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Solvent free oxidation of primary alcohols and diols using thymine iron(III) catalyst†

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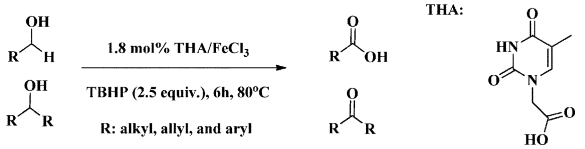
In this study, we developed an efficient and selective iron-based catalyst system for the synthesis of ketones from secondary alcohols and carboxylic acids from primary alcohol. *In situ* generated iron catalyst of thymine-1-acetate (THA) and $FeCl_3$ under solvent-free condition exhibits high activity. As an example, 1-octanol and 2-octanol were oxidized to 1-octanoic acid and 2-octanone with 89% and 98% yields respectively.

Selective oxidation of alcohols to the corresponding carbonyl compounds is a fundamental transformation in organic synthesis.[1] In particular, selective oxidation of alcohols to the carbonyl compounds such as primary alcohols to aldehydes or acids or oxidation of secondary alcohols to ketones is attractive because the target molecules can be obtained directly in one-pot sequences. Many catalytic methods have been developed for oxidation of aliphatic alcohols. The most commonly utilized homogeneous catalysts are based on different transition metals such as Pd,[2] Cu,[3] Ru,[4] and Co.[5] Unfortunately, most of these reported systems suffer from high reagent load, stringent reaction conditions, functional group incompatibility and high cost or toxicity of the metal. In response to this, metal-free nitroxyl radical-catalyzed oxidations and their heterogeneously immobilized variants have been reported recently.[6] However, the metal-free oxidation catalysis for primary aliphatic alcohols seems to afford only moderate selectivities. To improve the selectivity toward the corresponding aldehydes or acids, halogenated reagents or co-catalysts and high catalyst loads are needed.

Apparently, despite these improvements in the catalyst development, addressing these challenges will require more efficient, cheaper, chemoselective, and greener catalyst; the low cost and non-toxicity of iron render it a particularly attractive metal in this regard. Iron has drawn particular attention in catalyst design because of its essential role in fundamental biological processes such as oxygen transport and sensing, small-molecule metabolism, and electron transfer.[7–11] Although it was recently reported that iron(III) complexes can be used in carbonyl compound formation, it was not until 2002 that the first iron(III)-catalyzed alcohol oxidation was reported.[12] Recent iron complexes, clayfen[13] (iron(III) nitrate supported onto montmorillonite K-10)[14] or zeofen (zeolite HZSM-5 and ferric nitrate),[15] have gained popularity in alcohol oxidation studies. However, most of these catalysts lack selectivity and possess limited substrate reactivity.

Our research focuses on developing organic and metall-organic catalysts being capable of performing benign redox reactions. Inspired by flavin[1] and DAPHEN[16] systems we report herein a new *in situ* generated iron(III) catalyst that efficiently and selectively oxidizes primary and secondary aliphatic alcohols into their corresponding carbonyl compounds, acids and ketones; even a wide range of diols are converted to the corresponding acids and ketones. The novel catalyst system described herein consists of thymine-1-acetate (THA) and Fe(III)Cl_3. With this cheap and convenient catalyst *tert*-butyl hydroperoxide (TBHP) can be used as a terminal oxidant in solvent free reactions (Scheme 1).

To explore the reactivity and selectivity of the iron/THA catalyst, 2-octanol was used as a model substrate. Various solvents were examined in the presence of the iron/THA catalyst (Table 1, entries 1–4). Gratifyingly, it was found that under solvent free conditions, the catalyst gave quantitative conversion to 2-octanone with 91.5% isolated yield (Table 1, entry 4). Subsequently, various iron precursors were evaluated in solvent free conditions (Table 1, entries 5–8). A control experiment in the absence of the iron/THA complex confirmed the crucial role of iron in catalyzing the efficient oxidation. THA alone gave 10% conversion. This indicates that THA possesses organocatalytic activity for the oxidation of alcohols. Especially π activated alcohols such as benzyl alcohols gave moderate (53%) conversions and in this respect THA resembles the previously reported flavin catalyst.[17] In addition, other transition metal cations were investigated with THA in similar reaction conditions. However, from the first row transition metals Fe was the most efficient one while manganese was the second most active metal giving 77% conversion.[18]



Scheme 1 Thymine acetate iron complex catalyzed oxidation of alcohols to acids and ketones.

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† Electronic supplementary information (ESI) available: Experimental procedures, optimization condition and HRMS spectral data. See DOI: 10.1039/c0cc04043f

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Table 1 Influence of solvents and iron precursors for the oxidation of 2-octanol[a]

Entry	Solvent[b]	Iron salt	Conversion (%)
1	MeCN	$FeCl_3$	92
2	Toluene	$FeCl_3$	62
3	H_2O	$FeCl_3$	12
4	Solvent free	$FeCl_3$	100[d]
5	Solvent free	$Fe(OAc)_3$	88
6	Solvent free	$Fe(NO_2)_2$	84
7	Solvent free	$FeBr_3$	56
8	Solvent free	None[c]	10

[a] 2-Octanol (250 mg, 2.0 mmol), Fe complex (0.036 mmol, 1.8 mol%), TBHP (4.5 mmol 80% solution in decane). [b] Solvent amount 2 ml, if needed the results were collected *via* GC-MS. [c] THA no Fe precursor. Reaction conditions: see Scheme 1. [d] Isolated yield 91.5%.

In order to evaluate the efficiency of the *in situ*-generated catalyst[19] various structurally diverse secondary and primary alcohols were also investigated under the optimized reaction conditions.[18] As Table 2 shows, α,β-unsaturated primary alcohols, such as allylic and benzylic alcohols, can be selectively oxidized to the corresponding carboxylic acids in excellent yields. Similarly, α,β-saturated primary alcohols such as 1-octanol and 1-decanol produced their corresponding acids in good yield (89–93%). Based on our GC-MS analysis data the reaction proceeds *via* aldehyde and further oxidized to carboxylic acids. The capability of the catalyst to oxidize primary aliphatic alcohols into carboxylic acids in very good yield is worth noticing.

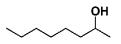
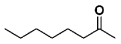
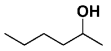
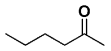
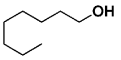
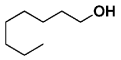
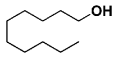
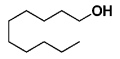
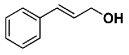
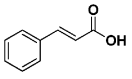
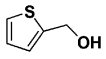
As well as primary alcohols, secondary aliphatic alcohols were oxidized selectively to the corresponding ketones in excellent yields (70–100%, Table 2, entries 1–4). Not only sterically demanding secondary alcohols such as those in entries 3 and 4 in Table 2 but also α,β-unsaturated secondary alcohols such as phenyl propanol (95%, Table 2, entry 7) gave almost quantitative yields. Interestingly, 2-thiophenemethanol (entry 10) was also smoothly oxidized to the corresponding acid with high conversion and selectivity. In general, it is considered as a difficult substrate for most oxidation systems involving transition metals because of their strong coordination ability with the sulfide group. Noteworthily, the sulfide group that is susceptible to oxidation remained here unreacted. Typically, the oxidation reactions were carried out in 3–6 hours, but a prolonged reaction time (12–16 h) was essential for reactions with the secondary aliphatic alcohols.

Following the success of studies with primary and secondary alcohols oxidation we applied the catalyst to a series of diols (Scheme 2). As illustrated in Table 3 internal *vic*-diols such as diphenyl ethanediol as well as cyclic *vic*-diols such as 1,2-cyclohexanediol are selectively oxidized to diketones with good yields (Table 3, entries 1 and 2). 1,4-Benzenedimethanol bearing two primary benzylic alcohols was oxidized to phenyl dicarboxylic acid in very good yield (Table 3, entry 4). Intriguingly, 1-phenyl-1,2-ethanediol was cleanly converted to phenylglyoxylic acid. With the applied iron/THA catalysts diols can be oxidized in excellent yield without oxidative cleavage of products.

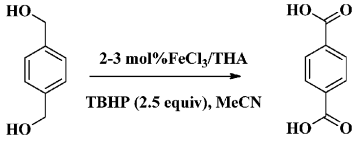
In conclusion, the iron-based catalyst system described herein is efficiently oxidizing alcohols in solvent free conditions when TBHP is used as an oxidant. Although there have been enormous number of procedures for conversion of alcohols into aldehydes or even acids, this method is a practical alternative because of its simplicity, environmental acceptability, inexpensiveness, and the broad substrate compatibility. Both primary and secondary aliphatic alcohols were oxidized into their corresponding carbonyl compounds, acids and ketones in good to excellent yields. Further studies to improve the reaction rate through catalyst modifications and mechanistic studies are ongoing.

Support of this work by grants from *Academy of Finland* project nos 1118044 and 217224.

Table 2 Oxidation of various alcohols with TBHP catalyzed by THA combined with $FeCl_3$[a]

Entry	Substrate	Product	Time/h	Yield (%)
1			16	99
2			16	91
3			3	94
4			3	70
5[b]			16	89
6			16	93
7			3	95
8[b]			6	85
9[b]			3	98
10			3	74

[a] Reaction conditions: substrate (2.6 mmol), $FeCl_3$ (1.8 mol%), THA (3.6 mol%), TBHP (80% solution in decane, 6.5 mmol), the results were collected *via* GC-MS. Yield refer to GC/MS using acetophenone as internal standard, and ^1H spectra. [b] The amount of catalyst is 1.5 mol%.



Scheme 2 Iron catalyzed oxidation of diols.

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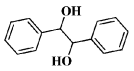
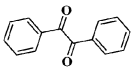
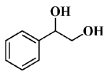
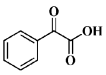
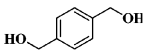
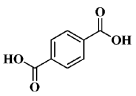
Table 3 Oxidation of various diols with TBHP catalyzed by THA combined with $FeCl_3$[a]

Entry	Substrate	Product	Time/h	Conv. (%)
1[b]			16	76
2[b]			16	80
3[a]			6	96
4[a]			6	71

[a] Reaction conditions: 2.4 mmol of alcohol, 2.0 mol% of catalyst, 2.5 eq. TBHP, 80 °C for specific time. [b] 3 mol% catalysts. The selectivity and the conversion were determined *via* GC-MS.

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18 See ESI† for experimental details and the optimized procedures such as time effect, catalyst amount, oxidant amount and different oxidant effect.

19 The *in situ* catalyst has been studied *via* ESI-MS. When *in situ* catalyst in reaction mixture is dissolved in MeOH, the electrospray ionization-mass spectrometry (ESI-MS) measurements show the dominating peak patterns of moderate peaks at m/z = 419.9525 and 343.88. According to the isotope distribution they can be assigned as $[C_{14}H_{14}N_4O_8FeCl_2]$ and $[C_7H_7N_2O_4FeCl_3]$ cations, respectively. The software used for the simulations is Bruker Daltonics Data Analysis (version 3.3) (see ESI†).

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