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Aerobic oxidations with *N*-hydroxyphthalimide in trifluoroacetic acid

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ABSTRACT

The potential of highly polar trifluoroacetic acid as a media for the metal-free aerobic oxidations propagated by phthalimide *N*-oxyl- (PINO) radical was demonstrated experimentally utilizing *N*-hydroxyphthalimide (NHPI) as a catalyst and HNO_3 or $NaNO_2$ as promoters. The oxidations of toluene, cyclohexane, adamantane, diamantane, and 3-oxadiamantane gave, respectively, benzaldehyde, adipic acid, 1-hydroxyadamantane, 1-hydroxydiamantane, and 9-hydroxy-3-oxadiamantane with up to 90% selectivities under high conversions of starting material. From the density functional theory computations at the M06-2X and B3LYP-D3 levels the polarized transition structures (TS) for the hydrogen abstraction from toluene and benzyl alcohol with highly electrophilic PINO-radical are substantially stabilized by non-covalent interactions (π–π stacking). Such additional stabilization is not present in the TS for the H-abstraction from benzaldehyde thus retarding its over-oxidation to benzoic acid.

1. Introduction

Partial oxidation of toluene to benzaldehyde represents a formidable challenge both for the laboratory and industry as over-oxidation to benzoic acid dominates already at the moderate conversions of starting material. Aerobic oxidations [1] of toluene are particularly unselective: While the oxidation with O_2 in the presence of Co^{II}-complexes gave benzaldehyde and benzyl alcohol only in 60% selectivity even at very low conversions (8.9%), [2] benzaldehyde forms in 68% preparative yield from the oxidation of toluene with *tert*-butyl hydroperoxide [3]. In many other aerobic transition-metal-based systems [4] benzaldehyde was found as a major product only under moderate conversions (<20%) of toluene [5]. The oxidation in various solvents [6], with additives [7], in presence of copper binary oxides, [8,9] MOFs, [10,11] porous carbon nitride C_3N_4 [12,13], Au-Pd alloy carbon nanoparticles,[14] cerium nanocubes,[15] $CuCr_2O_4$ spinel nanoparticles [16], and zeolites [17] led to little improvements. Remarkably, benzaldehyde is the main product of toluene photocatalytic aerobic oxidation on the Ru-doped TiO_2 nanotubes at 650 °C where the formation of benzoic acid is completely suppressed, though, no preparative yields were reported [18]. Satisfactory selectivities at high conversions of starting material were observed only for enzymatic oxidations of toluene with Cu-laccase [19–22] or oxidation with NHPI and Co^{II}-salts in HFIP [23].

Powerful "green" [24] organocatalyst *N*-hydroxyphthalimide (NHPI, Scheme 1) occupies an outstanding position in aerobic oxidations [25–29] as it is effective both in the presence of transition metals [30] and under metal-free conditions [31–35] operating for CH-bonds in alkylaromatics and even in unactivated alkanes. At the initiation step (typically with metal-peroxo species or with the NO_2-radical, ***A***, Scheme 1) NHPI generates highly electrophilic phthalimide *N*-oxyl- (PINO) radical, which is involved into the CH-abstraction step (***B***) from hydrocarbon (RCH_3). This recovers the catalyst NHPI [36] and thus formed hydrocarbon radicals $RCH_2^{\bullet}$ are trapped (***C***) with molecular oxygen to form peroxyl-radicals $RCH_2OO^{\bullet}$ that propagate the oxidation by generating PINO from NHPI (***D***) [37]. Hydroperoxides RCH_2OOH thus formed undergo dehydrations/exchanges/oxidations typical for hydrocarbon aerobic chemistry (***E***).

The mild aerobic oxidations of toluene with NHPI in the presence of Co^{II}-salts occur at room temperature either in CH_3CN or CH_3COOH, however even at *ca.* 50% of toluene conversion 45% of benzoic acid forms with only traces of benzaldehyde. The catalytic system based on the combination of NHPI and $VO(acac)_2$ oxidizes toluene with conversion of 14.4% in 93/7 benzaldehyde/benzyl alcohol ratio [38]. Heterogeneous transformations usually require harsher conditions. The NHPI immobilized on mesoporous molec-

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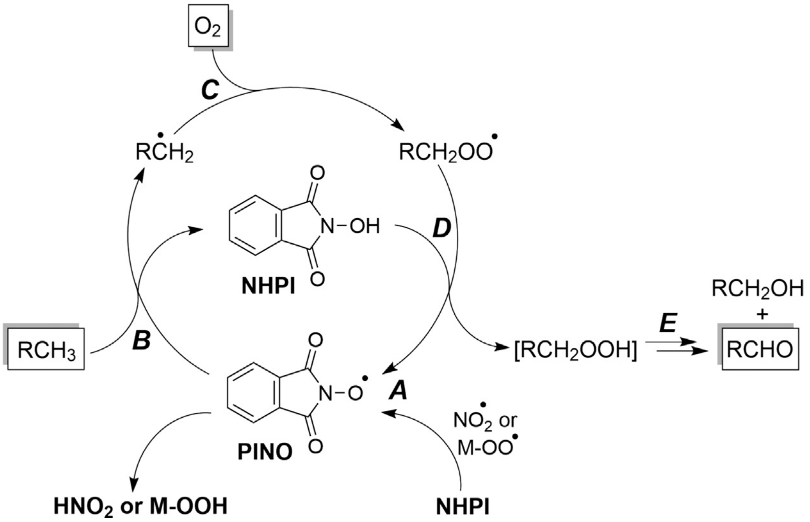


Scheme 1. The aerobic oxidations of the methyl group carried by the phthalimide *N*-oxyl- (PINO) radical generated from *N*-hydroxyphthalimide (NHPI) and initiated by the $NO_2^{\bullet}$ or metal-peroxo (M-OO•) radicals.

ular sieves catalyzes an aerobic liquid-phase oxidation of toluene in acetonitrile at 190 °C that gives benzaldehyde as a main product only at very low conversions still together with benzoic acid and benzyl alcohol [39]. The oxidation in acetic acid at 100 °C on SiO_2-supported Co(II)/NHPI heterogeneous catalyst yields only 18% of oxidation products [40]. The aerobic oxidation on polymer-supported NHPI in the presence of Co^{II} and AIBN at 80 °C even at 20% conversion produces a comparable amounts of benzyl alcohol, aldehyde, and acid [41]. The oxidation on MOFs at 110 °C under conversions <10% leads to benzaldehyde and benzyl alcohol in ca. 5/1 ratio [10]. The *o*-phenanthroline-mediated, metal-free catalytic system with Br_2 produces benzaldehyde and benzoic acid at 1:4 ratio already at ca. 20% toluene conversion [42]. An efficient oxidation of methylarenes to corresponding aldehydes in hexafluoroisopropan-2-ol in presence of NHPI was recently suggested but still requires the presence of the Co^{II}-salts [23].

The general conclusion is that, despite enormous efforts, the preparative synthesis of aldehydes by direct metal-free aerobic oxidations of methylaromatics, in particular toluene conversion to benzaldehyde, still is problematic even with such remarkable catalyst as NHPI. Herein we first model the aerobic oxidation of toluene with and without NHPI computationally at the density functional theory (DFT) level and then study the oxidation of toluene experimentally. We then apply our new reactive system for the preparative CH-oxidations of cyclohexane, adamantane, and diamantane as well as otherwise extremely unreactive 3-oxadiamantane.

2. Experimental

2.1. General

All computations were performed with the GAUSSIAN09 program suite utilizing analytical first and second energy derivatives. The NMR spectra were recorded with a Bruker Advance II spectrometer, the chemical shifts are given in ppm relative to TMS. GC–MS analyses were performed with an HP5890 GC with an HP5971A mass-selective detector. Products were purified by chromatography on 100–160 mesh silica gel. All melting points were determined without correction. Commercially available reagents and solvents were used without further purification. No special inert conditions were established and free access of the atmospheric oxygen was allowed in the experiments where the presence of O_2 is mentioned. Detailed spectroscopic characterization of new compounds are provided in the Supplementary Information.

2.1.1. Oxidation of adamantane (**9**) in the TFA/HNO_3/O_2 system (1 eq. of HNO_3)

0.6 mL (0.8 g, 7.5 mmol) of 56% HNO_3 was added to a stirred mixture of 1 g (7.4 mmol) of adamantane (**9**) in 11 mL of CF_3COOH. The mixture was heated to 50 °C and stirred for 4 h, strong nitrous oxides evolution occurred and starting material dissolved during the course of reaction. The GC–MS analysis of reaction mixture identified 53% of 1-adamantyl-trifluoroacetate, 44% of 1-nitroadamantane (**11**) and 3% of 1-hydroxy adamantane (**10**). 1-Adamantyl-trifluoroacetate was identified by comparative GC–MS analysis with standard sample. Then CF_3COOH was removed in vacuum and 8 mL of 10% ethanol solution of KOH was added. The residue after evaporation of ethanol was dissolved in ether (20 mL), washed with water (2 × 5 mL) and dried. Evaporation followed by column chromatography on silica gel (ethyl acetate/hexane = 1/9) gave 0.56 g (42%) of 1-nitroadamantane [43] (**11**) and 0.61 g (54%) of 1-hydroxyadamantane (**10**) identical to the standard samples.

2.1.2. Oxidation of adamantane (**9**) in the TFA/HNO_3/O_2 system (cat. HNO_3)

The same as above, but 0.06 mL (0.08 g, 0.74 mmol, 0.1 eq) of 56% HNO_3 was used. Evaporation of the extract after ethanol/KOH hydrolysis gave 1.05 g (94%) of 1-hydroxyadamantane (**10**) identical to the standard sample.

2.1.3. Oxidation of adamantane (**9**) in the TFA/NHPI/HNO_3/O_2 system (cat. HNO_3)

The same as above, but 0.121 g (0.74 mmol, 0.1 eq.) of NHPI was added, 1.05 g (94%) of 1-hydroxyadamantane (**10**) identical to the standard sample was isolated as above.

2.1.4. Oxidation of diamantane (**12**) in the TFA/HNO_3/O_2 system (1 eq. of HNO_3)

0.43 mL (0.57 g, 5.31 mmol) of 56% HNO_3 was added to a stirred mixture of 1 g (5.31 mmol) of diamantane (**12**) in 8 mL of CF_3COOH. Column chromatography on silica gel (ethyl acetate/hexane = 1/9) gave 0.51 g (41%) of 1-nitrodiamantane [43] (**14**) and 0.56 g (52%) of 1-hydroxydiamantane (**13**) identical to the standard samples.

2.1.5. *Oxidation of diamantane (**12**) in the TFA/HNO_3/O_2 system (cat. HNO_3)*

The same as above, but 0.043 mL (0.057 g, 0.53 mmol, 0.1 eq.) of 56% HNO_3 was used. Evaporation of the extract after ethanol/KOH hydrolysis gave 1.05 g (97%) of 1-hydroxydiamantane (**13**) identical to the standard sample [44].

2.1.6. *Oxidation of diamantane (**12**) in the TFA/NHPI/HNO_3/O_2 system (cat. HNO_3)*

The same as above, but 0.087 g (0.53 mmol, 0.1 eq.) of NHPI was added, 1.05 g (97%) of 1-hydroxydiamantane (**13**) identical to the standard sample [44].

2.1.7. *Oxidation of cyclohexane (**15**) in the TFA/NHPI/HNO_3/O_2 system*

0.194 g (1.19 mmol) of NHPI and 1.93 mL (2.55 g, 23.8 mmol) 56%-HNO_3 was added to a stirred solution of 1.28 mL (1 g, 11.9 mmol) of cyclohexane (**15**) and 18.2 mL of CF_3COOH. The mixture was heated to 50 °C and stirred for 4 h, strong nitrous oxides evolution occurred during the course of reaction. Then CF_3COOH and **15** were removed in vacuum and 10% solution of NaOH (20 mL) was added to the residue, stirred for 30 min, extracted with CH_2Cl_2 (3 × 10 mL), the aqueous layer was refluxed with 0.2 g of activated carbon for 6 h and filtered. Residue was washed with small portions of water (3 × 10 mL). Filtrate was acidified with diluted HCl and crystals thus formed were filtered off and dried under vacuum to give 800 mg (45%) of **16**, identical to the standard sample.

2.1.8. *Oxidation of 3-oxadiamantane (**17**) in the TFA/NHPI/HNO_3/O_2 system*

The mixture of 0.57 g (3 mmol) 3-oxadiamantane (**17**), [45] 0.048 g (0.1 mmol) NHPI, 0.24 mL (0.32 g, 3 mmol) 56% nitric acid, in 5 mL of TFA. The mixture was heated to 50 °C and stirred for 4 h, strong nitrous oxides evolution occurred during the course of reaction. The GC–MS analysis of reaction products identified mixture of 3-oxadiamantane trifluoroacetates and ketones. Then CF_3COOH was removed in vacuum and 8 mL of 10% ethanol solution of KOH was added. The residue after evaporation of ethanol was dissolved in ether (20 mL), washed with water (2 × 5 mL) and dried. Evaporation followed by column chromatography on silica gel with CH_2Cl_2/Methanol = 9/1 gave 0.19 g, (34%) of starting 3-oxadiamantane (**17**) and 0.105 g, (17%) of 6-hydroxy-3-oxadiamantane (**19**) identical to standard sample, [45] 0.05 g, (8%) of 1-hydroxy-3-oxadiamantane (**18**), 0.093 g, (15%) of 11-hydroxy-3-oxadiamantane (**20**), 0.062 g, (10%), of 9-hydroxy-3-oxadiamantane (**21**), 0.037 g, (10%) of 3-oxadiamantane-8-one (**22**), and 0.061 g, (10%) of inseparable mixture identified (GC–MS) as isomeric ketones.

1-Hydroxy-3-oxadiamantane (**18**)

Mp = 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.95 (bs, 1H), 3.55 (bs, 1H), 2.95 (s, 1H), 2.46–2.39 (m, 1H), 2.75 (s, 1H), 2.11 (s, 1H), 2.4 (m, 1H), 1.99–1.91 (m, 1H), 1.9–1.79 (dd, 2H), 1.73–1.55 (m, 7H), 1.45 (dd, 1H). ^{13}C NMR: 78.9 (CH), 68.2 (C), 65.5 (CH), 42.4 (CH_2), 41.9 (CH), 38.1 (CH), 37.8 (CH), 36.6 (CH_2), 36.1 (CH_2), 35.7 (CH_2), 34.6 (CH), 31.0 (CH_2), 28.9 (CH). HR-MS: found 206.1321 (calculated for $C_{13}H_{18}O_2$: 206.1311).

11-Hydroxy-3-oxadiamantane (**20**)

Mp. = 264–266 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.9 (bs, 1H), 3.68 (bs, 1H), 2.29 (bs, 2H), 2.13 (dd, 2H), 2.05 (m, 1H), 1.8 (m, 3H), 1.75 (dd, 2H), 1.65 (m, 4H), 1.55 (dd, 2H). ^{13}C NMR: 73.5 (CH), 70.0 (C), 65.6 (CH), 45.8 (CH_2), 41.7 (CH), 39.1 (CH), 35.4 (CH_2), 31.6 (CH_2), 29.6 (CH). HR-MS: found 206.1335 (calculated for $C_{13}H_{18}O_2$: 206.1302).

9-Hydroxy-3-oxadiamantane (21)

Mp = 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.98 (bs, 1H), 3.82 (bs, 1H), 2.2 (bs, 2H), 2.11 (bs, 1H), 2.05 (dd, 2H), 1.9 (bs, 2H), 1.79 (dd, 2H), 1.72 (dd, 2H), 1.7 (dd, 4H), 1.58 (dd, 1H). ^{13}C NMR: 73.7 (CH), 66.8 (C), 65.4 (CH), 44.9 (CH_2), 43.4 (CH_2), 38.2 (CH), 38.2 (CH), 36.6 (CH_2), 34.8 (CH). HR-MS: found 206.1329 (calculated for $C_{13}H_{18}O_2$: 206.1317).

3-Oxadiamantane-8-one (**22**)

Mp = 204–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 4.1 (1H, m), 4.0 (1H, m), 2.65–2.6 (1H, m), 2.45–2.4 (1H, m), 2.25–2.2 (4H, m), 2.2–2.15 (2H, dd), 1.99–1.92 (4H, m), 1.72–1.64 (2H, dd). ^{13}C NMR: 216.1 (C), 73.0 (CH), 65.2 (CH), 54.1 (CH), 42.5 (CH), 37.5 (CH), 36.4 (CH_2), 35.5 (CH), 34.9 (CH_2). HR-MS: found 204.1219 (calculated for $C_{13}H_{18}O_2$: 204.1206).

2.1.9. *Toluene (**1**) oxidation to benzaldehyde (**3**), method **A***

Under oxygen atmosphere 6 mL of TFA was slowly added in portions to a stirred mixture of 2 mL (18.9 mmol) of toluene (**1**), 750 mg (4.6 mmol) of NHPI, 525 mg (7.6 mmol) of $NaNO_2$ in 6 mL of co-solvent (*n*-hexane or CH_2Cl_2) at 0 °C. The reaction mixture was stirred at room temperature for 13 h, quenched by the 10 mL of water. Organic layer was separated and water part was extracted with *n*-hexane (2 × 5 mL). Combined extracts were washed with 10%-$NaHCO_3$ solution (3 × 5 mL), water (2 × 5 mL), shaked with saturated solution of $NaHSO_3$ (10 mL) for 2 h and diluted with water to dissolve the precipitate. Water layer was separated, washed with *n*-hexane (2 × 5 mL) and 10 mL of 20%-NaOH solution was added. A free aldehyde was extracted by pentane (3 × 5 mL), combined extracts washed with water (2 × 5 mL), dried over $MgSO_4$ and evaporated to give 0.7 g (35%) of benzaldehyde (**3**) identical to the standard sample.

2.1.10. *Toluene (**1**) oxidation to benzaldehyde (**3**), method **B***

The same as **Method A**, but without a co-solvent gave 0.76 g (38%) of benzaldehyde (**3**) isolated as above.

2.1.11. *Toluene (**1**) oxidation to benzaldehyde (**3**), method **C***

Under the oxygen atmosphere a solution of 525 mg (7.6 mmol) of $NaNO_2$ in 1 mL of water was added in portions to a stirred mixture of 2 mL (18.9 mmol) of toluene (**1**), 750 mg (4.6 mmol) of NHPI, 6 mL of TFA at room temperature over 1 h. Reaction mixture stirred at room temperature for 3.5 h to give 0.74 g, (37%) of benzaldehyde (**3**) isolated as above.

3. Results and discussion

3.1. *Consecutive PINO-promoted oxidations of toluene from theoretical viewpoint*

The high rates of the NHPI-catalyzed oxidations of toluene are determined by pronounced electrophilicity of the PINO-radical. This is seen from the accelerations of the H-abstractions from toluene derivatives with electron-donating substituents (negative Hammett ρ-values) [46],[47]. Due to high polarization of the transition structures for the hydrogen abstraction the reaction is highly sensitive to the polarity of the solvent [48]. In order to estimate the influence of PINO on the aerobic oxidations of toluene we first modeled the transformations computationally [49]. As the non-covalent interactions, in particular π–π stacking, may contribute substantially to the H-abstractions with PINO from aromatics [50] and the traditional DFT-models may be not relevant, [51] we employed the M06-2X method, [52] which is parametrized to account dispersions through the medium-range electron correlations. This method was previously successfully applied for different classes of hydrogen-bonded, van der Waals π–π stacked clusters [53–56]. We compare the results with empirically dispersion-corrected method B3LYP-D3 [57]. To account for the solvent effects we utilize a polarizable

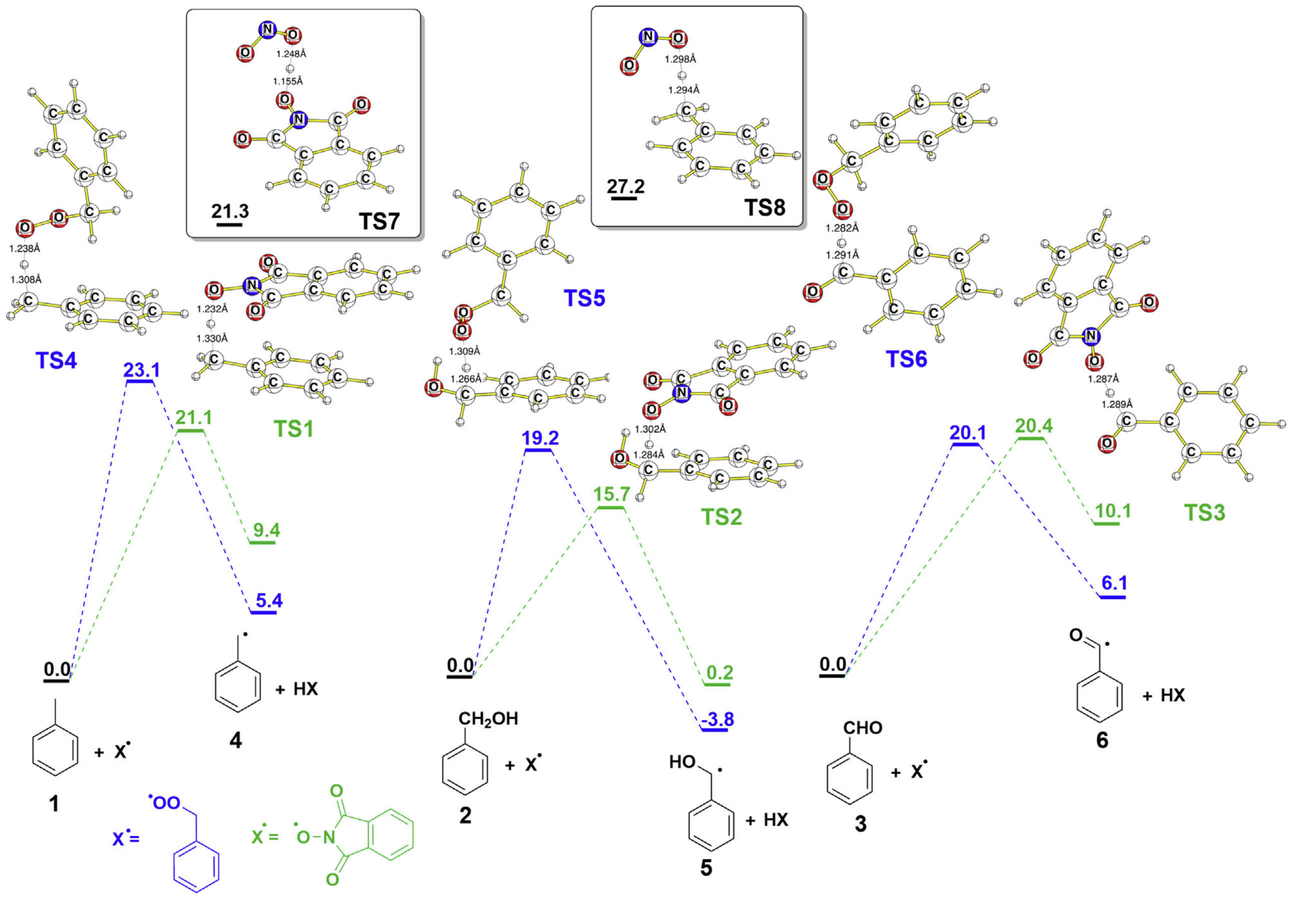


Fig. 1. Consecutive H-abstractions from toluene (**1**), benzyl alcohol (**2**), and benzaldehyde (**3**) with PINO- (**TS1**–**TS3**), peroxybenzyl- (**TS4**–**TS6**) radicals, and from NHPI (**TS7**) and toluene (**TS8**) with NO_2-radical (relative ΔG_{298} at PCM(H_2O)-M06-2X/cc-pVDZ).

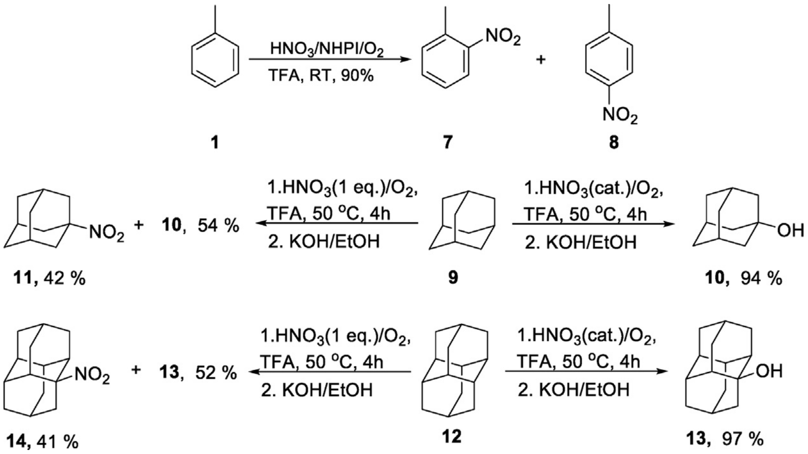
continuum model (PCM) as implemented in Gaussian09 program [58].

The oxidation proceeds as a consecutive H-abstractions from toluene (**1**), benzyl alcohol (**2**), and benzaldehyde (**3**, Fig. 1). The first H-abstraction by PINO from toluene (**1**) to form benzyl radical (**4**) requires a barrier of $\Delta G_{298}{}^{\neq}$ = 21.1 kcal/mol (M06-2X/cc-pVDZ, **TS1**, Fig. 1) [59]. The **TS1** in the *cis*-conformation is substantially stabilized by π–π-stacking as the respective *trans*-form (not shown) is *c.a.* 4 kcal/mol higher in energy both at M06-2X and B3LYP-D3. As the net NBO charge and spin on the hydrocarbon part of **TS1** is substantial (+0.3*e* and 0.6, respectively) mechanistically the reaction is best viewed as the proton-coupled electron transfer previously suggested for the CH-activations of hydrocarbons with charged electrophiles [60,61]. Such pronounced polarization makes the reaction markedly solvent-dependent (*vide infra*) [62]. As the **1** → **4** transformation is substantially endergonic (ΔG_{298} = +9.4 kcal/mol), the H-abstraction with PINO is effective only in the presence of molecular oxygen [63], which traps benzyl radical (**4**) and makes the process irreversible (step ***C***, Scheme 1). Recently the TSs for the H-abstraction from toluene ($\Delta G_{298}{}^{\neq}$ = 20.6 kcal/mol) with PINO were located at the B3LYP-DCP/6-31G(2d,2p) level of theory and the contribution of π–π stacking was revealed [64]. The barrier agrees well with our computations at M06-2X/cc-pVDZ ($\Delta G_{298}{}^{\neq}$ = 21.1 kcal/mol).

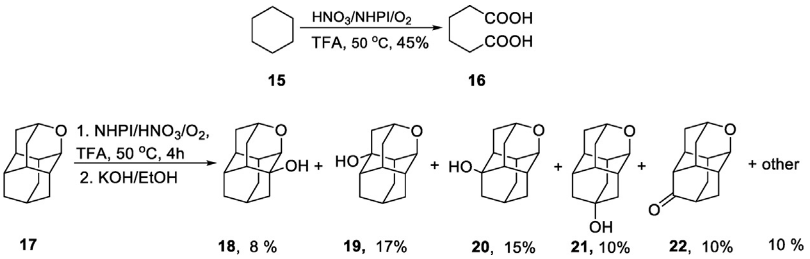
The next oxidation step, the H-abstraction from benzyl alcohol (**2**) with PINO through **TS2**, requires only moderate barrier of 15.7 kcal/mol and this reaction, in contrast to the first step, is thermoneutral. As in the case of **TS1**, the π–π stacking substantially stabilizes **TS2** and reduces the barrier even further. This is an agreement with the experiment where **2** typically is a minor component in the reaction mixtures of toluene oxidations [28,65]. The critical is that the barrier for the H-abstraction from benzaldehyde (**3**) through **TS3** is substantial ($\Delta G_{298}{}^{\neq}$ = 20.4 kcal/mol) and is close to that for H-abstraction from **1** (**TS1**). Remarkably, the π-π stacking is not present in **TS3** due to distant location of the aromatic moieties. Relatively high barrier and high endergonicity (ΔG_{298} = +10.1 kcal/mol) of **3** → **6** step facilitate the termination of the reaction at the stage of aldehyde **3**. The fact that toluene is only slightly less reactive than benzaldehyde towards PINO• ($\Delta G_{298}{}^{\neq}$ = 21.1 vs 20.4 kcal/mol) is in accord with the experiment which displays $k_{\text{toluene}}/k_{\text{benzaldehyde}} = 0.67$ (see SI for details).

All above is in a sharp contrast with the reaction without PINO where the peroxybenzyl- (BnOO) radicals are responsible for the H-abstractions. The oxidation consequently proceeds through **TS4** → **TS5** → **TS6** without contribution of π–π stacking (Fig. 1). The barrier for the H-abstraction from toluene is 2 kcal/mol higher for BnOO• than for PINO• (cf. **TS4** and **TS1**) that agrees well with the experimental kinetics, which displays that the PINO-radical is much more reactive than the peroxyl-radicals [62]. Additionally, toluene (**1**) reacts much slower with BnOO• ($\Delta G_{298}{}^{\neq}$ = 23.1 kcal/mol, **TS4**) than aldehyde **3** ($\Delta G_{298}{}^{\neq}$ = 20.1 kcal/mol, **TS6**). Thus, the over-oxidation to benzoic acid is more favored for BnOO• than for the PINO-radical.

We also estimated the barriers for the H-abstractions with NO_2-radical from NHPI that is a primary initiation step under the metal-free conditions (step ***A***, Scheme 1). The barrier for this reaction ($\Delta G_{298}{}^{\neq}$ = 21.3 kcal/mol, **TS7**) is much lower than



Scheme 2. The NHPI-catalyzed and HNO_3-promoted aerobic oxidations of hydrocarbons **1**, **9** and **12** in trifluoroacetic acid (yields are preparative).



Scheme 3. The NHPI-catalyzed and HNO_3-promoted aerobic oxidations of nonactivated substrates **15**, and **17** in trifluoroacetic acid (yields are preparative).

the barrier for the H-abstraction from toluene with the NO_2-radical ($\Delta G_{298}{}^{\neq}$ = 27.2 kcal/mol, **TS8**). The latter cannot compete for toluene with the PINO-radical due to much lower energy of **TS1** ($\Delta G_{298}{}^{\neq}$ = 21.1 kcal/mol).

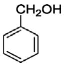
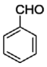
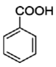
3.2. *Preparative aerobic oxidations with NHPI in trifluoroacetic acid initiated by HNO_3*

Exceptionally high polarizations of the transition structures for the H-abstraction from toluene with PINO favor the oxidations with NHPI in polar solvents. Acetic acid was first demonstrated the efficiency as a solvent for aerobic NHPI-catalyzed oxidations of cyclooctane [66] and then for many other hydrocarbons [28,48]. The fast equilibrium between $PINO^{\bullet}$ and $ROO^{\bullet}$ exists even in H-bonding solvents and this, together with the high rate constants for the H-abstractions by PINO, determine the propagation efficiency of the NHPI-catalyzed oxidations in protic acids [67].

Trifluoroacetic acid (TFA) is among the most polar organic solvents and is characterized by the highest known acceptor number of 105.3 (*cf.* 52.9 for acetic acid) [68]. To the best of our knowledge it has never been tested as a media for the NHPI-chemistry. Considering the significance of "green" nitroxide-catalyzed aerobic oxidations [69] we employ a standard transition-metal-free oxidative system with NO_2 as an initiator [48]. We first utilize the nitric acid as the NO_2-source, however, the transformation of toluene in the NHPI/TFA/O_2 system displays almost exclusive formation of a mixture of *ortho*- (**7**) and *para*- (**8**) nitro toluenes as a result of well-documented [70] electrophilic aromatic substitutions in TFA (Scheme 2). The same product ratio was found in absence of NHPI. Taking to account that relatively high reactivity of **9** towards nitric acid or nitronium reagents have already been reported by many [71–74], similar behavior for adamantane (**9**) and diamantane (**12**) is expected. The ratio of the products depends on the amounts of HNO_3 employed. With one equivalent of HNO_3 **9** forms 1-nitro adamantane (**11**) in 42% preparative yield and **12** forms 1-nitrodiamantane (**14**) in 41% preparative yield in the HNO_3/TFA/O_2 system. In contrast, the nitration is suppressed in the presence of catalytic amounts of HNO_3 where alcohols **10** and **13** form exclusively (Scheme 2). The formation of respective alcohols (**10** and **13**) and nitro-derivatives (**11** and **14**) in the TFA/HNO_3/O_2 system could be attributed to the TFA-mediated electrophilic CH-substitution [75–77]. Note, that the presence of NHPI has no influence on the ratio of the products for cage substrates **9** and **12** as it would be expected for non radical reaction. Changing the solvent from TFA to acetic acid gave unchanged starting materials for all substrates (**1**, **9** and **12**), even in presence of nitric acid excess. We conclude that TFA/HNO_3/O_2 system promotes electrophilic reactions and is not suitable for toluene conversion to benzaldehyde.

Nevertheless, this system appears to be very effective for the oxidations of saturated hydrocarbons that are less reactive than **1**, **9**, and **12** towards nitronium electrophiles. In particular, we were able to oxidize cyclohexane (**15**) to adipic acid (**16**) in NHPI/HNO_3/TFA/O_2 system. To achieve satisfactory conversions for such deep oxidations larger NHPI loadings (up to 10%) are required. The reaction displays exceptional selectivity as it allows to achieve 45% preparative yield of **16** at 50% conversion of starting material. Note, that the most successful previous NHPI-catalyzed aerobic oxidation of **15** (with $Mn(acac)_2$ in acetic acid at 100 °C) [78] reached 73% preparative yield of **16** at 73% conversion. Our NHPI/HNO_3/TFA/O_2 system is preparatively convenient as TFA and unreacted cyclohexane (**15**) are easily recovered from the reaction mixture by distillation. All the attempts to oxidize **15** in acetic acid or without NHPI gave no conversion of starting material, which displays the key role of TFA in the PINO-promoted H-abstraction step. From this point of view, the behavior of 3-oxadiamantane (**17**), which is low reactive towards electrophiles [45] is instructive. It is noteworthy that the transformation of **17** occurs in the HNO_3/TFA/O_2 system only in the presence of NHPI that is the strong evidence for the radical process promoted by the PINO-radical. While in the NHPI/HNO_3/AcOH/O_2 system **17** is unreactive,

Table 1
The oxidations of toluene (**1**) in trifluoroacetic acid (TFA).

#	Method[a]	Temp.	Time, h	Conv. of **1**, %	 (**2**), %	 (**3**), %	 (**23**), %	Isolated yield of **3**, %
1	**A**[b]	RT	25	4	traces	0.1	0.3	–
2	**A**	RT	13	83	2	38	0	35
3	**A**	10 °C	4.5	12	0.5	0.6	0	–
4	**B**[c]	35 °C	13	98	7	48	5	38
5	**B**[c]	45 °C	2	90	4	31	11	–
6	**C**[d]	RT	4.5	89	3	42	3	37
7	**A**[e]	RT	22	18	traces	1.4	3	–
8	**A**[f]	RT	20	0	0	0	0	–
9	**A**[g]	RT	13	7	traces	1.1	0	–

[a] Method **A**: 18.9 mmol of toluene, 4.6 mmol of NHPI, 6.2 mmol of $NaNO_2$, 6 mL of hexane, 6 mL of TFA.
[b] Acetic acid used instead of TFA.
[c] Method **B**: Same as Method **A**, but without *n*-hexane.
[d] Method **C**: The same as Method **B** but $NaNO_2$ was added in 1 mL of water dropwise over 1 h.
[e] without NHPI.
[f] without $NaNO_2$.
[g] under argon atmosphere.

the oxidations in TFA gave 1-hydroxy-3-oxadiamantane (**18**), 6-hydroxy-3-oxadiamantane (**19**), 11-hydroxy-3-oxadiamantane (**20**), 9-hydroxy-3-oxadiamantane (**21**) and ketone (**22**) (Scheme 3, for the structure assignments see SI). Performing the reaction of 3-oxadiamantane (**17**) in this system followed by alkaline hydrolysis allowed us to synthesize and isolate previously inaccessible alcohols (**18**, **20**, and **21**) and ketone (**22**). Note, that the substitution with electrophiles [45] give exclusively the products of medial substitution in position "6". Apically substituted 9-hydroxy-3-oxadiamantane (**21**) obtained in the NHPI/TFA/HNO_3/O_2 system is useful for surface depositions as the apical diamondoid derivatives are characterized by superior surface affinities [79].

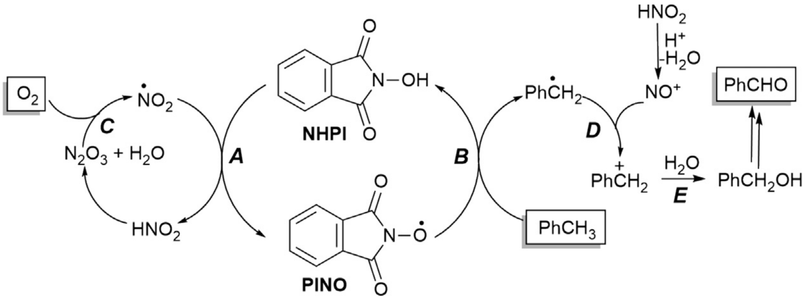
We conclude, that while the TFA/HNO_3 system demonstrates great potential as a media both for nitronium reagents mediated electrophilic reactions and deep NHPI-catalyzed aerobic oxidations, but, again, it is not applicable for target selective oxidation of methyl group in toluene due to fast electrophilic substitutions.

3.3. Aerobic oxidations of toluene with NHPI in trifluoroacetic acid initiated by $NaNO_2$

In order to avoid undesired electrophilic aromatic substitutions, the next logical step is to replace the nitric acid by alternative source of the NO_2-radical. Sodium nitrite ($NaNO_2$) is an environmentally friendly inexpensive transition-metal-free "green" [80–84] catalyst and produces NO under the mildly acidic conditions. It is useful for the aerobic oxidations of alcohols to aldehydes and ketones in the presence of 2,2,6,6-tetramethyl-piperidyl-1-oxyl (TEMPO) in the acetic acid [85] and TFA [86]. In contrast, TEMPO acts as a radical scavenger and inhibits the aerobic oxidations of the sp^3C-H bonds: In the $NaNO_2$/TFA system [87] cyclohexanol is oxidized to **16** quantitatively with 2 eq. of $NaNO_2$, whereas cyclohexane (**15**) is inert under these conditions [88]. The $NaNO_2$-promoted aerobic oxidations in aqueous HCl, were recently applied for activated benzylic positions [89]. Previously, $NaNO_2$ in trifluoroacetic acid was used for selective nitration of aromatic compounds [75–77]; remarkably, no oxidation products of methylarenes were observed.

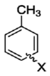
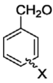
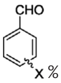
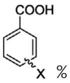
We first tested the acetic acid as a media for the oxidations of **1** with $NaNO_2$/NHPI and found a negligible conversion even at prolonged reaction times (Table 1, Entry 1). In contrast, in TFA at room temperature in the presence of catalytic amounts of $NaNO_2$ the reaction proceeds smoothly displaying high conversions of **1**. To our surprise even at 83% conversion of **1** benzaldehyde (**3**) still dominates in the reaction mixture and benzoic acid (**23**) forms only in trace amounts (Table 1, Entry 2). The by-products were separated after **3** was washed out from the reaction mixture with saturated $NaHSO_3$ solution. The GC/MS analyses identified the formation of nitro-toluenes **7** and **8** as main by-products together with isomeric nitro-benzaldehydes. We compared two different procedures, namely the addition of solid $NaNO_2$ with (Method **A**, Table 1, Entries 2 and 3) or without (Method **B**, Entry 4) co-solvent *n*-hexane and did not find any substantial differences. The signs of the over-oxidation were observed only under slight heating, which substantially accelerates the reaction but lowers its selectivity due to formation of substantial amounts of benzoic acid (Table 1, Entry 5). As some previous NHPI-oxidations in biphasic systems [90,91] or in the aqueous organic solvents [92] were successful, we also utilize $NaNO_2$ as a saturated water solution (Method **C**, Entry 6). All three procedures (**A**–**C**) gave benzaldehyde (**3**) in 35–38% preparative yield. Note that the transformations require relatively large amounts of NHPI (up to 25%) to complete; reducing the amounts of $NaNO_2$ also substantially slower the reaction. The fact that only minor amounts of benzyl alcohol (**2**) and benzoic acid (**23**) were found in the reaction mixtures at room temperature agrees well with the computations where the barrier for the H-abstraction with PINO-radical is much higher from **3** (Fig. 1, **TS3**) than from **2** (**TS2**). Only very slow reaction was observed in the absence of NHPI (Table 1, Entry 7), where benzoic acid dominates over **3** that again is in agreement with the computational picture of the reaction carried on by BnOO-radical (Fig. 1). The reaction is completely suppressed in the absence of promotor $NaNO_2$ (Table 1, Entry 8) and only traces of oxidation products form under argon atmosphere (Table 1, Entry 9) demonstrating the true aerobic nature of the reaction. In the $NaNO_2$/NHPI system the main by-products resulted from the electrophilic nitration and are identical to those obtained with HNO_3 (**7** and **8**, Scheme 2).

Relatively unstable nitrous acid HNO_2 formed from the reaction of $NaNO_2$ with TFA produces both radical (NO) and electrophilic (NO^+) [93] species (note that acetic acid is not effective, presumably due to its low acidity) [77,94]. Consequently, two different reaction paths, namely radical and electrophilic were previously identified for alkylbenzenes in the $NaNO_2$/TFA system [77]. The first path led to the conventional aromatic nitration at room temperature, while the free-radical side-chain oxidations require heating [77]. In our case, due to the presence of radical source (NHPI) and oxidant (O_2), radical processes (Paths ***A***–***C***, Scheme 4) dominate over electrophilic substitutions. Additionally, electrophilic nitrosonium cation NO^+, which is present in the reaction media [93] may facilitate the side-chain reactions through the oxidation of intermediately-formed radicals (Path ***D***, Scheme 4). Indeed, while the H-abstraction from toluene with PINO$^\bullet$ to give $PhCH_2^\bullet$ (**4**) is



Scheme 4. The aerobic oxidation of toluene ($PhCH_3$) carried by the phthalimide *N*-oxyl (PINO) radical generated from *N*-hydroxyphthalimide (NHPI) in the $NaNO_2$/TFA system with involvement of the nitrosonium cation (NO^+).

Table 2
The aerobic oxidations of substituted toluenes in trifluoroacetic acid (TFA)[a].

#	Substrate 	Temp., °C	Time, h	Conv., %	 %	 %	 %	Isolated yield of aldehyde,[b] %
1	*p*-CH_3	RT	1.5	100	10	46	–	35
2	*p*-Cl	45	3	67	2	49	traces	45
3	*m*-Cl	45	3	65	3	27	17	16
4	*o*-Cl	45	3	46	3	18	14	12
5	*p*-Br	45	3	60	4	36	traces	22
6	*m*-Br	45	3	37	1	21	traces	13
7	*o*-Br	45	3	37	2	12	traces	10
8	*p*-NO_2	45	3	0	0	0	0	–

[a] Method **C** (18.8 mmol of toluene derivative, 4.6 mmol of NHPI, 6.2 mmol of $NaNO_2$ in 1 mL of water, 8 mL of TFA).
[b] For the ^{1}H- and ^{13}C NMR spectra of the isolated aldehydes see SI.

9.4 kcal/mol endergonic (Fig. 1 and Path ***B***, Scheme 4) the reaction with electrophile $PhCH_2^{\bullet} + NO^+ = PhCH_2^+ + NO^{\bullet}$ is 22.5 kcal/mol exergonic (M06-2X/cc-pVDZ, Path ***D***).

Thus formed NO-radical (or N_2O_3 formed from the decomposition of HNO_2, Path ***C***) is oxidized with molecular oxygen to give the NO_2-radical, which generates PINO$^{\bullet}$ from NHPI (Path ***A***), while $PhCH_2^+$is trapped with water to give benzyl alcohol (Path ***E***). Note that the NO-radical is a very poor hydrogen abstractor, and its reaction with NHPI is not operative under the reaction conditions (the reaction NHPI + NO = PINO + HNO is ca. 32 kcal/mol endergonic at M06-2X/cc-pVDZ; in contrast' the hydrogen abstraction from NHPI with NO_2 (Path ***A***) is slightly exergonic). The involvement of the electrophilic PINO-radical into the H-abstraction step (Path ***B***) determines the high sensitivity of the reaction towards the substituents present in the phenyl ring. With *p*-xylene (Table 2, Entry 1) the reaction proceeds slightly faster than for **1** as the 100% conversion was achieved after 1.5 h. The preparative yield of *p*-methyl benzaldehyde is close to that of toluene (35%).

In contrast, the oxidation of isomeric chloro- (Table 2, Entries 2–4) and bromo- (Entries 5–7) toluenes requires slight heating due to the presence of electron-withdrawing groups in the benzene ring. Substantial amounts of corresponding chlorobenzoic acids form at this temperature and the yields of aldehydes are reduced. The highest preparative yields of the respective haloaldehydes was achieved for the oxidation of *p*-chloro (49%, Entry 2) and *p*-bromo toluenes (36%, Entry 5). This is in full agreement with the previous kinetic studies of the reactions with PINO in acetic acid,[46] where *para*-substituted toluenes are the most and *ortho*- are the least reactive. Due to strong electron withdrawing effects of the NO_2-group *p*-nitro toluene remains unchanged under this reaction conditions (Table 2, Entry 8) that is also a characteristic for the NHPI-catalyzed reaction in the acetic acid [6]. All above data evidence strongly for the exclusive participation of the PINO-radical in the H-abstractions from the methyl group in TFA.

4. Conclusions

Highly polar trifluoroacetic acid demonstrates its efficiency as a solvent for the metal-free aerobic NHPI-catalyzed oxidations of toluenes as well as saturated systems such as cyclohexane and 3-oxadiamantane. In contract, with moderately reactive adamantane and diamantane NHPI is inactive as faster electrophilic H-substitutions take place. While with the HNO_3 as the initiator the reaction is effective for the oxidations of nonactivated saturated substrates, the electrophilic aromatic substitutions take place for toluene. Markedly, the utilization of catalytic amounts of sodium nitrite $NaNO_2$ allows to achieve unprecedentedly high selectivities for toluene conversion to benzaldehyde almost completely avoiding over-oxidations. Besides the ability to generate HNO_2, trifluoroacetic acid encourages the formation of low-electrophilic nitrozonium cation, which is able to oxidize the radical intermediates and shift the otherwise unfavorable radical equilibria *en route* to benzaldehyde.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2017.12.017.

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