JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 08 May 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Aerobic Oxidation of 4-Alkyl-*N,N*-dimethylbenzylamines Catalyzed by *N*-Hydroxyphthalimide. Protonation Driven Control over Regioselectivity

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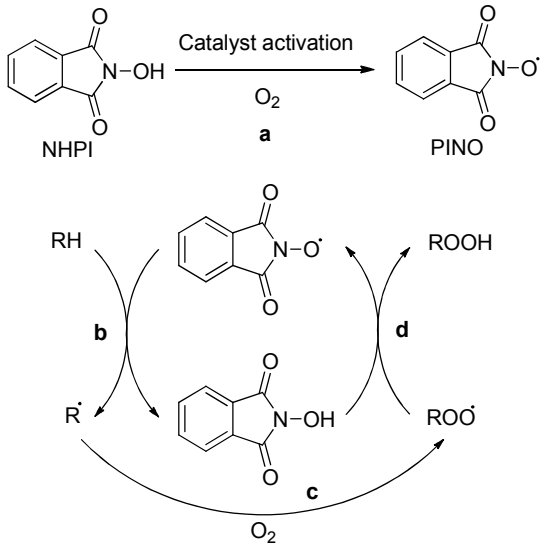
Abstract: A change in regioselectivity has been observed in the hydrogen atom transfer (HAT) reactions from 4-alkyl-*N,N*-dimethylbenzylamines (alkyl = ethyl, isopropyl and benzyl) to the phthalimide *N*-oxyl radical (PINO) by effect of protonation. This result can be rationalized on the basis of an acid induced deactivation of the C–H bonds α to nitrogen towards HAT to PINO as evidenced by the 10^4-10^7 fold decrease in the HAT rate constants in acetonitrile following addition of 0.1 M $HClO_4$. This acid induced change in regioselectivity has been successfully applied for selective functionalization of the less activated benzylic C–H bonds *para* to the $CH_2N(CH_3)_2$ group in the aerobic oxidation of 4-alkyl-*N,N*-dimethylbenzylamines catalyzed by *N*-hydroxyphthalimide in acetic acid.

Introduction

Since the pioneering studies by Ishii and coworkers, the aerobic oxidation of hydrocarbons catalyzed by *N*-hydroxyphthalimide (NHPI) has deserved an increasing attention.[1] This particular interest is associated to the mild reaction conditions, in terms of O_2 pressure and temperature, required in these oxidative processes. The key intermediate is represented by the phthalimide *N*-oxyl radical (PINO), which can be formed by several different metal or nonmetal based activation systems and O_2 (Scheme 1, path a).[1,2] Hydroperoxide oxidation products are then formed in a catalytic cycle after hydrogen atom transfer (HAT) from the substrate (R–H) to PINO followed by HAT from NHPI to the peroxyl radical ($RO_2^{\bullet}$) (Scheme 1, paths b and d, respectively).



Scheme 1. Catalytic cycle for the aerobic oxidation of hydrocarbons catalyzed by NHPI

HAT promoted by PINO plays a fundamental role in the catalytic cycle. Accordingly, a clear dependence of the overall catalytic efficiency on the bond dissociation energy (BDE) differences between the R–H and NO–H bonds was observed in HAT from alkylaromatics.[3] Beside this enthalpic factor, several studies showed that NHPI catalyzed aerobic oxidations are also significantly influenced by polar effects due to the partial charge transfer from the substrate to PINO in the HAT transition state (TS) as shown in Figure 1 for HAT from the benzylic C-H bond of a generic alkylaromatic substrate to PINO.[4]

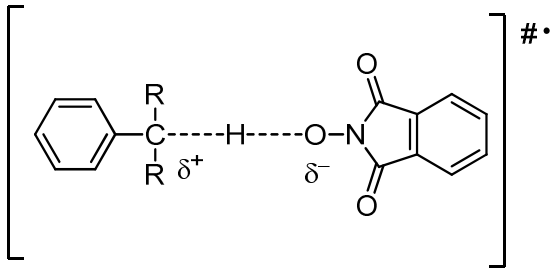


Figure 1. Partial charge transfer in the transition state for HAT from benzylic C-H bonds to PINO

Polar effects have been invoked to rationalize the high reactivity observed in HAT from electron rich C–H bonds α to heteroatoms that are able to stabilize the partial positive charge that develops on carbon in the HAT TS.[4] On these basis, it was not surprising that, in aerobic oxidations promoted by NHPI, tertiary amines are excellent substrates, in view of the presence of the electron donating nitrogen atom. Accordingly, tertiary benzyl amines were shown to be efficiently oxidized to the corresponding benzaldehydes by the NHPI/O_2 system at room temperature and 1 atm of O_2.[5,6]

It has been recently shown that in HAT from the α-C–H bonds of alkylamines to alkoxyl radicals the addition of Lewis or Brønsted acids determines a significant decrease in reactivity.[7] This effect was attributed to acid-base interactions that lead to an increase in the C–H BDE[8] and destabilize the HAT TS by increasing the extent of positive charge on the nitrogen center. In order to investigate the deactivating effect of protonation on HAT from the α–C–H bonds of alkylamines to PINO, we have explored kinetically the reactions of a series of tertiary amines with PINO in CH_3CN, acetic acid (AcOH) and in CH_3CN containing 0.1 M $HClO_4$.

From a synthetic perspective the decrease in reactivity of an otherwise activated C–H bond by protonation represents a useful tool to control the HAT regioselectivity, favoring the reaction of less activated C–H bonds which are normally quite difficult to functionalize. This approach has been successfully applied to the remote functionalization of amine substrates in metal based catalytic systems,[9] with potassium persulfate,[10] and with methyl(trifluoromethyl)dioxirane.[11] However no metal free oxidation procedures using oxygen as terminal oxidant have been reported so far.

The acid-induced change of regioselectivity in the HAT reactions promoted by PINO has been analyzed by a kinetic and product study of the oxidation of tertiary 4-alkyl-*N,N*-dimethylbenzylamines (Figure 2, **1-3**). These substrates are characterized by the presence of benzylic C–H bonds that are in a remote position from the nitrogen atom and were chosen to investigate the possible competition of HAT from these positions and from the more activated benzylic C–H bonds that are α to the heteroatom.

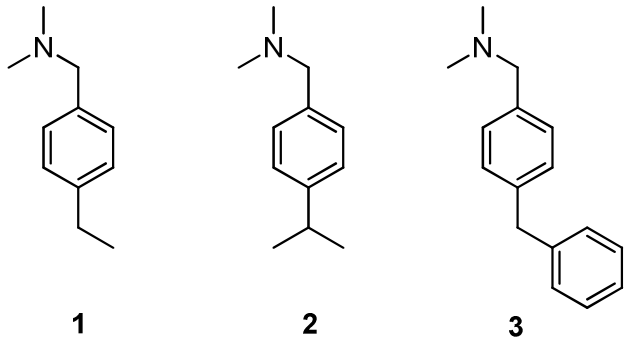
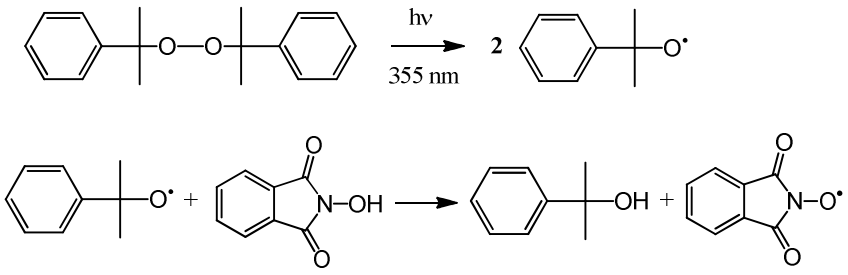


Figure 2. 4-Alkyl-*N,N*-dimethylbenzylamines investigated in this work.

Results and discussion

A kinetic study of the reactions of a series of tertiary amines, including 4-X-*N,N*-dimethylbenzylamines **1-3**, to PINO was initially carried out in CH_3CN, in the absence or in the presence of $HClO_4$ (0.1 M) and in AcOH, in order to quantitatively analyze the deactivating effect of amine protonation on HAT from the C–H bonds that are α to nitrogen.

In MeCN HAT was in all cases too fast to be followed by conventional spectrophotometry, therefore the reactions were kinetically investigated by the laser flash photolysis (LFP) technique, where PINO was generated by HAT from NHPI to the cumyloxyl radical, which in turn was formed by 355 nm LFP of dicumyl peroxide (Scheme 2).[12]

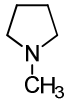
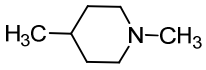
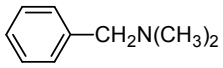
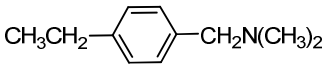
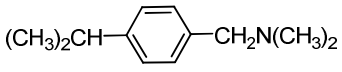
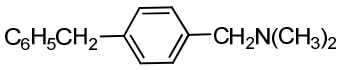
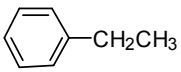
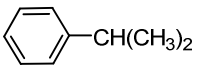


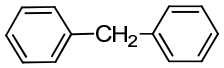
Scheme 2. Generation of PINO by laser flash photolysis

Under pseudo first-order conditions, using an excess of the amine substrate, the observed rate constants (k_{obs}) were measured following the decay of PINO at the absorption maximum (380

nm).[13] From the slope of the k_{obs} vs [amine] plots, the second order rate constants for HAT (k_H) were determined (see Figures S17-S25 in the Supporting Information). The k_H values thus obtained are collected in Table 1.

Table 1. Second order rate constants (k_H) for HAT from tertiary amines and alkylaromatics to PINO in CH_3CN, in $CH_3CN/HClO_4$ (0.1 M) and AcOH measured at T = 25 °C.

Substrate	k_H ($M^{-1}s^{-1}$)[a]		
	CH_3CN	$CH_3CN/HClO_4$ (0.1 M)	AcOH
$(CH_3CH_2)_3N$	2.0×10^4	0.018	0.04
$(CH_2{=}CHCH_2)_3N$	6.8×10^3	0.12	0.85
$(C_6H_5CH_2)_3N$	1.7×10^3	0.14	53
DABCO	$\leq 10^3$		
	7.4×10^4	$< 3\times10^{-3}$	0.07
	2.3×10^4	$< 3\times10^{-3}$	0.2
	4.8×10^3	$< 3\times10^{-3}$	0.11
	9.2×10^3	1.3	2.7
	9.4×10^3	6.7	18
	6.4×10^3	4.8	17
	1.9[b]	3.5[b]	5.4[c]
	3.25[d]		27[c]

		13[c]

[a] Average of at least three determinations. Error ± 5%. [b] Ref. 14. [c] Ref. 15. [d] In benzene + 10% CH_3CN, Ref. 3b.

From the data reported in Table 1 it can be noted that in CH_3CN, with the exclusion of 1,4-diazabicyclo[2,2,2]-octane (DABCO), the k_H values for HAT from the tertiary amines to PINO are the highest so far determined in HAT from C–H bonds promoted by this short-lived aminoxyl radical,[1c] ranging from 1.7×10^3 to 7.4×10^4 $M^{-1}s^{-1}$. These values are from 3 to 4 orders of magnitude higher than those measured for the corresponding reactions of alkylbenzenes,[3b,14,15,] a result that is in full accordance with the aforementioned activating effect of an α-nitrogen atom. The relevance of polar effects and the positive charge stabilization in the HAT TS is also in line with the observed increase in k_H with increasing the electron donating properties of the substituent in 4-X-*N,N*-dimethylbenzylamines [k_H (Et) ~ k_H (*i*Pr) > k_H (Bz) > k_H (H)] as well indicated by the good linear correlation obtained by plotting $\log(k_H(X)/k_H(H))$ vs Hammett σ constants (ρ = -1.9, r^2= 0.97, see Figure S41 in the SI).

With DABCO, only an upper limit to the HAT rate constant could be given ($k_H \leq 10^3$ $M^{-1}s^{-1}$). This result is in accordance with previous kinetic studies on HAT from tertiary amines to alkoxyl radicals[16] and can be rationalized on the basis of the operation of stereoelectronic effects. With this substrate the overlap between the nitrogen lone pair and the α-C–H bonds is reduced by the geometrical restrictions imposed by the locked conformation, that reduce the activating effect exerted by the nitrogen atom.

Stereoelectronic effects are also responsible for the relatively high k_H value measured for *N*-methylpyrrolidine ($k_H = 7.4 \times 10^4$ $M^{-1}s^{-1}$). In this system optimal overlap between the α-C-H

bonds and the nitrogen lone pair can be achieved resulting in a weakening of these bonds and a more efficient stabilization of the radicals formed following HAT.[17]

Kinetic studies were also carried out in AcOH and in CH_3CN containing 0.1 M $HClO_4$ (see Figures S28-S40 in the Supporting Information). In both cases the remarkable decrease in reactivity observed as an effect of amine protonation allowed us to determine the HAT rate constants by UV-vis spectrophotometry generating PINO by oxidation of NHPI with lead(IV) tetraacetate.[15,18] The k_H values were determined as described above for the LFP experiments. It is important to point out that in the present study, for the first time, a combination of two techniques for kinetic analysis, differing significantly in time-resolution (LFP and UV-vis spectrophotometry) has been successfully applied for the determination of HAT rate constants to a single oxygen centered radical that span over than 7 orders of magnitude.

With all the amines, as compared to the reactions carried out in MeCN, a greater than 3-order of magnitude decrease in k_H was observed after addition of 0.1 M $HClO_4$. As an example, in the reaction of PINO with triethylamine, a ~ 10^6 fold decrease in k_H was observed in the presence of $HClO_4$. In most cases the decrease in reactivity was such that the self-decay of PINO occurred in competition with HAT and only an upper limit to the k_H values could be given (< 3×10^{-3} $M^{-1}s^{-1}$). Thus, upon protonation, the activating electron releasing amino group is converted into an electron withdrawing ammonium one, that strongly deactivates the α-C–H bonds towards HAT to PINO. In contrast, with alkylbenzenes the addition of acid determines only a small increase in k_H reasonably due to the increased electrophilicity of PINO upon protonation of the carbonyl oxygen.[14,19] Very interestingly, a smaller decrease in k_H by effect of $HClO_4$ addition was observed for 4-X-*N,N*-dimethylbenzylamines **1-3** all having additional benzylic C–H bonds in a remote position to the *N* atom.

Since AcOH is widely used as solvent in aerobic hydrocarbon oxidations catalyzed by NHPI,[1,15,18] the kinetic studies have been extended to this solvent. As reported in Table 1, also in this case a remarkable decrease in reactivity, with respect to CH_3CN, was observed. As compared to

$CH_3CN/HClO_4$, a smaller extent of C–H deactivation was observed in AcOH, and accordingly in this solvent k_H values for all the amines investigated could be determined.[20] Higher k_H values were again measured for substrates **1-3** containing remote benzylic C–H bonds with respect to the *N* atom.

The observation that higher k_H values were measured for the amines bearing remote benzylic C–H bonds in both neat AcOH and $CH_3CN/HClO_4$, suggests that in the reactions of **1-3** with PINO a change in HAT regioselectivity may result following nitrogen protonation from the activated C–H bonds α-to nitrogen to the remote benzylic ones. In accordance with this hypothesis is also the observation that in the presence of $HClO_4$ the k_H values measured for **1-3** are comparable with those measured previously for the corresponding reactions of alkylbenzenes.[22]

To test if the acid-induced change in regioselectivity can be employed for the functionalization of weakly activated benzylic C–H bonds in the aerobic oxidation of tertiary benzylamines, we have investigated the oxidation of 4-X-*N,N*-dimethylbenzylamines **1-3** with NHPI (10 mol %), $Co(OAc)_2$ as cocatalyst (1 mol %) and O_2 (1 atm) in CH_3CN and in AcOH according to the Ishii protocol (see experimental section).[18] In view of the previously discussed deactivation towards HAT of these substrates in AcOH, it was necessary to raise the temperature from r.t. to 50 °C , reaction time from 5 h to 22 h and the reactant concentration in order to obtain a satisfactory substrate conversion in AcOH with respect to CH_3CN.[23]

In CH_3CN, 4-X-benzaldehydes were formed in good yield as previously reported by Minisci et al. (see Table 2 and Figure 3a),[5] confirming that HAT occurs from the more activated benzylic position that is α- to nitrogen. In contrast, when the reaction was carried out in AcOH, product analysis showed the formation of 4-(dimethylaminomethyl)benzyl alcohol and/or 4-(dimethylaminomethyl)phenyl ketone products (Table 2 and Figure 3b). The oxidation products were all identified by comparison with authentic specimens (see Supporting Information).

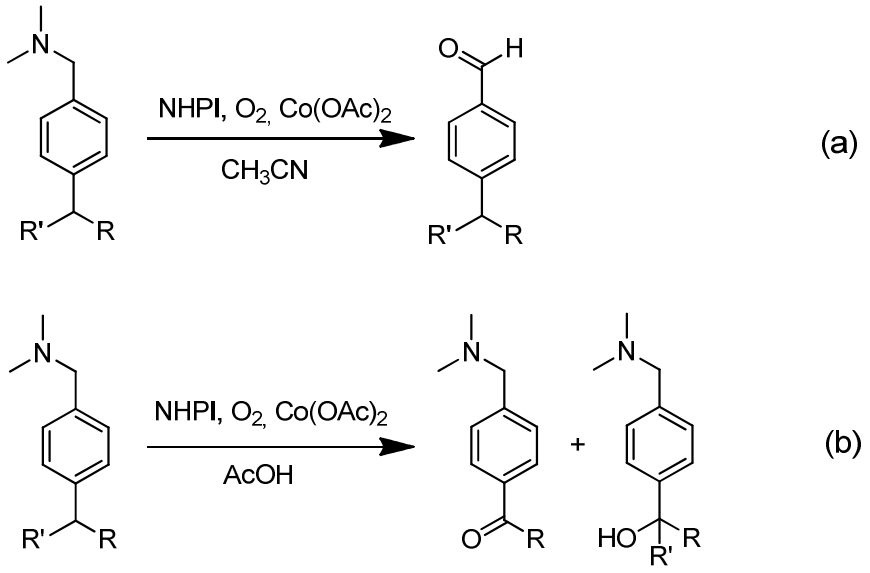
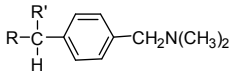
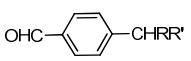
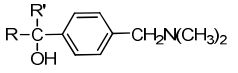
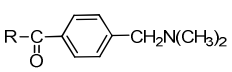


Figure 3. Products formed in the aerobic oxidation of 4-X-*N,N*-dimethylbenzylamines **1-3** catalyzed by NHPI (a) in CH_3CN and (b) in AcOH.

Table 2. Products and Yields observed in the aerobic oxidation of 4-X-*N,N*-dimethylbenzylamines (**1-3**) catalyzed by NHPI in CH_3CN[a] and in AcOH.[b]

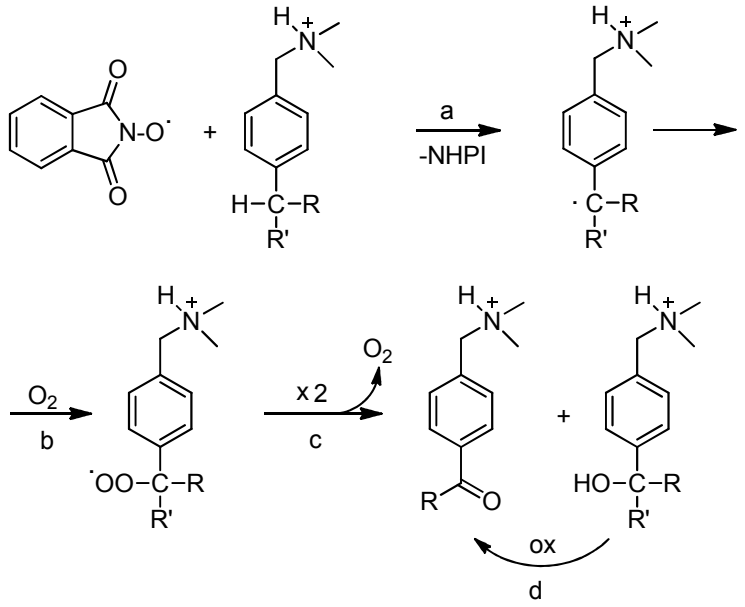
Substrate	Solvent	Convers.	Products (Yields%)[c]		
					
1 R=CH_3, R'=H	CH_3CN	99	80	-	-
	AcOH	70	-	25	41
2 R=R'=CH_3	CH_3CN	75	55	-	-
	AcOH	52	-	45	-
3 R=C_6H_5, R'=H	CH_3CN	81	67	-	-
	AcOH	51	-	9.7	37

[a] Reaction conditions: Amine (0.2 M), NHPI (2×10^{-2} M), $Co(AcO)_2$ (2×10^{-3} M) in MeCN (1 mL) under O_2 (1 atm) at room temperature for 5 h (3h for **3**).

[b] Reaction conditions: Amine (0.7 M), NHPI (7×10^{-2} M), $Co(AcO)_2$ (7×10^{-3} M) in AcOH (1 mL) under O_2 (1 atm), T=50 °C for 22 h.

[c] Determined by GC-MS and ^{1}H NMR analysis and referred to the initial amount of substrate.

In AcOH the reaction products are formed following HAT from the benzylic C–H bonds in the *para* position with respect to the $(CH_3)_2NH^+CH_2$- group to PINO. A plausible mechanism describing the formation of the oxidation products is reported in Scheme 3.



Scheme 3. Mechanism of products formation in the oxidation of **1-3** (X = Et, *i*-Pr, Bn) with the NHPI/$Co(OAc)_2$/O_2 system in AcOH.

Thus, in line with the kinetic predictions and in particular with the significantly higher k_H values measured in AcOH for 4-alkyl-*N,N*-dimethylbenzylamines **1-3** bearing remote benzylic C–H bonds (k_H between 2.7 and 19 $M^{-1}s^{-1}$) as compared to the unsubstituted *N,N*-dimethylbenzylamine (k_H = 0.11 $M^{-1}s^{-1}$), a change in HAT regioselectivity from the activated C–H bonds α-to nitrogen to the less activated benzylic C–H bonds has been accomplished in the NHPI catalyzed aerobic oxidation of **1-3** by changing the solvent from CH_3CN to AcOH. This method represents a suitable way to control the HAT regioselectivity in the oxidative functionalization of amine substrates with a great advantage with respect to the previously reported methodologies[9-11] represented by the use of the most environmentally benign oxidant (O_2).

Conclusions

In conclusion, in this study we have reported the first example of an acid induced change of regioselectivity in the HAT-based C–H bond functionalization of tertiary amines promoted by aminoxyl radicals. Formation of different products in the aerobic oxidation of a series of 4-alkyl-*N,N*-dimethylbenzylamines catalyzed by NHPI are observed in CH_3CN and AcOH, showing that acid-base interactions can represent a powerful tool to modulate site-selectivity. The application of these concepts to the selective C–H bond functionalization of more challenging target molecules containing amine functionalities is currently under investigation in our laboratories.

Experimental Section

Instrumentation

^1H NMR and ^{13}C NMR spectra were recorded on a 300MHz spectrometer. GC-MS analyses were performed on a gas chromatograph equipped with a methylsilicone capillary column (30 m x I.D. = 0.25 mm x df = 0.25 μm) coupled with a mass selective detector. UV-vis measurements were performed on a diode array spectrophotometer. Laser flash photolysis experiments were carried out with a laser kinetic spectrometer providing 8 ns pulses, using the third armonic (355 nm) of a Nd:YAG laser.

Materials

Acetonitrile (HPLC grade), acetic acid, *N*-hydroxyphthalimide, $Co(AcO)_2$ $(H_2O)_4$, $Pb(AcO)_4$ and $HClO_4$ were commercially available and used as received. *N,N*-Dimethylbenzylamine, triallylamine, tribenzylamine, DABCO, *N*-methylpyrrolidine and triethylamine were commercially available at their highest purity and used as received. 4-Ethyl-*N,N*-Dimethylbenzylamine (**1**), 4-isopropyl-*N,N*-dimethylbenzylamine (**2**), 4-benzyl-*N,N*-dimethylbenzylamine (**3**) and *N*-methyl-4-methylpiperidine were prepared following procedures reported in the literature.

*4-Ethyl-N,N-Dimethylbenzylamine (**1**).* The compound was prepared according to a procedure reported in the literature[24] modified as follows. A mixture containing 4-ethylbenzaldehyde (4.1 g,

31 mmol), dimethylamine hydrochloride (5.0 g, 62 mmol), triethylamine (6.1 g, 60 mmol) and titanium isopropoxide (18 mL, 60 mmol) in absolute ethanol (50 mL) was stirred at room temperature for 18 h, then $NaBH_4$ (1.7 g, 45 mmol) was added. The mixture was stirred at 25 °C for 6 h and then treated with 2 M ammonia solution (50 mL). The slurry thus obtained was centrifuged to eliminate the solid precipitate. The solution was extracted with CH_2Cl_2 (three aliquots, 100 mL each). The collected organic phases were concentrated to ca. 50 mL by rotary evaporator and then extracted with 2 M HCl (three aliquots, 30 mL each). The aqueous phases were basified by adding 10 % NaOH and then extracted with CH_2Cl_2 (four aliquots, 100 mL each) carefully maintaining a basic pH in the aqueous phase. The collected organic phases were dried over anhydrous Na_2SO_4 and, after solvent removal, the clear liquid obtained was filtered over silica gel using ethyl acetate as the eluent. After solvent removal, pure 4-ethyl-*N,N*-dimethylbenzylamine (**1**). was obtained as a clear liquid (2.6 g, 16 mmol, 53 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.21-1.26 (t, 3H), 2.26 (s, 6H), 2.60-2.68 (q, 2H), 3.43 (s, 2H), 7.15-7.26 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.6, 28.5, 45.3, 64.1, 127.7, 129.0, 136.0, 142.9.

EI-MS (70 eV) *m/z* (relative intensity): 163 (M^+, 100), 162 (89), 119 (78), 91 (40), 58 (80).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{18}N$ 164.1439; Found 164.1436.

Both ^{1}H and ^{13}C NMR data were in agreement with those reported in the literature.[9d]

*4-Isopropyl-N,N-dimethylbenzylamine (**2**)*. The compound was prepared according to a procedure reported in the literature[9d] modified as follows. A 25 mL round bottom flask containing 4-isopropylbenzylamine (1.49 g, 10 mmol) was cooled to 0 °C (ice/water bath) and then formic acid (1.9 mL, 50 mmol) was slowly added. After addition of formaldehyde (36 wt %, 1.8 mL, 22 mmol), the mixture was refluxed for 16 h. After cooling to room temperature, aqueous HCl (2M, 5 mL) was added and the solvent removed by rotary evaporation. The resulting material was dissolved in H_2O (5 mL), basified with aqueous NaOH (20 % w/v) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. After

chromatographic purification (basic alumina, $CHCl_3$) pure 4-isopropyl-*N,N*-dimethylbenzylamine (**2**) was obtained as a pale yellow liquid (1.24 g, 7.0 mmol, 70 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (d, 6H), 2.24 (s, 6H), 2.90 (septet, 1H), 3.40 (s, 2H), 7.17-7.25 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.0, 34.8, 46.4, 65.1, 127.3, 130.1, 137.1, 148.7.

EI-MS (70 eV) *m/z* (relative intensity): 177 (M^+, 100), 176 (89), 134 (24), 133 (65), 117 (23), 105 (21), 91 (26), 58 (74).

All the spectral data were in agreement with those reported in the literature.[25]

*4-Benzyl-N,N-dimethylbenzylamine (**3**)*. The title compound was prepared by reduction of *N,N*-dimethyl-4-benzyl benzamide prepared according a literature procedure[26] modified as follows. *t*-Butylhydroperoxide (70 % in H_2O, 3.6 mL, 25.7 mmol) was added over 5 min in a 100 mL round bottom flask containing 4-benzyl benzoic acid[27] (3.63 g, 17.1 mmol) and Cu(II) triflate[28] (0.62 g, 1.71 mmol) in DMF (34 mL). The mixture was then stirred at 100 °C for 20 h. After cooling to room temperature H_2O, (100 mL) was added and the mixture extracted with ethyl acetate (4 × 80 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2 × 100 mL), water (100 mL) and brine (100 mL). After solvent removal by rotary evaporator the dark liquid obtained was dissolved in hot EtOH. Hot water was then added until precipitation of a dark compound that was filtered off. The cooled clear solution thus obtained was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated yielding *N,N*-dimethyl-4-benzyl benzamide as a viscous pale yellow oil (2.48 g, 10.4 mmol, 61 %) enough pure to be used in the next step without further purification. [^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.99 (s, 3H), 3.11 (s, 3H), 4.00 (s, 2H), 7.2-7.4 (m, 9H). EI-MS (70 eV) *m/z* (relative intensity): 239 (M^+, 29), 238 (38), 195 (100), 165 (28), 152 (18)]. The amide thus obtained (2.38 g, 9.97 mmol) was dissolved in dry THF (10 mL) and slowly added in a three necks 50 mL round bottom flask cooled at 0 °C (ice/water bath) containing 1M $LiAlH_4$ in THF (11 mL, 11 mmol) under N_2 atmosphere. The solution was then refluxed under N_2 atmosphere for 7 h. After cooling to 0 °C,

NaOH (300 mg) in H_2O (8 ml) was slowly added. The mixture was then diluted in H_2O (80 mL) and extracted with diethyl ether (4 × 80 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. After filtration, solvent evaporation and chromatographic purification (basic alumina, $CHCl_3$), pure 4-benzyl-*N,N*-dimethylbenzylamine (**3**) was obtained as a clear liquid (1.39 g, 6.18 mmol, 62 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.25 (s, 6H), 3.41 (s, 2H), 3.99 (s, 2H), 7.1-7.3 (m, 9 H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.8, 45.6, 64.3, 126.2, 128.6, 129.0, 129.1, 129.4, 136.8, 140.1, 141.4.

EI-MS (70 eV) *m/z* (relative intensity): 225 (M^+, 100), 224 (74), 181 (45), 166 (24), 165 (40), 91 (22), 58 (55).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}N$ 226.1596; Found 226.1598.

N-methyl-4-methylpiperidine. The compound was prepared according to a procedure reported in the literature[29] modified as follows. Zn powder (10.4 g, 65 mmol) was slowly added in a round bottom flask containing a stirred solution of 4-methylpiperidine (9.6 mL, 81 mmol) and aq. Formaldehyde (37 %, 8.9 mL, 120 mmol) in glacial acetic acid (18 mL) at 0 °C (ice/water bath). The mixture was stirred at room temperature for 2.5 h after which aqueous ammonia (30 %, 160 mL) was added and the reaction mixture was extracted with diethyl ether (4 × 80 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the solvent removed by rotary evaporator. After distillation, pure *N*-methyl-4-methylpiperidine was obtained as a colorless oil (2.1 g, 18.7 mmol, 23 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.80 (d, J = 11.8 Hz, 2H), 2.25 (s, 3H), 1.90 (t, J = 11.4 Hz, 2H), 1.61 (d, J = 10.7 Hz, 2H), 1.29-1.21 (m, 3H), 0.91 (d, J = 5.9 Hz, 3H).

^{13}C NMR (CDCl3, 75 MHz) δ: 21.8, 30.1, 34.3, 46.4, 55.9.

EI-MS (70 eV) m/z (relative intensity): 113 (M^+, 38), 112 (100), 98 (7), 70 (20), 58 (7).

^{13}C NMR spectrum was in agreement with that reported in the literature.[30]

Product Characterization.

4-Ethylbenzaldehyde, 4-isopropylbenzaldehyde and 4-benzylbenzaldehyde obtained in the NHPI promoted oxidation of **1-3** in MeCN were characterized by comparison with commercial samples. The oxidation products obtained in AcOH were compared with that obtained as follows.

1-[4-(dimethylaminomethyl)phenyl]-ethanone: An O_2 saturated solution of 4-ethyl-*N,N*-dimethylbenzylamine (500 mg, 3.1 mmol), *N*-hydroxyphthalimide (51 mg, 0.32 mmol) and $Co(AcO)_2$ (5.4 mg, 0.02 mmol) in AcOH (4 mL) was stirred in a Schlenk tube for 30 h at 50 °C under O_2 atmosphere. After solvent removal by rotary evaporator, 100 mL of 30 % NaOH were added and then extracted with of Et_2O (4×20mL). The collected organic fractions were washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed by rotary evaporator. GC-MS analysis of the crude residue showed the presence of 1-[4-(dimethylaminomethyl)phenyl]-ethanone (ca. 30 %) and 1-[4-(dimethylaminomethyl)phenyl]-ethanol (ca. 8 %). Basic alumina chromatography (hexane/ethyl acetate 9:1) afforded 1-[4-(dimethylaminomethyl)phenyl]-ethanone as a clear liquid (160 mg, 25 %). Both ^{1}H NMR and ^{13}C NMR analyses were in agreement with those reported in the literature.[31]

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.25 (s, 6H), 2.59 (s, 3H), 3.47 (s, 2H), 7.39-7.42 (m, 2H), 7.90-7.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 26.5, 45.4, 63.9, 128.3, 129.0, 136.0, 144.5, 197.8.

EI-MS (70 eV) *m/z* (relative intensity): 177 (M^+, 70), 176 (46), 133 (21), 105 (19), 90 (14), 89 (14), 58 (100).

1-[4-(dimethylaminomethyl)phenyl]-ethanol: Attempts to isolate 1-[4-(dimethylaminomethyl)-phenyl]-ethanol from the reaction mixture obtained in the aerobic oxidation of 4-ethyl-*N,N*-dimethylbenzylamine catalyzed by NHPI in AcOH, as described above, were unsuccessful, thus it was synthesized by reduction of 1-[4-(dimethylaminomethyl)phenyl]-ethanone with $NaBH_4$ in EtOH. $NaBH_4$ (17 mg, 0.45 mmol) was added to a stirred solution of 1-[4-(dimethylaminomethyl)phenyl]-ethanone (53 mg, 0.3 mmol) in absolute EtOH (5 mL) and allowed to react for 24 h at room temperature. After solvent removal by rotary evaporator, the residue was

diluted in CH_2Cl_2 (25 mL), washed with three portions (25 mL each) of water, dried over anhydrous Na_2SO_4 and the solvent removed. The residue was purified by preparative TLC (silica gel, ethyl acetate) affording 1-[4-(dimethylaminomethyl)phenyl]-ethanol (48 mg, 89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H), 2.30 (s, 6H), 3.52 (s, 2H), 4.91 (q, 1H), 7.30-7.37 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.1, 45.2, 64.0, 70.1, 125.3, 129.2, 132.3, 144.7.

EI-MS (70 eV) *m/z* (relative intensity): 179 (M^+, 94), 178 (72), 134 (20), 117 (19), 91 (31), 58 (100).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{18}NO$ 180.1388; Found 180.1391.

2-(4-dimethylaminomethyl-phenyl)-propan-2-ol. The title compound was isolated by chromatography (basic alumina, $CHCl_3$) from the reaction mixture obtained for the NHPI mediated oxidation of **2** in AcOH. Pure 2-(4-dimethylaminomethyl-phenyl)-propan-2-ol (41 mg) was obtained as a clear liquid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.56 (s, 6H), 2.20 (s, 6H), 3.40 (s, 2H), 7.25 (m, 2H), 7.43 (m, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 31.8, 45.4, 64.0, 72.3, 124.5, 129.1, 136.9, 148.2

EI-MS (70 eV) *m/z* (relative intensity): 193 (M^+, 100), 192 (74), 177 (24), 176 (18), 175 (29), 174 (24), 134 (24), 131 (34), 91 (20), 58 (100)

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{20}NO$ 194.1545; Found 194.1548.

(4-dimethylaminomethyl-phenyl)-phenyl-methanol. This compound was found as side product in the synthesis of **3** (see experimental section), maybe derived from the $LiAlH_4$ reduction of *N,N*-dimethyl-4-benzoyloxy benzamide impurity present in the *N,N*-dimethyl-4-benzyl benzamide used. Pure (4-dimethylaminomethyl-phenyl)-phenyl-methanol (70 mg) was then isolated during chromatography purification of **3**.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.20 (s, 6H), 3.38 (s, 2H), 5.81 (s, 1H), 7.24-7.37 (m. 9 H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 44.5, 63.3, 75.8, 126.65, 126.72, 127.5, 128.5, 129.8, 136.0, 143.8, 144.4

EI-MS (70 eV) *m/z* (relative intensity): 241 (M^+, 100), 240 (65), 134 (20), 105 (56), 77 (21), 58 (90)

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}NO$ 242.1545; Found 242.1542.

4-dimethylamminomethyl-benzophenone. The title compound was obtained by Jones oxidation of (4-dimethylaminomethyl-phenyl)-phenyl-methanol following a literature procedure[32] modified as follows: 120 μL of 8 N Jones reagent dissolved in acetone (1.5 mL) were added over 20 min in a 5 mL round bottom flask containing a magnetically stirred solution of (4-dimethylaminomethyl-phenyl)-phenyl-methanol (50 mg, 0.207 mmol) in acetone (1 mL) cooled to 0 °C (ice/water bath). 2-Propanol was then added dropwise until the solution turned to deep green. Saturated aqueous K_2CO_3 (6 mL) was then added and the solution extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were then washed with water (50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. After solvent removal by rotary evaporator, pure 4-dimethylamminomethyl-benzophenone (41 mg, 0.172 mmol, 83 %) was obtained as a white solid.

^1H NMR ($CDCl_3$, 300 MHz) δ: 2.26 (s, 6H), 3.49 (s, 2H), 7.41-7.49 (m, 4H), 7.54-7.58 (m, 1H), 7.56-7.80 (m, 4H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 45.6, 64.1, 128.4, 128.9, 130.1, 130.3, 132.4, 136.5, 137.8, 144.1, 196.6

EI-MS (70 eV) *m/z* (relative intensity): 239 (M^+, 100), 238 (55), 167 (23), 165 (19), 105 (17), 77 (18), 58 (98)

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1389.

Aerobic oxidations of 1-3 catalyzed by NHPI/$Co(OAc)_2$.

In CH_3CN: The amine (0.2 mmol, 32.6 mg for **1**, 35,4 mg for **2** and 45.0 mg for **3**) and NHPI (3.3 mg, 0.02 mmol) were added in a Schlenk tube containing a solution of $Co(OAc)_2$ (0.5 mg, 0.002 mmol) in CH_3CN (1 mL). After O_2 bubbling (10 min), the mixture was stirred at room temperature for 5 h (3 h for **3**) under an O_2 atmosphere obtained by connecting the Schlenk tube to a O_2 filled latex balloon. An internal standard (4-methoxybenzophenone) was then added and, after addition of saturated sodium carbonate (10 mL), the mixture was extracted with 3 aliquots of ethyl

acetate (20 mL each). The collected organic phases were then washed with brine and dried over anhydrous Na_2SO_4. After solvent removal by rotary evaporator, the mixture was analyzed by GC-MS and ^1H NMR that showed the presence of the corresponding 4-alkylbenzaldehydes (identified by comparison with authentic specimen) as the main product, (80 %, 55 %, 67 % for **1**, **2** and **3** respectively; yields referred to the initial amount of substrate). No products were formed in blank experiments carried out in the absence of the NHPI catalyst.

In AcOH: The amine (0.7 mmol, 114 mg for **1**, 124 mg for **2** and 158 mg for **3**) and NHPI (11.4 mg, 0.07 mmol) were added in a Schlenk tube containing a solution of $Co(OAc)_2$ (1.7 mg, 0.007 mmol) in AcOH (1 mL). After O_2 bubbling (10 min), the mixture was stirred at 50 °C for 22 h under an O_2 atmosphere obtained by connecting the Schlenk tube to a O_2 filled latex balloon. An internal standard (4-methoxybenzophenone) was then added and the AcOH partially removed by rotary evaporator (up to ca 0.1 mL). After addition of saturated sodium carbonate (10 mL), the mixture was extracted with 3 aliquots of ethyl acetate (20 mL each). The collected organic phases were then washed with brine and dried over anhydrous Na_2SO_4. GC-MS and ^1H NMR analyses of the reaction mixture that showed the exclusive presence of unreacted amine accompanied by the oxidation products (identified by comparison with the authentic samples, see SI for details) listed below with the relative yields referred to the initial amount of substrate:

*N,N-Dimethyl-4-ethyl-benzylamine (**1**)*. 1-[4-(dimethylaminomethyl)phenyl]-ethanone (41 %) and 1-[4-(dimethylaminomethyl)phenyl]-ethanol (25 %).

*N,N-dimethyl-4-isopropyl-benzylamine (**2**).* 2-(4-dimethylaminomethyl-phenyl)-propan-2-ol (45 %).

*N,N-dimethyl-4-benzyl-benzylamine (**3**).* (4-dimethylaminomethyl-phenyl)-phenyl-methanol (9.7 %) and 4-dimethylamminomethyl-benzophenone (37 %).

No products were formed in blank experiments carried out in the absence of the NHPI catalyst.

Laser Flash Photolysis Studies. LFP experiments were carried out with a laser kinetic spectrometer, equipped with a Q-switched Nd:YAG laser, delivering 8 ns pulses at 355 nm. The laser energy was adjusted to < 3 mJ/pulse by the use of the appropriate filter. A 3 mL quartz cell (10

mm × 10 mm) was used in all experiments. Argon saturated CH_3CN solutions containing dicumyl peroxide (1 M), NHPI (5.5-10.5 mM) and the amine (0.4 to 4 mM) were employed. All of the experiments were carried out at T = 25 ± 0.5 °C under magnetic stirring. Experiments in the absence of the amine showed that the PINO absorption intensity was significantly stable and its decay negligible in the milliseconds scale. The observed pseudo first-order rate constants (k_{obs}) were measured following the decay of the PINO radical absorption band at 380 nm. They were obtained by averaging 3−5 individual values and were reproducible to within 5%. Second-order rate constants (k_H) for the reactions of the PINO radical with the amines were obtained from the slopes of the k_{obs} versus [substrate] plots.

Spectrophotometric Kinetic Studies with tertiary amines. PINO was generated by the oxidation of NHPI (2 mM) with $Pb(OAc)_4$ (0.25 mM) in AcOH or in CH_3CN containing 0.1M $HClO_4$ at 25 °C. A solution of the substrate was added into the PINO solution in the cuvette (substrate concentration in the range 4-25 mM for $CH_3CN/HClO_4$ and 5-125 mM for AcOH) and the absorbance change was monitored at 380 nm. For all the substrates investigated each kinetic trace obeyed a first-order kinetic. Second-order rate constants were obtained from the slopes of plots of the observed rate constants k_{obs} vs substrate concentration.

Acknowledgements. Thanks are due to the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) for financial support and to the CIRCC, Interuniversity Consortium of Chemical Catalysis and Reactivity.

Supporting Information Available: ^1H and ^{13}C NMR spectra of synthesized amines and oxidation products, dependence of k_{obs} for the decay of PINO on the concentration of tertiary amines, Hammett plot for HAT from 4-X-*N,N*-dimethylbenzylamines to PINO in CH_3CN. This material is available free of charge via the Internet at http://pubs.acs.org.

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same solvent (3.5 $M^{-1}s^{-1}$) (ref. 14). The lower k_H value determined for **1** can be attributed to the EW effect of the $(CH_3)_2NH^+CH_2$- group.

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