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# Aerobic oxidation of secondary alcohols with nitric acid and iron(III) chloride as catalyst in fluorinated alcohol

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KEYWORDS: Aerobic oxidation of alcohols • nitric acid •iron catalysis• template catalysis • fluorinated alcohol

**ABSTRACT:** Fluorinated alcohols as solvents strongly influence and direct chemical reaction through donation of strong hydrogen bonds while being weak acceptors. We used 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as activating solvent for a nitric acid and FeCl<sub>3</sub> catalyzed aerobic oxidation of secondary alcohols to ketones. Reaction proceeded selectively with excellent yields with no reaction on primary alcohol group. Oxidation of benzyl alcohols proceeds selectively to aldehydes with only HNO<sub>3</sub> as catalyst, while reaction on tertiary alcohols proceeds through dehydration and dimerization. Mechanistic study showed *in situ* formation of NOCl that converts alcohol into alkyl nitrite, which in presence of Fe<sup>3+</sup> ions and fluorinated alcohol decomposes into ketone. The study indicates that iron(III) acts also as single electron transfer catalyst in regeneration of NOCl reactive species.

## INTRODUCTION

Oxidation is very common transformation of organic compounds and often used in synthesis of a complex molecules.<sup>1</sup> While there is broad option for unselective oxidation<sup>1, 2</sup> there are more limited tools for selective oxidation of specific alcohol groups such as primary, secondary, benzyl or allylic alcohol groups. To achieve selective oxidation of the primary alcohol group over secondary ones methods take advantage of less crowded environment around primary ones.<sup>1, 2</sup> Thermodynamics usually favors oxidation of secondary alcohols to ketones over primary ones to aldehydes, though oxidation potential difference is usually too small for practical use.<sup>3</sup> Hence, for a selective transformation of an explicit functional group a protective group is used. This though leads to a longer reaction time and lower yield due to two additional steps (protecting and deprotecting of functional group).

In recent years traditional stoichiometric inorganic 49 oxidants (chromium(VI), hypervalent iodine compound 50 etc.) are getting replaced with cleaner and environmentally 51 friendlier oxidants such as H2O2 and O2.47 Although, 52 molecular oxygen is a powerful oxidant, high-energy 53 barrier and low reactivity prevent its reaction with 54 common organic compounds. Therefore catalytic cycles, 55 inspired by the Nature's aerobic respiratory chain, were 56 developed<sup>8, 9</sup> that combine different catalysts such as 57

(2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or its derivatives and/or transition metals.<sup>2, 10-16</sup> Rather high price of TEMPO and precious metal catalysts (Pd, Pt, Au) demands for efficient recycling.<sup>4</sup> It is estimated that only 1% of precious metals are being recycled for reuse,<sup>17</sup> despite being metals at risk of supply disruption.<sup>18</sup> In a search for new methods for aerobic oxidation two approaches emerged - metal free catalysis and base metal catalysis, such as iron. Nitrogen oxides, obtained from sodium nitrate or nitric acid,19 are potent catalysts for aerobic oxidation in conjunction with a co-catalyst such as TEMPO,<sup>20-22</sup> bromine,<sup>23</sup> solid acids,<sup>24</sup> carbon based catalyst<sup>25</sup> and HFIP.<sup>26</sup> However, they can suffer from formation of an undesired side product N<sub>2</sub>O which is formed from dimerization of HNO. This represents a deadend side reaction as N<sub>2</sub>O is not renewed and it reduces available nitrogen oxides for further catalytic cycles.27 Positive aspects of using iron as a base metal catalyst are that iron is the second most abounded metal, inexpensive and therefore has much lower supply risk index as noble metals.<sup>17</sup> Furthermore, platinum group of metals are considerably more toxic compared to the iron. Difference is immense as platinum group metals are "Class 2 metals: route-dependent human toxicants", while iron is unclassified due to low inherent toxicity (permitted daily exposure for Pt is 10 µg/kg per day).<sup>13, 28, 29</sup> There are some known methods of using iron and its salts as catalysts for aerobic oxidation, however successful methods are scarce compared to other metal catalysts.<sup>30-37</sup>

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Fluorinated alcohols, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), act as template catalysts where complementary charge template to transition state is formed resulting in lowering a of a reaction barrier<sup>38</sup>. Unique properties such as high ionizing power, high hydrogen bond donor ability, low hydrogen bond acceptor ability, high polarity and low nucleophilicity enables this effect of fluorinated alcohols.39-41 Template catalysis was mainly demonstrated in reactions with H<sub>2</sub>O<sub>2</sub><sup>38, 42-50</sup> and in oxidative halogenation<sup>51, 52</sup>. In our previous work we used tandem catalysis of nitric acid and fluorinated alcohol for aerobic oxidation of benzyl alcohols, where HFIP activated oxidants (nitric acid and NO<sub>x</sub>) and increased the selectivity for formation of benzaldehyde over benzoic acid.<sup>26</sup> For secondary alcohols, catalytic system was not effective and an equimolar amount of oxidant was necessary (Scheme 1). In this report we show that by introducing an iron cocatalyst we were able to use the catalytic system HNO<sub>3</sub>/HFIP for selective aerobic oxidation of secondary alcohol group.

Scheme 1. Aerobic oxidation of alcohols catalyzed by HNO<sub>3</sub>/HFIP catalytic system



R = -Alkyl, -Ph

#### **RESULTS AND DISCUSION**

We focused our research on the additional activation of HNO<sub>3</sub>/HFIP catalytic system for aerobic oxidation of alcohols through use of simple base metal salts as cocatalyst. We tested iron and copper salts since they have lower price and higher sustainability potential in comparison with precious metals. As a model substrate 2octanol (1a) was chosen. Reaction was performed by adding 1 mol% of the metal salt and 5 mol% HNO3 into HFIP followed by addition of 1a. Balloon filled with molecular oxygen was attached to the flask and reaction was stirred at ambient temperature for 24h. The best result was obtained with FeCl<sub>3</sub> where quantitative conversion into 2-octanone (1b) was obtained (Figure 1). Chloride anion as the counter ion is essential for obtaining high conversion as lower yields were obtained in reactions with  $K_3$ [Fe(CN)<sub>6</sub>] and Fe(NO<sub>3</sub>)<sub>3</sub>. However, presence of chloride

anion or Lewis acid is not enough for oxidation of **1a** into **1b**, as can be seen by reaction with NaCl or AlCl<sub>3</sub>, respectively. With HCl complete conversion was also obtained, though FeCl<sub>3</sub> was better co-catalyst with less reactive substrates (*vide supra*). Iron(II) chloride was not as effective, while yields of oxidation with copper salts as co-catalysts was very low.



Figure 1. Conversion of 1a into 1b depending on the cocatalyst

Conversion of **1a** depens on the amount of the FeCl<sub>3</sub> in a reaction mixture (Figure 2). The best result was obtained with 1 mol% of FeCl<sub>3</sub>. Decreasing the amount of FeCl<sub>3</sub> to 0.5 mol% stopped the reaction. Similarly, increasing the amount of FeCl<sub>3</sub> catalyst decreased the overall yield.



**Figure 2.** Influence of the amount of the  $\text{FeCl}_3$  on conversion of the **1a** into **1b** 

The influence of the solvent was examined in order to elucidate the role of HFIP as a template catalyst. Oxidations of **1a** were performed under optimized conditions (5 mol% HNO<sub>3</sub> and 1 mol% FeCl<sub>3</sub>) in various solvents (TFE, EtOH, MeCN, DCM and 2-Me-THF), but in all cases the product was obtained only in trace amounts. From this we gather that HFIP has an essential role in aerobic HNO<sub>3</sub> and FeCl<sub>3</sub> catalyzed oxidation. Next, we extended the substrate scope of HNO<sub>3</sub>/FeCl<sub>3</sub>/HFIP catalyzed aerobic oxidation (Table 1). Less reactive substrates were not oxidized completely under the

reaction conditions used for 1a and the reactivity was tuned by increasing the amount of HNO<sub>3</sub> up to 20 mol% for the least reactive cyclopentanol (3a). Comparison between the strength of HCl and FeCl<sub>3</sub> co-catalysts was tested in oxidation of cycloheptanol (5a) using 5 mol% HNO<sub>3</sub>. With HCl (3 mol%) as co-catalyst only 4 % of cylcloheptanone (5b) was formed, while using FeCl<sub>3</sub>(1 mol%) 27 % conversion was achieved. Complete oxidation of 5a was achieved with 15 mol% of HNO<sub>3</sub>. Importantly we did not observe any oxidation of the primary aliphatic alcohol group when the primary and the secondary alcohol group were present in the same molecule (Table 1, entry 9-11).

Table 1. Selective catalytic aerobic oxidation of secondary alcohols<sup>[a]</sup>

HNO<sub>3</sub>/1 mol% FeCl<sub>3</sub>/O<sub>2</sub>

OH

	$R^{\prime}R_{1}$	HFIP, r. t.	`R₁	R	
	1b - 10b		- 10a	1a -	
	Product	Conversion (yield) [%]	Time [h]	HNO <sub>3</sub> [mol%]	N
ıb	0	100 (100) <sup>[b]</sup>	24	5	1
2b	O L	100 (77) <sup>[b]</sup>	7	12	2
zh	O L	43	23	10	3
٥ر		100 (88)	23	20	4
4b		100 (74)	6.5	15	5
5b		90 (59)	23	15	6
6b		100 (83)	5	12	7
7b	<b>O</b>	100 (83)	5	10	8
8b	ОН	96 (95)	22	15	9
9b	ОН	100 (96)	5	12	10
10b	ОН	98 (98) <sup>[c]</sup>	22	10	11

[a] Reaction conditions: 1 mmol of substrate, 1 mL HFIP, 65 % aq. HNO<sub>3</sub>, 1 mol% FeCl<sub>3</sub> (1.7 mg), O<sub>2</sub>, room temperature, 5-24 hours. [b] Yield obtained from 'H NMR spectra with naphthalene as internal standard. [c] Yield obtained from 'H NMR spectra with naphthalene as internal standard with no isolation.

For some alcohols such as **1a**, **2a**, **3a** and **7a** oxidation was complete and the corresponding ketones were obtained in a pure form. Therefore, their isolation needed only simple washing with water and evaporation of solvent under reduced pressure. HFIP can be easily removed under reduced pressure (b. p. 59°C) as well as easily condensed and recovered in cold trap (m. p. -4°C) which reduces produced waste.<sup>26</sup>

Oxidation of a primary alcohol group in octan-1-ol (11a) occurred only by using 1 equivalent of HNO<sub>3</sub> ending in quantitative formation of octanoic acid (11b) (Scheme 2). No products were obtained when catalytic system with 11a was used. On contrary, catalytic oxidation of benzyl alcohol yields benzaldehyde as the sole product.<sup>26</sup> Hence we performed aerobic oxidation of hexanal (12a) with 10 mol% of HNO<sub>3</sub> and 1 mol% of FeCl<sub>3</sub> in HFIP under molecular oxygen atmosphere. After 22 h only 13 % conversion was obtained (Scheme 2). From this we gather that oxidation of primary alcohol 11a occurs with nitric acid, while second step – oxidation of aldehyde occurs also under catalytic conditions.

# Scheme 2. Oxidation of primary alcohol group by HNO<sub>3</sub>/FeCl<sub>3</sub> in fluorinated alcohol



In the final part of our study of the aerobic oxidation of alcohols, allyl alcohols and tertiary alcohols were examined. All reactions with allyl alcohols ended in polymerization and no product could be isolated. Contrary to the expectation, reaction with tertiary alcohol proceeded smoothly. 2-Phenyl-propan-2-ol (13a) was converted into three products (Table 2).

Table 2. Transformation of tertiary alcohol in  $HNO_3/FeCl_3/fluorinated$  alcohol system<sup>[a]</sup>



13a		13	b	13c	13d
N	HNO <sub>3</sub> [mol%]	FeCl <sub>3</sub> [mol%]	Time [h]	Conversi on [%]	13b/13c/13d [%] <sup>[c]</sup>
L	10	1	2	100	0/93/0
2	10	0	2	100	0/65/35
3	0	1	3	100	0/76(57)/24(18)

4 <sup>[b</sup>	<sup>]</sup> o	1	3	100	84(62)/7/9
5	0	0	22	0	-/-/-

[a] Reaction conditions: 2-phenyl-propan-2-ol (12a, 1.0 mmol, 140.4 mg), 1 mL of HFIP, 65 % aq. HNO<sub>3</sub> (0-10 mol%), FeCl<sub>3</sub> (0-1 mol%), room temperature, 3-22 hours. [b] TFE was used as a solvent. [c] Product distribution obtained from <sup>1</sup>H NMR spectra, values in parentheses represent isolated yield.

The distribution of the products was noticeably influenced by the solvent. In TFE, (4-methylpent-1-ene-2,4diyl)dibenzene (13b) was the main product. In HFIP, 13b was converted further into 1,1,3-trimethyl-3-phenyl-2,3dihydro-1H-indene (13c) in major yield. For reaction to proceed only one catalyst was needed and no reaction occurred in the absence of catalyst (Table 2, entry 5). Oxygen does not have any effect on the transformation as the same results were obtained in inert atmosphere. Reaction with tertiary alcohols proceeds by initial dehydration into the corresponding alkene (13e) (Scheme 3).53 In the next step, alkene reacts either with another 13e or with the carbocation of 13a forming 13b, which is the main product when TFE is used as solvent. Reaction performed in HFIP proceeds further and compound 13c is formed through intramolecular cyclisation of 13b.

Scheme 3. Reaction mechanism of tertiary alcohols depends on the solvent



Finally, we tried to elucidate the mechanism of iron catalysis in this reaction. To oxidize secondary alcohol **1a** into **1b** presence of chloride anions from iron salt were essential for successful reaction. We switched the sources of chloride and nitrate ions and performed reaction with  $Fe(NO_3)_3$  (1 mol%) and HCl (5 mol%) under the same reaction conditions. In this case we obtained 77 % conversion of the **1a** into **1b**. When we replaced HCl (5 mol%) with HBr (5 mol%) and used  $Fe(NO_3)_3$  (1 mol%) as co-catalyst we observed 25 % conversion of **1a** into **1b**. This points to the *in situ* formation of the NOX (X = Cl, Br) as a reactive species. NOCl is more electrophilic than NOBr and reacts at higher rate with alcohols to form alkyl nitrites.<sup>54</sup> While benzyl nitrites decompose rapidly in HFIP,<sup>26</sup> the alkyl nitrates are more stable. The

commercially available iso-pentyl nitrite (14a) was stirred in the HFIP for 30 min in the presence and in absence of the FeCl<sub>3</sub> under argon. In the reaction without FeCl<sub>3</sub>, 14a was mostly hydrolyzed to 3-methyl-1-butanol (14b) (32%) and only 4 % converted into 3-methyl-butanal (14c). However, the decomposition of the 14a into aldehyde 14c was substantially increased in the presence of 1 mol% of FeCl<sub>3</sub> where the 14c was formed with 41 % yield (Scheme 4).

# Scheme 4. Influence of FeCl<sub>3</sub> on decomposition of isopentyl nitrite in HFIP



By following the same reaction with *in situ* ATR-IR probe we could clearly see formation of aldehyde **14c** from **14a** (Figure S1) and after 20 h only aldehyde **14c** was isolated (Figure S3, Scheme 4). We did not detect any formation of the N<sub>2</sub>O (peak at 2236 cm<sup>-1</sup>) with *in situ* ATR-IR probe. Needless to say, isopentyl nitrite was stable in i-PrOH.

The iron catalyst usually works as a single electron transfer catalyst.<sup>55</sup> We showed that the iron(III) plays a crucial role in the decomposition of the nitrite. This action could be due to its Lewis acid properties or it could act as oneelectron oxidant. To determine which mechanism is operative, we tried to confirm the formation of the Fe<sup>2+</sup> during the reaction by formation of Prussian blue. The reaction mixture (1 mmol 1a, 5 mol% HNO3, 1 mol% FeCl3, HFIP) was stirred for 1 h under an inert atmosphere so that FeCl<sub>3</sub> would be converted to its reduced form in the reaction cycle. After 1 h we added  $K_3[Fe(CN)_6]$  to the reaction mixture, followed by the addition of 3 mL of water to increase solubility of the salt and to quench the reaction. The reaction mixture turned blue and the UV-VIS spectrum of the reaction mixture was similar to the independently prepared sample of Prussian blue  $(Fe_4[Fe(CN)_6]_3 xH_2O)$  (Figure 3) proving the presence of Fe<sup>2+</sup> ions and the role of iron catalyst as a single electron transfer catalyst.



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**Figure 3.** UV-VIS spectra of Prussian blue formed in reaction sample and reference

Therefore, our conclusion is that the iron catalyst has double role in the FeCl<sub>3</sub>/HNO<sub>3</sub>-catalysed aerobic oxidation of alcohols. First, it accelerates the decomposition of alkyl nitrite into a carbonyl compound and HNO, as it was confirmed by the in situ ATR-IR experiments. HNO molecules are known to dimerize and form N2O,27 however Fe<sup>3+</sup> seems to prevent dimerization of HNO by oxidizing it into NO. In the next step NO is further oxidized into NO, by molecular oxygen (Scheme 5). The second role would be formation of NOCl from NO, and regeneration of Fe<sup>3+</sup> (Scheme 5). The ability of  $NO_2$  to oxidize  $Fe^{2+}$  was confirmed by the independent experiment (Scheme S1). H<sub>2</sub>SO<sub>4</sub> was added to the flask containing NaNO<sub>2</sub> to form NO<sub>2</sub>, which was transferred by diffusion through a tube to a second flask containing the solution of the FeCl<sub>2</sub> in HFIP. After 1 h the reaction was stopped and aqueous solution of  $K_4$ [Fe(CN)<sub>6</sub>] was added. Prussian blue was immediately formed (proved by UV-VIS spectra) confirming the formation of Fe<sup>3+</sup> species with NO<sub>2</sub>. A blank reaction with FeCl, did not form any coloration, which has been clearly confirmed with the UV-VIS spectroscopy. Solvent clearly influences the reaction. Although we could not detect formation of alkyl nitrite by in situ ATR-IR, its disproportionation into carbonyl compound is facilitated by HFIP. With primary alcohols, formation of alkyl nitrite is slow and stoichiometric amount of nitric acid is needed for oxidation.



**Scheme 5**. Mechanism for aerobic oxidation catalyzed by HNO<sub>3</sub> and FeCl<sub>3</sub>

# CONCLUSION

We developed a simple and a practical method for selective aerobic oxidation of secondary alcohols catalyzed by inexpensive HNO<sub>3</sub> and FeCl<sub>3</sub>. As a terminal oxidant molecular oxygen was used. Presence of HFIP is essential as it increases reactivity of reagents as template catalyst. Various secondary alcohols were oxidized into the corresponding ketones with excellent yields with 5-20 mol% of HNO<sub>3</sub> and 1 mol% of FeCl<sub>3</sub> in HFIP. Oxidation is selective for secondary alcohols over primary. The later were oxidized to carboxylic acid only with equimolar amount of nitric acid in HFIP. Tertiary alcohols were converted through dehydration reaction. Mechanistic studies imply that NOCl is formed in situ and reacts further with the alcohol group to form alkyl nitrite. Iron(III) catalyst acts as a single electron catalysts (SET) in decomposition of alkyl nitrate, while ketone and NO are formed as products. After oxidation of NO into NO, by molecular oxygen, NO<sub>2</sub> reacts with iron(II) forming reactive species NOCl and iron(III).

#### **EXPERIMENTAL SECTION**

All reagents, substrates and solvents were used as obtained from commercial sources without further purification. Flash chromatography was performed with 60 Å (63-200 µm) silica gel. Analytical TLC was performed on aluminum plates pre-coated with silica gel (0.2 mm). Compounds were detected by exposure to UV light or by revealing the plates in a solution of 5 % KMnO<sub>4</sub> in water. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Varian INOVA 300 spectrometer. Chemical shifts ( $\delta$ ) are shown in ppm using TMS as internal standard for <sup>1</sup>H ( $\delta$ H 0.0 ppm) and CDCl<sub>3</sub> for <sup>13</sup>C{<sup>1</sup>H} ( $\delta$ C 77.00) spectra. Real time measurement of IR spectra of reaction was performed with ATR IR probe ReactIR<sup>TM</sup> 45 on Easymax 102 Mettler-Toleda reactor. UV/VIS spectra were measured on an UV/VIS spectrometer Perkin Elmer lamba 25.

General procedure for the scope of the metal co-catalyst

1.0 mol% of metal salt (FeCl<sub>3</sub>, FeCl<sub>2</sub>, CuI, CuCl, CuCl<sub>2</sub>  $\cdot$  2H<sub>2</sub>O, AlCl<sub>3</sub>, K<sub>3</sub>[Fe(CN)<sub>6</sub>], Fe(NO<sub>3</sub>)<sub>3</sub> or 3.0 mol% of catalyst (NaCl, HCl) was added to 1.0 ml of HFIP in a round bottomed flask followed by the addition of 65 % HNO<sub>3</sub> (5 mol%, 3.5 µL) and 1.0 mmol (159 µL) of 2-octanol (1a). A balloon filled with molecular oxygen was attached to a round bottom flask. The reaction mixture was stirred for 24 h at room temperature. After 24 h, 2 mL of DCM and brine were added, organic phase was separated from the water phase and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The conversion and selectivity of the reaction were determined by <sup>1</sup>H NMR analysis.

General procedure for the influence of the amount FeCl<sub>3</sub>

o - 5.0 mol% FeCl<sub>3</sub> were added to 1.0 ml of HFIP in round bottom flask followed by the addition of 65 % HNO<sub>3</sub> (5 mol%, 3.5  $\mu$ L) and 1.0 mmol (159  $\mu$ L) of 2-octanol (1a). In the end a balloon filled with molecular oxygen was attached to a round bottom flask. The reaction mixture was stirred for 24 h at room temperature. After 24 h, 2 mL of DCM and brine were added, organic phase was

separated from the water phase and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The conversion and selectivity of the reaction were determined by 'H NMR analysis. In some cases additional purification was needed with column chromatography on silica gel with eluent DCM:MeOH=20:1.

#### General procedure for the $Fe(NO_3)_3$ + HX reactions

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1.0 mol% of Fe(NO<sub>3</sub>)<sub>3</sub> (4.0 mg) was added to 1.0 ml of HFIP in round bottom flask followed by addition of 5 mol% of HX (HCl - 37 % aq., 4.2  $\mu$ L; HBr - 48 % aq., 5.65  $\mu$ L) and 1.0 mmol (159  $\mu$ L) of 2-octanol (1a). A balloon filled with molecular oxygen was attached to a round bottom flask. The reaction mixture was stirred for 23 h at room temperature. After 23 h, 2 mL of DCM and brine solution were added, organic phase was separated from the water phase and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The conversion and selectivity of the reaction were determined by 'H NMR analysis.

Procedure for experiments with isopentyl nitrite (13a)

Initially, the oxygen was removed from the reactor under a nitrogen flow. None or 1.0 mol% (5.1 mg) FeCl<sub>3</sub> was added to 3.0 ml of HFIP followed by the addition of 3.0 mmol (418  $\mu$ L) of isopentyl nitrite (13a). A balloon filled with argon was attached to the reaction mixture. The reaction mixture was stirred for 20 h at room temperature. The conversion and selectivity of the reaction were determined by 'H NMR analysis without additional isolation.

Confirmation of the formation of Fe<sup>2+</sup> ions in the reaction mixture

29 Initially, the oxygen was removed from the round bottom 30 flask under a nitrogen flow. o.o1 mmol (1,7 mg) FeCl<sub>3</sub> was 31 added to 1.0 ml of HFIP in round bottom flask followed by 32 the addition of 0.05 mmol  $(3.5 \,\mu\text{L})$  of 65 % HNO<sub>3</sub> and 1.0 33 mmol of 2-octanol (1a). The reaction mixture was stirred 34 for 2 h at room temperature. After 2 h 2 mL of water was 35 added. An aliquot of 150 µL was taken and UV-VIS spectra 36 recorded. To the rest of the reaction mixture 2.2 mg of 37  $K_3$ [Fe(CN)<sub>6</sub>] was added and an additional 1 mL of water. An 38 aliquot of 150 µL was taken and UV-VIS spectra recorded. 39

Confirmation of formation of  $Fe^{3+}$  ions in reaction with FeCl<sub>2</sub> and NO<sub>2</sub>

69 mg (1.0 mmol) of NaNO<sub>2</sub> and 55.7  $\mu$ L of 96 % H<sub>2</sub>SO<sub>4</sub> 42 were mixed in the first flask, where the balloon with 43 molecular oxygen was attached. The first flask was 44 connected by a glass tube to a second flask. The second 45 flask contained a solution of  $FeCl_2$  (0.1 mmol, 19.9 mg) in 46 1.0 mL of HFIP. After 2 h 4 mL of water and 31.6 mg (0.075 47 mmol) of  $K_4$ [Fe(CN)<sub>6</sub>] were added to the second flask. 48 Solution turned to a blue-green color. The sample taken 49 (150 µL) for UV-VIS spectroscopy was diluted with water to 50 9.4  $\times$  10<sup>-5</sup> M in regard to K<sub>4</sub>[Fe(CN)<sub>6</sub>]. 51

#### General procedure for oxidation of secondary alcohol

1.0 mol% (1.7 mg) of FeCl<sub>3</sub> was added to 1.0 ml of HFIP in round bottomed flask followed by the addition of 65 % HNO<sub>3</sub> (5-20 mol%, 3.5-14.0 μL) and 1.0 mmol of substrate
1a-10a. A balloon filled with molecular oxygen was attached to a round bottom flask. The reaction mixture

was stirred for 24 h at room temperature. After 24 h, 2 mL of DCM and brine were added, organic phase was separated from the water phase and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The conversion and selectivity of the reaction were determined by 'H NMR analysis. In some cases additional purification was needed with column chromatography on silica gel.

General procedure for oxidation of secondary alcohol with internal standard for volatile products

1.0 mol% (1.7 mg) of FeCl<sub>3</sub> was added to 1.0 ml of HFIP in round bottomed flask followed by the addition of 65 % HNO<sub>3</sub> (5-20 mol%, 3.5-14.0  $\mu$ L) and 1.0 mmol of substrate **1a-10a**. A balloon filled with molecular oxygen was attached to a round bottom flask. The reaction mixture was stirred for 24 h at room temperature. After 24 h, 2 mL of DCM and brine were added, followed by addition of 1 mmol of naphthalene (128.2 mg) used as internal standard. Organic phase was separated from the water phase and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The conversion and selectivity of the reaction were determined by 'H NMR analysis. In some cases additional purification was needed with column chromatography on silica gel.

General procedure for oxidation of terciary alcohols

1 mol% of FeCl<sub>3</sub> (1.7 mg) or 10 mol% of HNO<sub>3</sub> (7.0  $\mu$ L) was dissolved in 1.0 mL of solvent (HFIP, TFE) followed by addition of 1.0 mmol of 2-phenyl-propan-2-ol (**12a**The reaction mixture was stirred for 3 h. After the reaction was complete, 2 mL of DCM and brine solution were added, organic phase was separated from the water phase and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The substrates were separated with column chromatography on silica gel with n-Hex:DCM = 20:1 mobile phase.

#### 2-Octanone - (1b)

Standard procedure with 5 mol% of HNO<sub>3</sub> used as catalyst. Yield: 100 % - determined through NMR with internal standard, colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  0.88 (m, 3H), 1.28 (m, 6H), 1.57 (m, 2H), 2.14 (s, 3H), 2.43 (t, *J* = 7.5 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>):  $\delta$  14.0, 22.5, 23.8, 28.8, 29.8, 31.5, 43.8, 210.0.

#### Butan-2-one - (2b)

Standard procedure with 12 mol% of HNO<sub>3</sub> used as catalyst. Yield: 77 % - determined through NMR with internal standard, colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.06 (t, *J* = 7.3 Hz, 3H), 2.15 (s, 3H), 2.47 (q, *J* = 7.3 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>):  $\delta$  7.8, 29.4, 36.9, 209.7

#### Cyclopentanone - (3b)

Standard procedure with 15 mol% of  $HNO_3$  used as catalyst. Yield: 88 %, 73.7 mg, colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.97 (m, 4H), 2.18 (m, 4H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>):  $\delta$  23.2, 38.4, 221.6.

4-*t*-Butylcyclohexan-1-one – (4b)

Standard procedure with 15 mol% of  $HNO_3$  used as catalyst. Mobile phase in column chromatography:

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DCM/MeOH = 20/1, yield: 74 %, 111.7 mg – white crystals. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.92 (s, 9H), 1.47 (m, 3H), 2.10 (m, 2H), 2.38 (m, 4H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>): δ 27.6, 32.5, 41.3, 46.7, 212.6.

Cycloheptanone – (5b)

Standard procedure with 15 mol% of HNO<sub>3</sub> used as catalyst. Mobile phase in column chromatography *n*hexane:EtOAc=4:1, yield: 59 %, 65.9 mg – colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.69 (m, 8H), 2.50 (m, 4H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>): δ 24.3, 30.3, 43.8, 215.6.

Benzophenone – (6b)

13Standard procedure with 12 mol% of  $HNO_3$  used as14catalyst. Mobile phase in column chromatography: DCM,15yield: 83 %, 151.2 mg of product as orange oil. 'H NMR (30016MHz, CDCl\_3):  $\delta$  7.45-7.50 (m, 4H), 7.56-7.61 (m, 2H), 7.79-177.82 (m, 4H). '<sup>3</sup>C{'H} NMR (76 MHz, CDCl\_3):  $\delta$  128.2, 130.0,18132.4, 137.6, 196.7.

19 1-Phenylpropan-2-one – (7b)

20Standard procedure with 10 mol% of HNO3 used as21catalyst. Yield: 83 %, 154.3 mg - yellow oil. 'H NMR (30022MHz, CDCl3):  $\delta$  2.15 (s, 3H), 3.69 (s, 2H), 7.21 (m, 2H), 7.27-237.36 (m, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl3):  $\delta$  29.3, 51.0,24127.1, 128.7, 129.4, 134.2, 206.4.

25 2-Hydroxy-1-phenylethan-1-one – (8b)

 33
 1-Hydroxy-2,2,4-trimethylpentan-3-one - (9b)

 34
 1-Hydroxy-2,2,4-trimethylpentan-3-one - (9b)

 35
 Standard procedure with 12 mol% of HNO3 used as

 36
 catalyst. Isolation with column chromatography with

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 mobile phase DCM:MeOH=10:1 and yield: 96 %, 138.3 mg

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 white powder. <sup>1</sup>H NMR (300 MHz, CDCl3):  $\delta$  1.06 (d, J = 6.7 

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 Hz, 6H), 1.18 (s, 6H), 2.38 (br s, 1H), 3.09 (hept, J = 6.7 Hz,

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 1H), 3.55 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl3):  $\delta$  19.9, 21.1,

 41
 34.6, 49.6, 69.4, 221.8.

42 4-Hydroxybutan-2-one – (10b)

 43
 Standard procedure with 10 mol% of HNO3 used as

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 catalyst. Yield: 98 % (colorless oil) - determined through

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 NMR with internal standard. <sup>1</sup>H NMR (300 MHz, CDCl3):  $\delta$  

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 2.20 (s, 3H), 2.70 (t, J = 5.5 Hz, 2H), 2.75 (br s, 1H), 3.85 (t, J 

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 = 5.5 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl3):  $\delta$  30.4, 45.3,

 48
 57.6, 209.4.

49 (4-Methylpent-1-ene-2,4-diyl)dibenzene – (13b)

50Isolation with column chromatography, with mobile phase51*n*-hexane:DCM = 20:1 and yield: 62 %, 73.3 mg. 'H NMR52(300 MHz, CDCl\_3):  $\delta$  1.22 (s, 6H), 2.83 (s, 2H), 4.78 (d, *J*=1.953Hz, 1H), 5.14 (d, *J* = 1.9 Hz, 1H), 6.95 - 7.52 (m, 10H). <sup>13</sup>C{<sup>1</sup>H}54NMR (76 MHz, CDCl\_3):  $\delta$  28.7, 38.7, 49.6, 116.9, 125.4, 125.9,55126.5, 126.8, 127.8, 128.0, 143.4, 146.7, 149.4.56The shade and an algorithm of the shade and the shade and

1,1,3-Trimethyl-3-phenyl-2,3-dihydro-1*H*-indene (13c)

Isolation with column chromatography, with mobile phase *n*-hexane:DCM = 20:1 and yield: 57 %, 67.5 mg - colourless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.03 (s, 3H), 1.34 (s, 3H), 1.69 (s, 3H), 2.19 (d, *J* = 13.0 Hz, 1H), 2.42 (d, *J* = 13.0 Hz, 1H), 7.07 - 7.32(m, 9H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>):  $\delta$  30.4, 30.7, 30.9, 42.8, 50.8, 59.2, 122.5, 125.0, 125.5, 126.6, 126.7, 127.2, 128.0, 148.7, 151.0, 152.2.

1,1-Dimethyl-3-(2-methyl-2-phenylpropyl)-3-phenyl-2,3dihydro-1*H*-indene – (13d)

Isolation with column chromatography, with mobile phase *n*-hexane:DCM = 20:1 and yield: 18 %, 19.6 mg . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  0.66 (s, 3H), 1.06 (s, 3H), 1.12 (2s, 6H), 1.95 (d, *J* = 13.5 Hz, 1H), 2.02 (d, *J* = 13.5 Hz, 1H), 2.39 (d, *J* = 15.0 Hz, 1H), 2.84 (d, *J* = 15.0 Hz, 1H), 7.04 – 7.35 (m, 13H), 7.45 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (76 MHz, CDCl<sub>3</sub>):  $\delta$  28.6, 29.6, 29.6, 33.9, 38.8, 42.4, 51.2, 54.9, 55.6, 122.5, 125.3, 125.4, 125.7, 125.8, 127.2, 127.4, 127.7, 128.0, 147.6, 149.7, 150.4, 151.7, 153.9.

# ASSOCIATED CONTENT

Supporting Information includes experimental procedures, ATR-IR spectra and NMR spectra.

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