JOC Article

Aerobic Oxidation of Benzyl Alcohols Catalyzed by Aryl Substituted *N*-Hydroxyphthalimides. Possible Involvement of a Charge-Transfer Complex

Claudia Annunziatini,[†] Maria Francesca Gerini,[†] Osvaldo Lanzalunga,*,[†] and Marco Lucarini[‡]

Dipartimento di Chimica, Università degli Studi di Roma "La Sapienza" and Istituto CNR di Metodologie Chimiche (IMC-CNR), Sezione Meccanismi di Reazione, P.le A. Moro, 5 I-00185 Rome, Italy, and Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, via S. Donato 15, I-40127 Bologna, Italy

osvaldo.lanzalunga@uniroma1.it

Received January 20, 2004

A series of aryl-substituted *N*-hydroxyphthalimides (X-NHPIs) containing either electron-withdrawing groups ($4\text{-}CH_3OCO$, 3-F) or electron-donating groups ($4\text{-}CH_3$, $4\text{-}CH_3O$, $3\text{-}CH_3O$, $3,6\text{-}(CH_3O)_2$) have been used as catalysts in the aerobic oxidation of primary and secondary benzylic alcohols. The selective formation of aromatic aldehydes was observed in the oxidation of primary alcohols; aromatic ketones were the exclusive products in the oxidation of secondary alcohols. O−H bond dissociation enthalpies (BDEs) of X-NHPIs have been determined by using the EPR radical equilibration technique. BDEs increase with increasing the electron-withdrawing properties of the aryl substituent. Kinetic isotope effect studies and the increase of the substrate oxidation rate by increasing the electron-withdrawing power of the NHPI aryl substituent indicate a rate-determining benzylic hydrogen atom transfer (HAT) from the alcohol to the aryl-substituted phthalimide-*N*-oxyl radical (X-PINO). Besides enthalpic effects, polar effects also play a role in the HAT process, as shown by the negative ρ values of the Hammett correlation with σ^+ and by the decrease of the ρ values (from -0.54 to -0.70) by increasing the electron-withdrawing properties of the NHPI aryl substituent. The relative reactivity of $3\text{-}CH_3O\text{-}C_6H_4CH_2OH$ and $3,4\text{-}(CH_3O)_2\text{-}C_6H_3CH_2OH$, which is higher than expected on the basis of the σ^+ values, the small values of relative reactivity of primary vs secondary benzylic alcohols, and the decrease of the ρ values by increasing the electron-withdrawing properties of the NHPI aryl substituent, suggest that the HAT process takes place inside a charge-transfer (CT) complex formed by the X-PINO and the benzylic alcohol.

Introduction

Catalytic aerobic oxidation of organic compounds is of fundamental importance in the industrial synthesis of a large variety of oxy-functionalized chemicals from both economic and environmental points of view.[1] Therefore, the search for an efficient system for the catalytic oxidation of organic substrates with molecular oxygen under mild conditions remains an important challenge. Recently, particular attention has been given to the use of *N*-hydroxyphthalimide (NHPI) in combination with molecular oxygen and metal salt cocatalysts, like $Co(OAc)_2$ or $Co(acac)_2$, an oxidizing system developed by Ishii and his group.[2,3] The $NHPI/O_2/Co(II)$ system is able to efficiently catalyze the oxidation of a large variety of organic compounds, under mild conditions at moderate oxygen pressure and temperature.[4−6] Among the catalytic processes promoted by the $NHPI/O_2/Co(II)$ system, the oxidation of alcohols to carbonyl compounds is of particular synthetic importance since most of the reagents which perform this transformation are required in amounts of 1 equiv or more; moreover some of them are hazardous or toxic.[7] Oxidation of primary aliphatic alcohols with the $NHPI/O_2/Co(II)$ system leads to the corresponding carboxylic acids, while that of secondary alcohols leads to the corresponding ketones.[6,8] Oxidation of benzyl alcohol by the Ishii system in PhCN at 100 °C was reported to give a mixture of benzoic acid and benzaldehyde.[2] More recently, however, the selective

---

[†] Università degli Studi di Roma "La Sapienza" and Istituto CNR di Metodologie Chimiche (IMC-CNR).

[‡] Università di Bologna.

(1) *Dioxygen activation and homogeneous catalytic oxidation*; Simandi, L. L., Ed.; Elsevier: Amsterdam, 1991. *The activation of dioxygen and homogeneous catalytic oxidation*; Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds.; Plenum: New York, 1993.

(2) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934.

(3) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.

(4) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520.

(5) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.

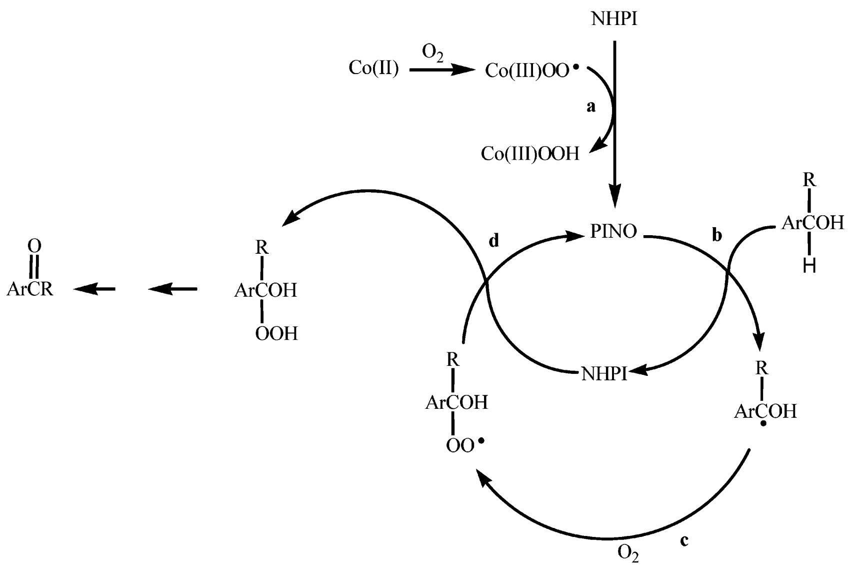
(6) Iwahama, T.; Yoshima, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502.

(7) Highlet, L. J.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 4399. Lee, D. G.; Spitzer, U. A. *J. Org. Chem.* **1970**, *35*, 3589. Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030. Menger, F. M.; Lee, C. *Tetrahedron Lett.* **1981**, *22*, 1655.

(8) Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1995**, *36*, 6923.

10.1021/jo049887y CCC: $27.50

SCHEME 1



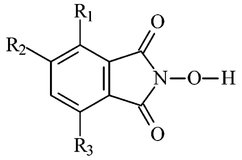
syntheses of aromatic aldehydes by oxidation of benzylic alcohols, without appreciable formation of carboxylic acids, using the NHPI/O_2/Co$(OAc)_2$ system has been accomplished at room temperature and atmospheric pressure in CH_3CN.[9,10] The fundamental steps of the proposed oxidation mechanism are reported in Scheme 1.[9–11] Formation, assisted by the Co(II) salt, of the phthalimide-*N*-oxyl radical (PINO) (path a) initiates a free-radical chain. Abstraction of a benzylic hydrogen atom from the substrate by PINO (path b) leads to an α-hydroxyl benzyl radical which then reacts with dioxygen to give an α-hydroxyl peroxyl radical (path c). The latter species abstracts an hydrogen atom from NHPI giving an hydroperoxide, precursor of the carbonyl product, and regenerating PINO (path d).

The use of NHPI in the catalytic aerobic oxidation offers the possibility of modifying the catalyst structure by the introduction of aryl substituents. Such a structural modification might influence the catalytic efficiency, as already observed in the oxidation of ethylbenzene to acetophenone[12] and *p*-xylene to terephthalic acid,[13] the reaction selectivity as well as the oxidation mechanism. We felt it is of interest to address this problem, and to this purpose we carried out a kinetic and product study of the aerobic oxidation of primary and secondary benzylic alcohols catalyzed by aryl-substituted *N*-hydroxyphthalimides. For a better interpretation of the results we also investigated the effect of the aryl ring substituent on the NHPI O−H bond dissociation energy (BDE) by using the EPR technique. The aryl-substituted *N*-hydroxyphthalimides used in this study (**1a**−**g**) contained either electron-withdrawing (4-CH_3OCO, 3-F) or electron-donating groups (4-CH_3, 4-CH_3O, 3-CH_3O, 3,6-$(CH_3O)_2$).

TABLE 1. O-H BDEs of Aryl-Substituted NHPIs (1a−g) and Hyperfine Splitting Constants of the Corresponding *N*-Oxyl Radicals Measured at −10 °C in CH_3CN

catalyst	a_N/G	a_{other}/G	BDE^a/kcal mol^{-1}
1a	4.55	0.35 (1H)	88.9
1b	4.70	0.25 (2H), 0.25 (F)	88.6
1c	4.76	0.50 (2H)	88.1
1d	4.84	0.56 (4H)	88.2
1e	4.94	0.83 (1H), 0.14 (4H)	87.3
1f	4.91	-	87.9
1g	5.01	-	87.1

[a] Estimated errors are ±0.2 kcal mol^{-1}.



1a	4-CH_3OCO-NHPI	R_1 = H	R_2 = CH_3OCO	R_3 = H
1b	3-F-NHPI	R_1 = F	R_2 = H	R_3 = H
1c	NHPI	R_1 = H	R_2 = H	R_3 = H
1d	4-CH_3-NHPI	R_1 = H	R_2 = CH_3	R_3 = H
1e	4-CH_3O-NHPI	R_1 = H	R_2 = CH_3O	R_3 = H
1f	3-CH_3O-NHPI	R_1 = CH_3O	R_2 = H	R_3 = H
1g	3,6-$(CH_3O)_2$-NHPI	R_1 = CH_3O	R_2 = H	R_3 = CH_3O

Results

EPR Measurements. The nitroxide radicals were generated in CH_3CN at −10 °C by photolysis with UV light in the presence of about 10% of di-*tert*-butyl peroxide. An examination of the measured nitrogen hyperfine splitting constants, a_N, reported in Table 1, shows that they increase by decreasing the electron-withdrawing character of the ring substituent.

The determination of the BDEs of ring-substituted NHPIs were done by using the EPR radical equilibration technique that has been previously used in order to

---

[9] Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 688.

[10] Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem.* **2004**, 109.

[11] Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini M. *J. Mol. Catal. A* **2003**, *204–205*, 63.

[12] Wentzel, B. B.; Donners, M. P. J.; Alsters, P. L.; Feiters, M. C.; Nolte, R. J. M. *Tetrahedron* **2000**, *56*, 7797.

[13] Saha, B.; Nobuyoshi, K.; Espenson, J. H. *J. Phys. Chem. A* **2004**, *108*, 425.

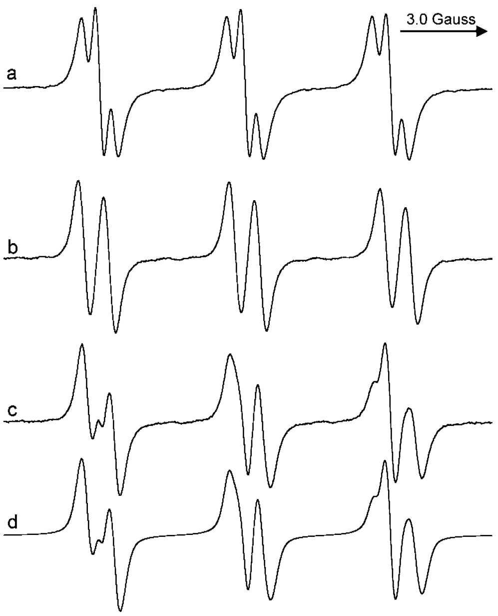
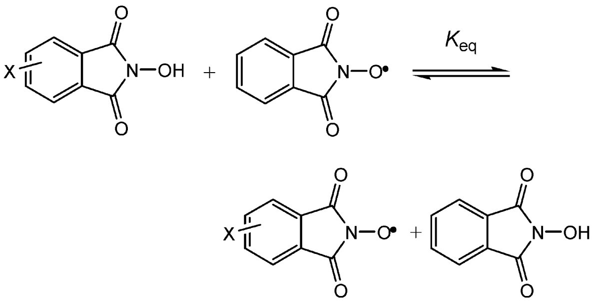


FIGURE 1. EPR spectra obtained in CH_3CN at −10 °C by photolysis of **1c** (a) and **1e** (b) with UV light in the presence of about 10% of di-*tert*-butyl peroxide. (c) EPR spectrum obtained, under the same experimental conditions, by photolysis of a solution containing **1c** (15 mM) and **1e** (6.2 mM). (d) Computer simulation of spectrum (c).

measure the O−H BDE of the unsubstituted NHPI.[14] This technique consists of measuring the equilibrium constant for the hydrogen atom transfer reaction between the aryl-substituted NHPIs, an appropriate reference compound, whose BDE is already known, and the corresponding radicals. In the present case, the reference derivative used was the unsubstituted NHPI (eq 1), whose BDE (88.1 kcal/mol) has been already measured in *tert*-butyl alcohol.[14]



(1)

The BDEs for the aryl substituted NHPIs were calculated, in the assumption that the entropic term can be neglected,[15] by means of eq 2 from K_{eq} and the known BDE of NHPI.[16]

$$\mathrm{BDE(X{-}NHPI)} = \mathrm{BDE(NHPI)} - RT\ln(K_{eq}) \quad (2)$$

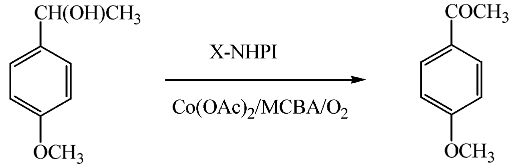
As an example, in Figure 1 are reported the EPR spectra of **1c** (a) and **1e** (b), the EPR spectrum (c) obtained by photolysis of a solution containing **1c** (15 mM) and **1e** (6.2 mM), and its computer simulation (d). BDEs for the investigated NHPIs are reported in Table 1.

TABLE 2. Intermolecular Deuterium Kinetic Isotope Effects (k_H/k_D) in the Oxidations of Benzyl Alcohol with 1a, 1c, 1e, or 1g/Co(II)/O_2 Systems

catalyst	k_H/k_D[a]
1a	14.3
1c	15.5
1e	17.7
1g	19.5

[a] Molar ratio measured via GC−MS by the ratio between the corrected signal intensities of the two molecular ions at $m/z = 107$ and 106. Average of at least three determinations; the error is ±2%.

SCHEME 2



Kinetic Isotope Effect Studies. Intermolecular kinetic isotope effects have been determined in CH_3CN (3 mL) at 25 °C under oxygen by mixing equimolar amounts (0.3 mmol) of benzyl alcohol and [1-$^2H_2$]-benzyl alcohol, the catalyst **1a**, **1c**, **1e**, or **1g** (10 mol %), *m*-chlorobenzoic acid (MCBA) (5 mol %), and $Co(OAc)_2$ (0.5 mol %). k_H/k_D have been calculated by the molar ratio between the benzaldehyde and [1-^2H]-benzaldehyde measured via GC−MS by the ratio between the corrected signal intensities of the two molecular ions at $m/z = 107$ and 106. The results are reported in Table 2.

Effect of NHPI Aryl Substituents on the Catalytic Activity. This effect was evaluated in the oxidation of 1-(4-methoxyphenyl)ethanol (**2**). The oxidations were carried out in AcOEt/dioxane 1:1 (10 mL)[17] at 25 °C under oxygen by mixing **2** (3 mmol), the catalyst **1a**−**f** (10 mol %), MCBA (5 mol %), and $Co(OAc)_2$ (0.5 mol %). GC analysis of 1 mL aliquots of the reaction mixtures taken at different times revealed that, with all of the X-NHPI, the oxidation led to the formation of 4-methoxyacetophenone as the exclusive reaction product (Scheme 2).

The regular increase of the yields of 4-methoxyacetophenone during the first 30 min of the reaction is shown in Figure 2. The plot is linear, and the initial rates of formation of 4-methoxyacetophenone have been calculated within 10% of substrate conversion (Table 3).

Competitive Oxidations. The effect of the NHPI aryl substituents on the selectivity and mechanism of the oxidation of benzylic alcohols has been evaluated by the analysis of the competitive oxidations of substituted primary benzylic alcohols and the competitive oxidations of primary vs secondary benzylic alcohols.

(1) Competitive Oxidation of Substituted Primary Benzylic Alcohols. The competitive experiments

---

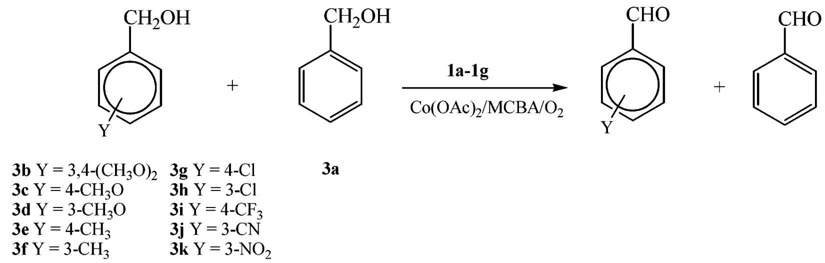
[14] Amorati, R.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Minisci, F.; Recupero, F.; Fontana, F.; Astolfi, P.; Greci, L. *J. Org. Chem.* **2003**, *68*, 1747.

[15] Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063. Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259.

[16] It has been assumed that the BDE of NHPI is not significantly altered by passing from *tert*-butyl alcohol to CH_3CN.

[17] All the catalysts were completely soluble in AcOEt/dioxane 1:1 except for **1g** which was thus not used in the kinetic studies.

SCHEME 3



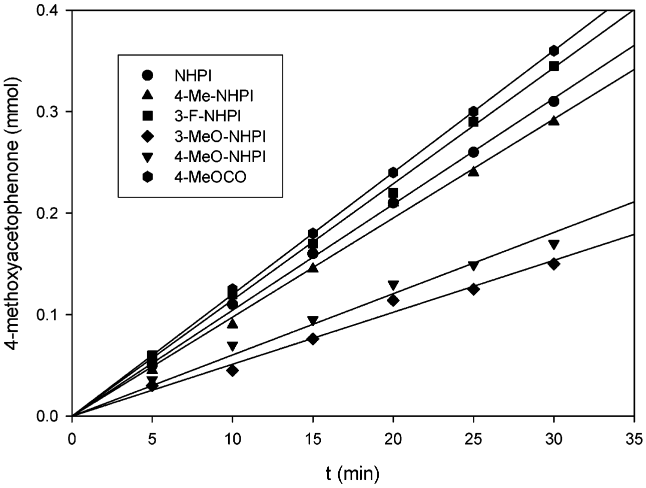


FIGURE 2. Formation of 4-methoxyacetophenone in the oxidation of 1-(4-methoxyphenyl)ethanol (**2**) by the **1a**−**f**/Co(II)/MCBA/O_2 systems.

TABLE 3. Initial Rate of Formation of 4-Methoxyacetophenone in the Oxidation of 1-(4-Methoxyphenyl)ethanol (2) with the 1a−f/Co(II)/MCBA/O_2 Systems

catalyst	initial rates (mmol/min)
1a	$(12 \pm 1) \times 10^{-3}$
1b	$(11 \pm 1) \times 10^{-3}$
1c	$(10 \pm 1) \times 10^{-3}$
1d	$(8.7 \pm 0.9) \times 10^{-3}$
1e	$(6.0 \pm 0.6) \times 10^{-3}$
1f	$(5.1 \pm 0.5) \times 10^{-3}$

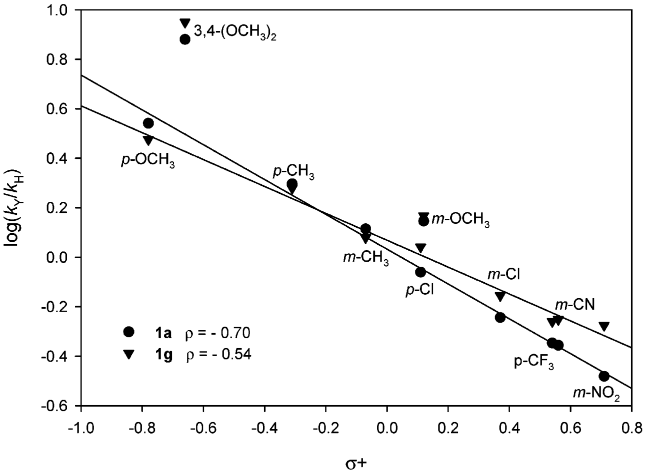


FIGURE 3. Hammett plot for the competitive oxidation of ring substituted benzylic alcohols with **1a**/Co(II)/MCBA/O_2 and **1g**/Co(II)/MCBA/O_2 systems (the points for the *m*-MeO and 3,4-(MeO)$_2$ groups are excluded from the correlations).

TABLE 4. ρ Values Calculated for the Hammett Correlation in the Oxidation of Ring-Substituted Benzylic Alcohols with the 1a−g/Co(II)/MCBA/O_2 Systems

catalyst	ρ
1a	−0.70
1b	−0.69
1c	−0.68
1d	−0.67
1e	−0.60
1f	−0.60
1g	−0.54

were carried out in CH_3CN (3 mL) at 25 °C under oxygen by mixing equimolar amounts (0.3 mmol) of ring-substituted benzyl alcohol (**3b**−**k**) and of benzyl alcohol (**3a**), the catalyst **1a**−**g** (10 mol %), MCBA (5 mol %), and $Co(OAc)_2$ (0.5 mol %) and determining the relative amounts of the benzaldehydes formed which are the only reaction products (Scheme 3).

The relative reactivities (k_Y/k_H) of the alcohols **3b**−**k** with respect to benzyl alcohol (**3a**), determined for all the catalysts **1a**−**g**, are reported in Table S1 (Supporting Information).

When the $\log(k_Y/k_H)$ values determined for each catalyst were plotted against the substituent constants σ^+, good Hammett correlations were obtained ($r^2 > 0.98$),[18] provided the points for the 3-MeO and 3,4-(MeO)$_2$ groups are excluded from the plots (vide infra). As an example in Figure 3 are shown the Hammett plots for the oxidation catalyzed by 4-CH_3OCO-NHPI (**1a**) and 3,6-$(CH_3O)_2$-NHPI (**1g**). The Hammett plots for the oxidations catalyzed by the other aryl-substituted NHPIs are available in the Supporting Information. The ρ values, which range from −0.70 to −0.54, are listed in Table 4.[20]

(2) Competitive Oxidation of Primary vs Secondary Benzylic Alcohols. The relative reactivity of primary vs secondary benzylic alcohols was studied with **1c** and **1e** as catalysts. The oxidations were carried out in CH_3CN (3 mL) at 25 °C under oxygen by mixing equimolar amounts (0.3 mmol) of benzyl alcohol (**3a**) and 1-phenylethanol (**4a**) or equimolar amounts (0.3 mmol) of 3,4-dimethoxybenzyl alcohol (**3b**) and 1-(3,4-dimethoxy-

---

[18] The correlation with the σ constants was not satisfactory ($r^2 < 0.79$); moreover, no improvement of the correlation is observed on replacing the single parameter Hammett equation ($\log k_Y/k_H = \rho\sigma^+$) with the dual parameter equation ($\log k_Y/k_H = \rho^{\bullet}\sigma_{\alpha}^{\bullet} + \rho\sigma^+$) proposed by Arnold and his associates.[19]

[19] Dust, J. M.; Arnold, D. R. *J. Am. Chem. Soc.* **1983**, *105*, 1221.

[20] A ρ value (−0.69) very close to that here reported was determined by Minisci et al. for the aerobic oxidation of benzylic alcohols by the unsubstituted NHPI.[10]

SCHEME 4

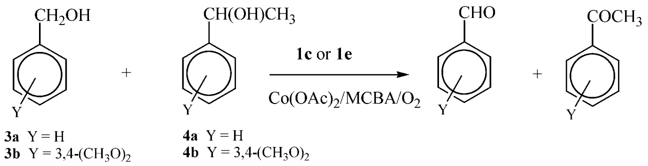
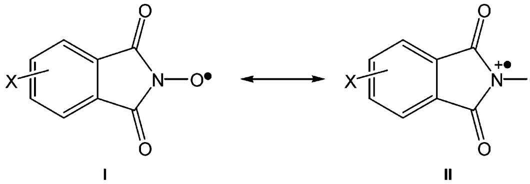


TABLE 5. Relative Reactivities ($k_{1°}/k_{2°}$) in the Competitive Oxidation of Primary vs Secondary Benzylic Alcohols with the 1c- or 1e/Co(II)/MCBA/O$_2$ Systems

	$k_{1°}/k_{2°}$[a]	
substrates	**1c**	**1e**
3a/4a	0.6	0.5
3b/4b	1.1	1.0

[a] Relative reactivities statistically corrected for the number of benzylic hydrogens.

SCHEME 5



phenyl)ethanol (**4b**), the catalyst (10 mol %), MCBA (5 mol %), and Co(OAc)$_2$ (0.5 mol %). The oxidation led selectively to the formation of benzaldehydes from the primary benzylic alcohols and of acetophenones from the secondary benzylic alcohols (Scheme 4).

The relative reactivity values ($k_{1°}/k_{2°}$), statistically corrected for the number of benzylic hydrogens, are reported in Table 5.

Discussion

O−H Bond Dissociation Energies and EPR Experiments. The results reported in Table 1 indicate that in the aryl-substituted NHPIs the O−H BDEs regularly decrease by increasing the electron-donating properties of the substituent. The effects are, however, small, the difference between the stronger O−H bond in 4-CH$_3$OCO-NHPI (88.9 kcal/mol) and the weaker O−H bond in 3,6-(MeO)$_2$-NHPI (87.1 kcal/mol) being only 1.8 kcal/mol.

An examination of the EPR data reported in Table 1 shows also that the nitrogen hyperfine splitting constant, a_N, increases by increasing the electron-donating character of the ring substituent. This observation can be interpreted on the basis of the two canonical forms I and II of the nitroxide function (Scheme 5).[10,21]

The greater the electron-donating nature of the substituent the more favored will be the structure II which bears larger electron density on oxygen and spin density on nitrogen. As a consequence, the nitrogen hyperfine splitting constant, a_N, increases.

Another interesting notation is that the a_N values correlate with the BDEs of the NHPIs, as shown in Figure 4. Namely, the BDE decreases as a_N increases. As said before, an increase in a_N indicates a greater contribution of the structure II in Scheme 5 and therefore a greater stability of the *N*-oxyl radical and a consequent smaller O−H BDE.

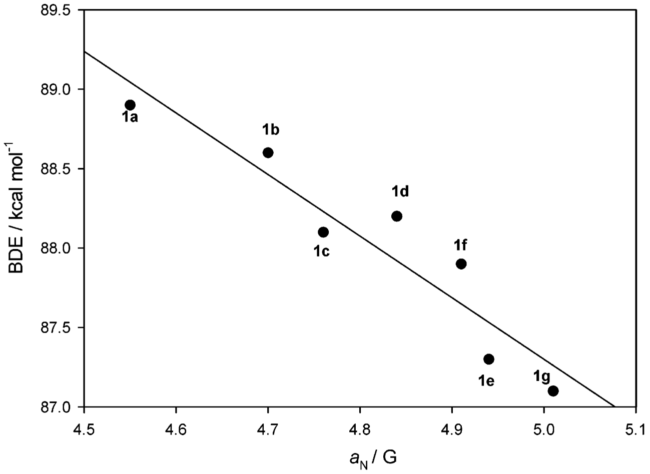


FIGURE 4. Correlation between O−H BDEs of aryl-substituted NHPIs and nitrogen hyperfine splitting constants, a_N.

Oxidation Rates and Reaction Mechanism. The data reported in Table 2 show that the aerobic oxidation of benzylic alcohols catalyzed by aryl-substituted NHPIs is characterized by high kinetic isotope effects (KIE) which increase from $k_H/k_D = 14.3$ for **1a** to $k_H/k_D = 19.5$ for **1g**.[22] Interestingly, the KIE determined in the competitive experiment catalyzed by NHPI ($k_H/k_D = 15.5$) was similar to that (16.9) recently measured in a kinetic study of the hydrogen abstraction by PINO, generated by oxidation of NHPI with Pb(OAc)$_4$, from benzyl alcohol and [1-^{2}H$_2$]-benzyl alcohol in AcOH.[24] This observation is very important as it indicates that, despite the multistep nature of the aerobic oxidations catalyzed by NHPIs (Scheme 1), the competitive experiments carried out by us provide reliable information on the relative reactivity of the benzylic substrates in the step of hydrogen atom abstraction by the aryl substituted PINO (Scheme 1, path b).

The data in Table 3 show that the initial rate of the oxidation of **2** increases by increasing the electron-withdrawing power of the aryl substituent in NHPI, and therefore, the reactivity order parallels the increase of O−H BDE in the substituted NHPIs (Table 1). This is in line with a rate-determining step involving the benzylic HAT from the alcohol to the aryl-substituted PINO.[25] Thus, a stronger O−H bond in the NHPIs favors the reaction from the enthalpic point of view. As expected, since the substituent effects on the BDEs are not very large, there is not much difference in the initial rates of oxidation with the various NHPIs, as shown by the fact that the highest rate observed with 4-CH$_3$OCO−NHPI

---

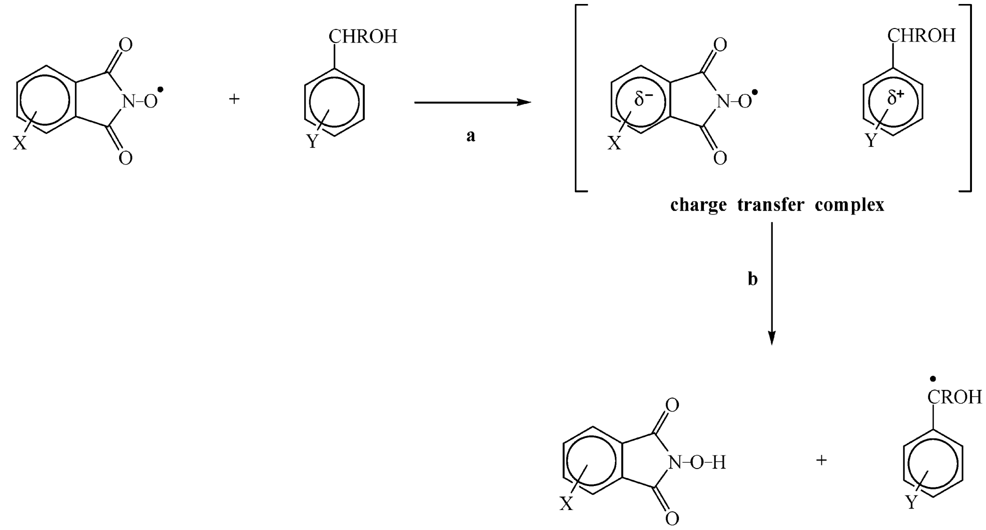
[21] Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671.

[22] The increase of KIE on going from **1a** to **1g** can be explained by the fact that the maximum magnitude of the KIE should be obtained when the HAT reaction is thermoneutral.[23] Since the reaction of the PINO with benzyl alcohol is exothermic for ca. 7−8 kcal/mol,[23] an increase of the KIE should be expected by decreasing the O−H BDE of the aryl substituted NHPI, i.e., by introducing electron-donating substituents.

[23] Nobuyoshi, K.; Cai, Y.; Espenson, J. H. *J. Phys. Chem. A* **2003**, *107*, 4262.

[24] Such a high isotope effect value was interpreted as due to quantum mechanical tunneling taking part in the benzylic HAT from the alcohol to the PINO. Nobuyoshi, K.; Saha, B.; Espenson, J. H. *J. Org. Chem.* **2003**, *68*, 9364.

SCHEME 6



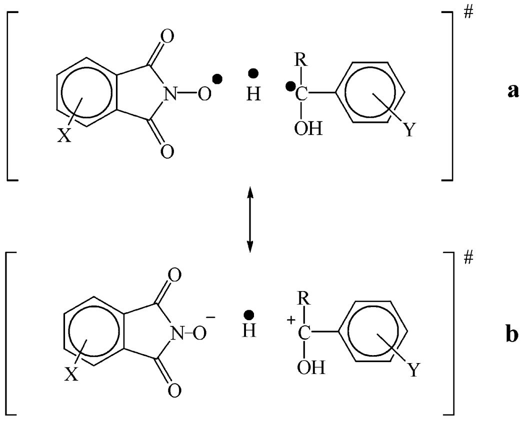


FIGURE 5.

(1.2×10^{-2} mmol min^{-1}) is about twice the lowest value which is observed with 3-CH_3O−NHPI (5.1×10^{-3} mmol min^{-1}).

Besides enthalpic effects, also polar effects must play a role as shown by the negative ρ values of the Hammett correlations for the aerobic oxidation of benzylic alcohols (**3a**−**k**) by X-NHPI. Thus, the transition state of the HAT process can be represented as hybrid of the two canonical resonance forms **a** and **b** (Figure 5). The increase of the substrate reactivity by increasing the electron-donating power of its substituent[26] is explained by the stabilization of the partial positive charge on the benzylic carbon atom in the resonance form **b** of the transition state.[27]

Even considering the polar effects, the mechanistic pattern described so far cannot take into account for all the experimental data. In fact, in the Hammett correlations, the reactivity of the substrates with 3-CH_3O and 3,4-$(CH_3O)_2$ substituents resulted significantly higher than expected (see Figure 3 for **1a** and **1g** and Figures S1−S5 in the Supporting Information for the catalysts **1b**−**f**). This result is surprisingly since in reactions occurring by a HAT mechanism, even though with a significant polar character, the 3-CH_3O group always exhibits a little rate-retarding kinetic effect due to the slight electron-withdrawing inductive effect, which destabilizes the partial positive charge developing in the transition state.[28]

To explain the rate-enhancing effect of the 3-CH_3O and 3,4-$(CH_3O)_2$ groups observed in our reactions, it might be suggested that the HAT process takes place inside a charge-transfer (CT) complex formed by the X-PINO and the benzylic alcohol, as illustrated in Scheme 6.[29] Several examples of hydrogen atom transfer process taking place inside a CT complex are reported in the literature, such as in the photoreduction of aromatic ketones[31] and the side-chain oxidation of benzyltrimethylsilanes by iodosylbenzene in the presence of iron porphyrin.[32] In the CT complex a partial positive charge resides on the aromatic ring of the alcohol, and therefore, some stabilization by a ring methoxy group is expected, whatever its position with respect to the side chain.[32,33]

Further support for the hypothesis of the formation of a CT complex comes from the analysis of the competitive oxidation of primary vs secondary benzylic alcohols. From the data reported in Table 5, we can observe that the

---

[25] Rate-determining hydrogen atom abstraction from C−H bonds by PINO (Scheme 1, path b) in aerobic oxidations catalyzed by NHPI is well documented.[3,9−11] The possibility of a rate-determining formation of aryl-substituted PINO (Scheme 1, path d) should be considered if a higher alcohol/X-NHPI molar ratio is used.[14]

[26] Similar substituent effects have been reported for the benzylic aerobic oxidation of substituted toluenes[5] and arylacetic esters[12] by the NHPI/Co(II)/O_2 system.

[27] A minor contribution of radical stabilization (resonance form **a**) vs polar effects is suggested by the lack of improvement of the correlation using the dual parameter equation ($\log k_Y/k_H = \rho^{\bullet}\sigma_{\alpha}^{\bullet} + \rho\sigma^+$) proposed by Arnold.[19]

[28] Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129. Martin, M. M.; Gleicher, G. J. *J. Org. Chem.* **1963**, *28*, 3266. Gleicher, G. J. *J. Org. Chem.* **1968**, *33*, 332.

[29] The rate enhancing effect of the 3-CH_3O and 3,4-$(CH_3O)_2$ groups could be also explained by an electron transfer mechanism from the alcohol to the X-PINO. We have excluded this possibility by the fact that the oxidation of the mechanistic probe 1-(3,4-dimethoxyphenyl)-2,2-dimethyl-1-propanol led to the formation of 1-(3,4-dimethoxyphenyl)-2,2-dimethyl-1-propanone as the only reaction product and no traces of 3,4-dimethoxybenzaldehyde have been detected (see the Experimental Section).[30]

[30] Baciocchi, E.; Belvedere, S.; Bietti, M.; Lanzalunga, O. *Eur. J. Org. Chem.* **1998**, 299. Baciocchi, E.; Belvedere, S.; Bietti, M. *Tetrahedron Lett.* **1998**, *39*, 4711.

[31] Cohen, S. G.; Parola, A.; Parsons, G. H. *Chem. Rev.* **1973**, *73*, 141. Coenjarts, C.; Scaiano, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 3635.

[32] Baciocchi, E.; Lanzalunga, O. *Tetrahedron* **1993**, *49*, 7267.

$k_{1°}/k_{2°}$ relative reactivities of 3,4-dimethoxybenzyl alcohol and 1-(3,4-dimethoxyphenyl)ethanol with the NHPI/Co(II)/O_2 and 4-MeO-NHPI/Co(II)/O_2 systems are close to unity. This unexpected result is in accordance with the occurrence of a CT complex since its rate of formation should be mainly determined by the electronic properties of the aromatic ring of the two alcohols, which are the same, and not by the side-chain substitution pattern. Clearly, the role of a CT complex should be less important with the unsubstituted benzylic alcohols, and accordingly, 1-phenylethanol is twice more reactive than benzyl alcohol.

Finally, the formation of a CT complex can also account for the variation of ρ values as a function of the aryl substituent in the NHPI. The ρ values regularly decrease by increasing the electron-withdrawing properties of the aryl substituent ranging from $\rho = -0.70$ for the most selective 4-CH_3OCO-NHPI to $\rho = -0.54$ for the least selective catalyst 3,6-$(CH_3O)_2$-NHPI (see Figure 3 and Table 4). Accordingly, electron-withdrawing substituents in NHPI stabilize the negative charge developing in the CT complex, thus increasing the degree of charge transfer from the benzylic alcohol to the X-PINO, as a consequence the oxidation is more sensitive to the effect of the aryl substituent of the alcohol.

Conclusions

Among the catalytic processes promoted by the NHPI/O_2/Co(II) system the oxidation of alcohols to carbonyl compounds is of particular synthetic importance. In this work, a kinetic study of the oxidation of a benzylic alcohol with the X-NHPI/Co(II)/O_2 systems has shown that it is possible to increase the catalytic efficiency by introducing electron-withdrawing substituents in the NHPI aryl ring. O−H bond dissociation energies (BDEs), determined by using the EPR technique, increase by increasing the electron-withdrawing properties of the NHPI substituent. An interesting correlation between the hyperfine splitting constants a_N and the O−H BDEs has been observed. The parallel increase of O−H BDEs and of the catalytic efficiency in the presence of electron-withdrawing NHPI substituents indicates that benzylic HAT from the alcohol to the aryl substituted PINO is the rate-determining step. This hypothesis is further supported by kinetic isotope effects studies. Besides enthalpic effects, polar effects also play a role in the HAT process, as shown by the negative ρ values of the Hammett correlation with σ^+. The higher than expected relative reactivity of 3-CH_3O-$C_6H_4CH_2OH$ and 3,4-$(CH_3O)_2$-$C_6H_3CH_2OH$, the surprisingly small values of relative reactivity of primary vs secondary benzylic alcohols and the decrease of the ρ values by increasing the electron-withdrawing properties of the NHPI aryl substituent suggest that the HAT process takes place inside a charge-transfer (CT) complex formed by the X-PINO and the benzylic alcohol.

Experimental Section

Substrates and Reagents. The benzylic alcohols and *N*-hydroxyphthalimide are commercially available and were used as received without further purification. 1-(3,4-Dimethoxyphenyl)-2,2-dimethyl-1-propanol was prepared according to a previously described procedure.[30] 4-Methoxycarbonyl-*N*-hydroxyphthalimide (**1a**), 3-fluoro-*N*-hydroxyphthalimide (**1b**), 4-methyl-*N*-hydroxyphthalimide (**1d**), 4-methoxy-*N*-hydroxyphthalimide (**1e**), and 3-methoxy-*N*-hydroxyphthalimide (**1f**) were synthesized as described in the literature.[12,34] 3,4-Dimethoxy-*N*-hydroxyphthalimide (**1g**) was synthesized by reacting 3,6-dimethoxyphthalic anhydride with NH_2OH, in anhydrous pyridine.[35] For the synthesis of 3,6-dimethoxyphthalic anhydride 1,4-dimethoxy-1,3-cyclohexadiene was reacted with dimethyl acetylenedicarboxylate to give dimethyl 3,6-dimethoxyphthalate[36] which was heated for 2 h under reflux in methanol/water with KOH to give 3,6-dimethoxyphthalic acid.[37] 3,6-Dimethoxyphthalic anhydride was then obtained by reaction of 3,6-dimethoxyphthalic acid with acetic anhydride.[35] Physical properties are identical to those reported in the literature.[38]

EPR Measurements. The equilibration experiments for the determinations of the bond dissociation enthalpies (BDEs) of ring-substituted NHPIs were done by preparing solutions of **1c** (ca. 0.1 M) and of **1a**−**1b**, **1d**−**1g** (ca. 0.1 M) in CH_3CN containing 10% of di-*tert*-butyl peroxide as photoinitiator. The nitroxide radicals were generated in CH_3CN at −10 °C by photolysis with UV light. Since these experiments were performed on concentrated solutions of the radical precursors, the initial concentration of NHPIs could be used in the calculation of K_{eq}, while the relative concentrations of the equilibrating radical species were determined by simulation of the EPR spectra.

Kinetic Isotope Effect Studies. Intermolecular kinetic isotope effects have been determined at 25 °C under oxygen by mixing 0.3 mmol of benzyl alcohol, 0.3 mmol of [1-$^2H_2$]-benzyl alcohol, 0.03 mmol of the catalyst (**1a**, **1c**, **1e**, or **1g**), 0.015 mmol of MCBA, and 0.0015 mmol of $Co(OAc)_2 \cdot 4H_2O$ in 3 mL of CH_3CN. k_H/k_D have been calculated by the molar ratio between the benzaldehyde and [1-^{2}H]-benzaldehyde measured via GC−MS by the ratio between the corrected signal intensities of the two molecular ions at $m/z = 107$ and 106.

Oxidation of 1-(4-Methoxyphenyl)ethanol (2). Solutions of 3 mmol of 1-(4-methoxyphenyl)ethanol, 0.3 mmol of X-NHPI, 0.15 mmol of MCBA, and 0.015 mmol of $Co(OAc)_2 \cdot 4H_2O$ in 10 mL of a AcOEt/dioxane 1:1 v/v were placed in a Schlenk tube equipped with a rubber baloon filled with O_2 and vigorously stirred at 25 °C. One milliliter aliquots of the reaction mixtures were taken at different times and, after addition of a solution of an internal standard (bibenzil) for GC analysis, were washed with water, dried over anhydrous Na_2SO_4, and analyzed by GC. The oxidations with all the X-NHPI lead to the formation of 4-methoxyacetophenone as the only reaction product. The initial rates of product formation were determined at low (<10%) substrate conversion.

Competitive Oxidation of Substituted Primary Benzylic Alcohols. Solutions of 0.3 mmol of ring-substituted benzylic alcohols, 0.3 mmol of benzyl alcohol, 0.03 mmol of X-NHPI, 0.015 mmol of MCBA, and 0.0015 mmol of $Co(OAc)_2 \cdot 4H_2O$ in 3 mL of CH_3CN were placed in a Schlenk tube equipped with a rubber balloon filled with O_2 and vigorously stirred at 25 °C for 2 h. After addition of a solution of an internal standard (4-methoxyacetophenone) for GC analysis and water (3 mL), the reaction mixtures were extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and analyzed by GC. The oxidations with all the X-NHPI led to the formation of the corresponding benzaldehydes as the only reaction products. A good recovery of materials (> 95%) was observed in all the experiments.

---

(33) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 7240. Baciocchi, E.; Crescenzi, M.; Fasella, E.; Mattioli, M. *J. Org. Chem.* **1992**, *57*, 4684.

(34) Gorgy, K.; Lepretre, J.-C.; Saint-Aman, E.; Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.-L. *Electrochim. Acta* **1998**, *44*, 385.

(35) Einhorn, C.; Einhorn, J.; Marcadal-Abbadi, C.; Pierre, J.-L. *J. Org. Chem.* **1999**, *64*, 4542.

(36) Harland, P. A.; Hodge, P *Synth. Commun.* **1982**, 223.

(37) Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2981.

(38) Parrick, J.; Ragunathan, R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 211.

Competitive Oxidation of Primary vs Secondary Benzylic Alcohols. Solutions of 0.3 mmol of unsubstituted or ring-substituted benzyl alcohol, 0.3 mmol of unsubstituted or ring-substututed 1-phenylethanol, 0.03 mmol of X-NHPI, 0.015 mmol of MCBA, and 0.0015 mmol of $Co(OAc)_2 \cdot 4H_2O$ in 3 mL of CH_3CN were placed in a Schlenk tube equipped with a rubber balloon filled with O_2 and vigorously stirred at 25 °C for 2 h. The reaction was performed in a similar way as described for the competitive oxidation of substituted primary benzylic alcohols. The oxidations with all the X-NHPI led selectively to the formation of benzaldehydes from the primary benzylic alcohols and of aromatic ketones from the secondary benzylic alcohols. A good recovery of materials (>95%) was observed in all the experiments.

Oxidation of 1-(3,4-Dimethoxyphenyl)-2,2-dimethyl-1-propanol. The oxidation of the mechanistic probe 1-(3,4-dimethoxyphenyl)-2,2-dimethyl-1-propanol was carried out at 25 °C by mixing 0.3 mmol of the substrate, 0.03 mmol of the catalyst (**1a**, **1c**, or **1g**), 0.015 mmol of MCBA, and 0.0015 mmol of $Co(OAc)_2$ in 3 mL of AcOEt/dioxane 1:1 v/v in a Schlenk tube equipped with a rubber balloon filled with O_2. After 24 h, water (3 mL) was added, and the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and analyzed by ^{1}HNMR. The oxidation led to the formation of 1-(3,4-dimethoxyphenyl)-2,2-dimethyl-1-propanone as the only reaction product. No traces of 3,4-dimethoxybenzaldehyde were observed with all the catalysts.

Acknowledgment. We thank the Ministero dell’ Istruzione, dell’Università e della Ricerca (MIUR), and the Consiglio Nazionale delle Ricerche (CNR) for financial support. We also thank Prof. Enrico Baciocchi for helpful discussions.

Supporting Information Available: Instrumentation. Determination of relative rates in the competitive oxidation of substituted primary benzylic alcohols and in the competitive oxidation of primary vs secondary benzylic alcohols. Relative reactivities (k_Y/k_H) in the competitive oxidation of substituted primary benzylic alcohols with the **1a**−**g**/Co(II)/MCBA/O_2 systems. Hammett plots for the competitive oxidation of ring substituted benzylic alcohols with the **1b**−**f**/Co(II)/MCBA/O_2 systems. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049887Y