, 1179, 1069 cm^{-1}. **7a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=5.32$ (m, 1H), 4.61 (dd, $J=2.9$, 10.3 Hz, 1H), 4.53 (m, 2H), 4.21 (m, 4H), 3.67 (t, $J=5.4$ Hz, 1H), 2.53 (m, 2H), 1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=173.3$, 173.1, 68.8, 68.6, 67.3, 61.9, 60.9, 54.9, 27.4, 14.1, 14.0; IR (NaCl) 3468, 2983, 1715, 1370, 1277, 1137 cm^{-1}. **7b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=5.31$ (m, 1H), 4.33 (m, 2H), 4.21 (m, 2H), 4.10 (m, 2H), 3.93 (s, 1H), 2.57 (m, 2H), 1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=190.3$, 170.0, 163.7, 73.9, 68.9, 62.9, 62.8, 57.9, 24.9, 14.1, 13.9; IR (NaCl) 2982, 1737, 1185, 1013 cm^{-1}. **8a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.62$ (dd, $J=2.7$, 10.5 Hz, 1H), 4.26 (m, 2H), 4.15 (m, 2H), 3.88 (m, 2H), 3.09 (d, $J=2.7$ Hz, 1H), 1.96 (m, 4H), 1.42 (s, 3H), 1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=173.8$, 170.5, 69.6, 69.0, 67.9, 61.8, 61.7, 56.9, 37.7, 23.6, 21.6, 14.1, 14.0; IR (NaCl) 3486, 2980, 1738, 1371, 1240, 1107, 1040 cm^{-1}. **8b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.15$ (m, 4H), 3.88 (m, 2H), 3.16 (s, 1H), 1.96 (m, 4H), 1.42 (s, 3H), 1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=195.5$, 173.8, 170.2, 69.4, 67.0, 60.6, 60.6, 56.7, 34.1, 23.6, 21.6, 14.0, 13.9; IR (NaCl) 2981, 1738, 1372, 1107, 1041 cm^{-1}. **9a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.68$ (d, $J=2.9$ Hz, 1H), 4.40 (m, 1H), 4.13 (m, 4H), 3.46 (m, 2H), 2.90 (dd, $J=2.9$, 9.3 Hz, 1H), 1.67 (m, 6H), 1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=173.4$, 171.3, 74.5, 68.9, 65.6, 61.8, 60.9, 53.6, 32.7, 30.4, 13.9; IR (NaCl) 3502, 2939, 1739, 1069, 1030 cm^{-1}. **9b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.23$ (m, 1H), 4.08 (m, 4H), 3.74 (dd, $J=13.0$, 27.8 Hz, 2H), 3.43 (s, 1H), 1.59 (m, 6H), 1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=190.0$, 172.9, 171.3, 68.7, 68.5, 61.8, 61.0, 53.4, 32.4, 29.7, 20.6, 14.0, 13.9; IR (NaCl) 2939, 1732, 1199 cm^{-1}. **10a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.62$ (dd, $J=2.4$, 7.3 Hz, 1H), 4.24 (m, 2H), 4.15 (m, 2H), 3.85 (m, 1H), 3.56 (m, 2H), 2.98 (dd, $J=2.4$, 8.3 Hz, 1H), 1.54 (m, 4H), 1.39 (m, 4H), 1.28 (m, 6H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=173.3$, 170.9, 70.8, 69.1, 69.0, 61.5, 60.9, 52.9, 35.3, 32.2, 19.4, 18.1, 14.2, 14.1, 14.0, 13.9; IR (NaCl) 3499, 2959, 2873, 1737, 1460, 1372, 1251, 1180, 1093 cm^{-1}. **10b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=4.26$ (m, 4H), 3.70 (m, 1H), 3.52 (d, $J=4.8$ Hz, 1H), 2.72 (m, 2H), 1.58 (m, 4H), 1.41 (m, 4H), 1.32 (m, 6H), 0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=191.4$, 173.1, 172.9, 64.8, 64.7, 62.9, 62.8, 49.7, 36.3, 27.9, 19.5, 16.0, 14.1, 13.9, 13.8, 13.7; IR (NaCl) 2965, 1731, 1300, 1103 cm^{-1}.

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