Fe(6-Me-PyTACN)-catalyzed, one-pot oxidative cleavage of methyl oleate and oleic acid into carboxylic acids with H_2O_2 and $NaIO_4$†

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The first Fe-based catalytic system for the oxidative cleavage of unsaturated fatty acids and esters to carboxylic acids is reported. The system comprises [Fe(OTf)$_2$(6-Me-PyTACN)] (**2**) (6-Me-PyTACN = 1-[(6-methyl-2-pyridyl)methyl]-4,7-dimethyl-1,4,7-triazacyclononane, OTf = trifluoromethane sulfonate anion) as the catalyst (3 mol%) either with a combination of hydrogen peroxide and $NaIO_4$ or exclusively with $NaIO_4$ as the oxidant, and operates at 0 °C or ambient temperature. Under these standard conditions (method A), methyl oleate is converted in a one-pot procedure into 50–55% of both nonanoic and azelaic acid, together with some epoxide and aldehyde intermediates as byproducts. These yields can be further improved by addition of sulfuric acid (method B) to hydrolyze the epoxide byproducts, by including a pH neutralization step and addition of more catalyst (1 mol%). Under the optimized conditions, both methyl oleate and oleic acid are converted into high yields of the corresponding carboxylic acids (80–85%). Overall, this catalytic system provides an alternative to the industrial ozonolysis of oleic acid and to catalytic Ru- and Os-based systems for the oxidative cleavage of unsaturated fatty acids and esters.

Introduction

Vegetable oils are an attractive renewable resource for the production of sustainable platform chemicals.[1] Indeed, in addition to biodiesel, higher value products such as lubricants, surfactants, pharmaceuticals and other chemicals can be obtained from this biomass source. Triglycerides are commonly transformed into fatty acids by hydrolysis or into fatty acid methyl esters by reaction with methanol. Further functionalization reactions often involve reactions on the internal C=C double bond in unsaturated fatty acids, for instance by metathesis to obtain terminal double bonds susceptible to further reaction.[2] A second typical example is

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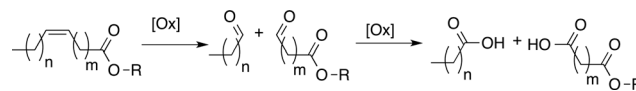
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the oxidation of the C=C bond to yield epoxides, which in turn can be used for polymerization purposes.[1] Alternatively, oxidation of the internal double bond of unsaturated fatty acids can also involve its oxidative cleavage into aldehydes or carboxylic acids (Scheme 1). This transformation can yield four potentially interesting products: aliphatic aldehydes, α,ω-aldehyde fatty acids, aliphatic carboxylic acids and α,ω-dicarboxylic acids. The oxidative cleavage route thus provides access to medium chain-length aliphatic aldehydes such as nonanal, representing an alternative, renewables-based route for the Rh-mediated hydroformylation of terminal olefins to saturated aldehydes. The α,ω-aldehyde fatty acids and α,ω-dicarboxylic acids can be used as lubricants and are valuable building blocks for the polymer industry. Finally, the long-chain carboxylic acids can find application as emulsifiers.[1,3–5]

Catalytic systems for the oxidative cleavage of alkenes typically comprise transition-metal complexes based on either expensive, toxic or scarce metals such as Ru,[6–11] W[12–19] or Os.[20–27] The use of first-row transition metal-based catalysts would make these reactions more sustainable given their
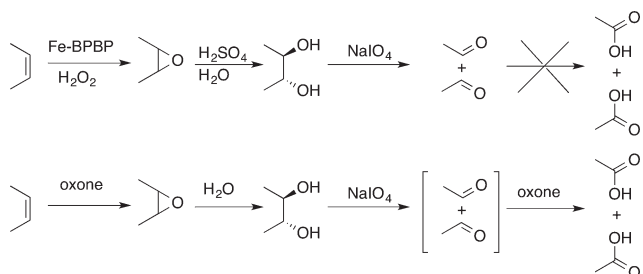

Scheme 1 Oxidative cleavage of unsaturated fatty acids into aldehydes and finally into carboxylic acids.

ready availability, low price and low toxicity. Fe-based catalysts are particularly interesting in this respect. However, reported oxidative cleavage reactions with this metal primarily concern activated styrene derivatives that are readily cleaved by complexes based on salen-type[28,29] and porphyrin-type[30–32] ligands. For unsaturated fatty acids, examples are mostly limited to second- and third-row transition metal systems for the catalytic cleavage into aldehydes.[19,24,33]

Currently, the oxidative cleavage of oleic acid is performed on an industrial scale by ozonolysis.[34] This process comes with disadvantages as ozone is a dangerous oxidant because of explosion risks and its use is unpractical because of the necessity of preparing the oxidant *in situ* prior to reaction.[3] Alternatives to this process are therefore of interest.

Recently, we reported on the first example of an Fe-catalyzed oxidative fatty acid cleavage.[35] Iron complexes based on the ligand *N,N′*-bis(2-picolyl)-2,2′-bipyrrolidine (BPBP) in combination with H_2O_2 and $NaIO_4$ as the oxidants are able to oxidatively cleave unsaturated fatty acids into aldehydes in a one-pot reaction. The reaction involves a sequence of steps, *i.e.* fatty acid epoxidation catalyzed by the Fe-catalyst, H_2SO_4-catalyzed epoxide hydrolysis and subsequent diol cleavage with $NaIO_4$ (Scheme 2, top).[35] Notably, this catalytic system does not further oxidize the aldehyde products to carboxylic acids.

Catalysts for the oxidative cleavage of unsaturated fatty acids into carboxylic acids (rather than into aldehydes) exclusively comprise second- and third-row systems based on Ru,[36–39] W[12–14,40–45] and Mo.[12] We also recently reported an oxidative cleavage method to yield carboxylic acids from these substrates following a similar but metal-free approach that uses a combination of oxone and periodate as sacrificial oxidants (Scheme 2, bottom).[46] In this approach, oxone epoxidizes the double bond of the fatty acid and the acidic nature of this oxidant subsequently induces the hydrolysis of the epoxide to the *trans*-diol. In turn, $NaIO_4$ oxidizes the *trans*-diol to the aldehydes, with oxone then rapidly over-oxidizing the products to the carboxylic acids. This protocol does involve high reaction temperatures, though, and the use of oxone as oxidant generates a considerable amount of waste. Therefore, catalytic alternatives to oxone that can be employed at ambient temperatures and generate less waste are of interest.
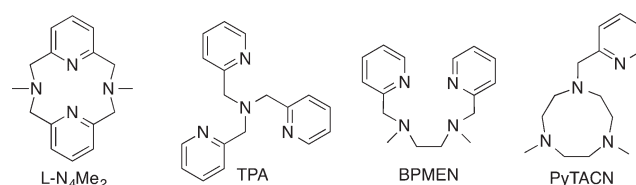
The first step of such a catalytic oxidative cleavage of fatty acids (esters) to carboxylic acids may entail an Fe-catalyzed epoxidation or *cis*-dihydroxylation of the double bond. The pathway involving *cis*-dihydroxylation of alkenes is in principle preferred over alkene epoxidation and subsequent acid-catalyzed hydrolysis, in the sense that alkenes can then be transformed into diols without the use of H_2SO_4 (Scheme 3). The transformation of the *cis*-diol to carboxylic acids can proceed *via* either an Fe-based diol oxidation into hydroxyl ketones[47] or a $NaIO_4$ mediated oxidation into aldehydes.[35,46] Subsequently, the Fe-catalyst can also catalyze the over-oxidation of either species into the carboxylic acid. $NaIO_4$ has been identified as a convenient oxidant in such a protocol, as the oxidation of the *cis*-diol intermediate into the aldehyde is most efficiently done with this oxidant, which can furthermore be regenerated electrochemically.[48]

Potential catalysts of interest for the set of reactions described above are Fe-complexes derived from tetradentate ligands, which have labile counter-ions bound in a *cis* fashion. Fe-complexes derived from the ligands dimethyl-diaza-pyridinophane (L-N_4Me$_2$),[49] tris(2-picolyl)amine (TPA),[50] bis-(2-picolyl)-dimethylethylenediamine (BPMEN)[50] and 2-picolyl-dimethyltriazacyclononane (PyTACN) are known to catalyze the *cis*-dihydroxylation of alkenes (Scheme 4).[51,52]
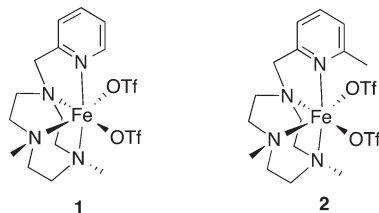
While these catalysts have shown good activity with a variety of different alkenes, these have not been widely studied in the oxidation of the internal electron-rich aliphatic double bonds such as those found in fatty acids. For example, $[Fe(Cl)_2(L-N_4Me_2)]$ together with oxone was optimized primarily for electron-poor alkenes such as dimethyl fumarate (99% diol yield), with *cis*-diol yields of only 36% being obtained from the electron-rich alkene *cis*-2-heptene.[49] $[Fe(OTf)_2(TPA)]$ and $[Fe(OTf)_2(BPMEN)]$ do catalyze the *cis*-dihydroxylation of electron-rich olefins, *e.g. cis*-2-heptene and *cis*-cyclooctene, with H_2O_2.[50] However, epoxides are formed as byproducts particularly under substrate-limiting conditions and significant amounts of diol are only generated under oxidant-limiting conditions. While the use of $[Fe(OTf)_2(PyTACN)]$ (1) also resulted
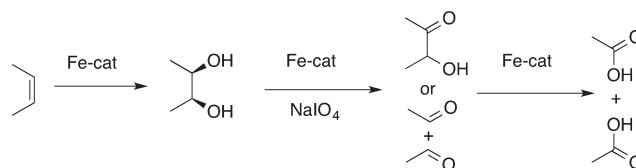
Scheme 3 Generalized Fe-catalyzed oxidative cleavage strategy of alkenes into carboxylic acids *via cis*-diol and hydroxyl ketone or aldehyde intermediates.

Scheme 2 Previously reported oxidative cleavage of unsaturated fatty acids into aldehydes by an Fe–BPBP catalyst with H_2O_2, H_2SO_4 and $NaIO_4$ (top),[35] and cleavage into carboxylic acids by oxone–$NaIO_4$ (bottom).[46]

Scheme 4 Common ligands for Fe-mediated alkene *cis*-dihydroxylation.

Scheme 5 Fe-catalysts **1** and **2** investigated in this work.

in a high diol/epoxide ratio under oxidant-limiting conditions,[51,52] the recently developed [Fe(OTf)$_2$(6-Me-PyTACN)] (**2**) (6-MePyTACN = 1-[(6-methyl-2-pyridyl)methyl]-4,7-dimethyl-1,4,7-triazacyclononane, **2**) showed good chemoselectivity for the formation of diols also under substrate-limiting conditions.[47] **1** is furthermore capable of converting diols into hydroxyl-ketones[39] and is known to oxidize the water molecule with NaIO$_4$.[53] **1** and **2** (Scheme 5) were therefore considered as catalyst candidates for the oxidative cleavage of unsaturated fatty acids into carboxylic acids.

Here, we report the one-pot oxidative cleavage of methyl oleate and oleic acid into carboxylic acids using **2** and a combination of H$_2$O$_2$ and NaIO$_4$. The reaction sequence involves the *cis*-dihydroxylation of methyl oleate by **2** (also investigated using **1**) and subsequent addition of NaIO$_4$ to induce further oxidation of the acids (Scheme 3). Our investigations reveal that **2** is a suitable catalyst for the general oxidative cleavage of fatty acids and fatty acid esters into carboxylic acids.

Results and discussion

X-ray crystal structure of 2

Complexes **1** and **2** were synthesized according to a previously published procedure.[51] Complex **2** was further characterized by X-ray crystal structure determination (Fig. 1). Yellow crystals of **2** were obtained by slow vapor diffusion of diethyl ether into a solution of **2** in CH$_2$Cl$_2$. The crystal structure of **1** has been reported before.[41]
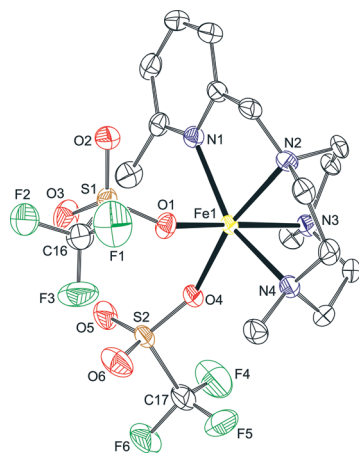

Fig. 1 Molecular structure of **2** in the crystal (50% probability level). Hydrogen atoms are omitted for clarity.
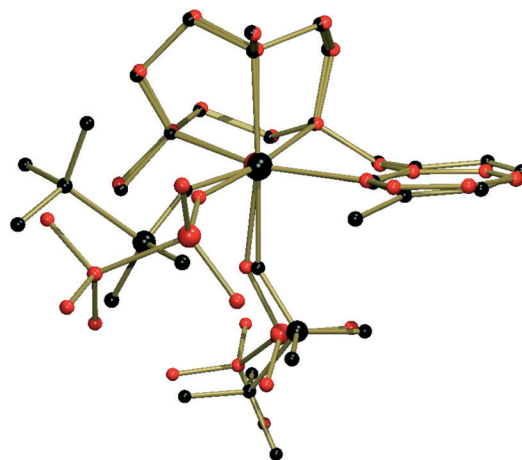

Fig. 2 Quaternion fit[57] of the molecular structures of **1** (red)[58] and **2** (black). The fit is based on the metal and its six coordinating atoms.

The molecular structure of **2** shows a 6-coordinate iron center with two triflate ions bound to iron in a *cis*-fashion and the 6-Me-PyTACN ligand coordinated through all four nitrogen donors (Fig. 1). From the overlay plot of the molecular structures of **1** and **2**, it is evident that the ligands bind to iron in a very similar fashion (Fig. 2). Small differences are seen for the orientation of the pyridine groups, while more significant differences are observed for the orientation of the triflate ligands in the crystal structure, which are exchangeable sites in MeCN solution. In terms of bond distances, the Fe–N (pyridine) distance is 2.165(4) Å in **1** and 2.246(2) Å in **2**. The Fe–N (amine) distances are between 2.205(4) and 2.252(4) Å in **1**, and between 2.199(2) and 2.238(2) Å in **2**. Overall, these long distances are indicative of a high spin ferrous center.[54,55] The O–Fe–O angle of 94.90(7)° in **2** is slightly larger than that in **1** (91.64(14)°), which might be a consequence of the larger steric demand of the ligand in **2**. Overall, the angular variance in the Fe octahedron (the deviation from perfect octahedral angles) is larger in **2** than in **1** (99.01 deg^2 *vs.* 71.07 deg^2).[56] A detailed comparison between complexes **1** and **2** is given in Table 1.

cis-Dihydroxylation of unsaturated fatty acids

In previous studies, it was shown that for optimal performance of complexes **1** and **2** in the *cis*-dihydroxylation of aliphatic alkenes, a carefully controlled amount of water

Table 1 Selected bond lengths [Å] and angles [°] for **1**[51] and **2**

Distance (Å)/angle (°)	(**1**)	(**2**)
Fe–O1	2.165(3)	2.1354(17)
Fe–O4	2.055(3)	2.0746(16)
Fe–N1	2.165(4)	2.246(2)
Fe–N2	2.205(4)	2.199(2)
Fe–N3	2.252(4)	2.231(2)
Fe–N4	2.231(4)	2.238(2)
N1–Fe–O1	96.28(13)	89.05(7)
N2–Fe–O1	94.70(14)	93.14(8)
O1–Fe–O4	91.64(14)	94.90(7)

needs to be added in order to maximize the formation of the proposed active $[Fe(O)(OH)(L)]^{2+}$ (L = ligand) oxidant and to facilitate product release from the final ferric hydrogen glycolate resting state.[52] For the oxidation of unsaturated fatty acid (esters), solubility is often a critical factor and typically requires conditions that are different from the ones used for aliphatic alkene oxidation.[46] Initially, erucic acid methyl ester was tested as substrate under conditions similar to those reported by Prat *et al.* for the *cis*-dihydroxylation of aliphatic alkenes,[47] *i.e.* 3 mol% catalyst loading with 2 eq. H_2O_2 in MeCN. No H_2O was added, however, because of expected solubility issues with this fatty substrate. Reactions with **1** and **2** showed almost complete conversion of the substrate within 15 minutes, yet only the latter gave a reasonable yield of the diol (48% compared to 12%; Table 2, entries 1–2). Likewise, reactions with **2** also yielded a five-fold higher diol/epoxide ratio. Despite the rather small structural differences, the selectivity towards *cis*-dihydroxylation of unsaturated fatty acid esters appears to greatly differ from **1** to **2** in favor of the second. Also, the selectivity difference between the complexes is significantly larger than what was previously observed for aliphatic alkenes.[47] Therefore, in subsequent reactions, only complex **2** was used. The addition of 15 eq. H_2O proved detrimental for the conversion of erucic acid methyl ester, giving lower diol yields but slightly higher diol/epoxide ratios. The drop in conversion with addition of water (15 eq.) is also observed in earlier reports on the oxidation of aliphatic alkenes (entries 3–4).[47,39] The drop in conversion for erucic acid methyl ester (96% compared to 54%) is higher than that previously observed for *cis*-cyclooctene (99% compared to 90%).[47] On the other hand, the D/E ratio in the case of erucic acid methyl ester proved less sensitive to the presence of water (1.2 compared to 1.6) than in the case of *cis*-cyclooctene (0.6 compared to 3.6).

Next, reactions with methyl oleate were investigated, which is a shorter chain fatty substrate than erucic acid methyl ester.

Using a similar protocol as for the previous substrate, reactions without addition of extra water resulted in 98% methyl oleate conversion and 56% diol yield, values that are both higher than those obtained with the previous substrate (entry 6). While the addition of extra water decreased the conversion and diol yield and increased the diol/epoxide ratio, these differences are less pronounced than with erucic acid methyl ester (entry 7). Optimization attempts other than omitting water failed to further improve the diol yield: neither reactions at −20 °C nor experiments with simultaneous addition of H_2O_2 and catalyst (over 12 h) showed a significant improvement (entries 8–9). Over-oxidation of the *cis*-diol into hydroxyl-ketones is known to occur under the applied conditions[47] and these byproducts were indeed observed and account for 2–6% of the converted substrate.

In contrast to the methyl esters, the oxidation of oleic acid proceeded to a very limited extent under the standard conditions, with only 7% of epoxide and no diol being obtained regardless of whether H_2O was added or not (entries 10–11). It should be noted that the addition of an acid additive such as acetic acid or other aliphatic acids is known to facilitate the formation of the epoxide at the expense of the diol.[47,59] Similar effects can therefore be anticipated with the use of oleic acid as substrate. However, the low conversions imply that substrate inhibition or solubility issues may be responsible for the drop in activity. The *cis*-dihydroxylation method thus works best for unsaturated fatty acids esters and good *cis*-diol yields can be achieved with catalyst **2**.

Oxidative cleavage of methyl oleate

Subsequent investigations were aimed at a one-pot cleavage of methyl oleate to carboxylic acids, exploiting the dihydroxylation activity of **2**. Accordingly, the *cis*-diol was formed using H_2O_2 in the conditions optimized for the methyl oleate *cis*-dihydroxylation (Table 2, entry 6), followed by the addition of $NaIO_4$ to the

Table 2 *cis*-Dihydroxylation of unsaturated fatty acids (esters) with **1** or **2** and H_2O_2,[a] forming epoxides as byproduct

Ent.	n	R	Cat.	H_2O_2 (eq.)	H_2O (eq.)	Conv.[b] (%)	Epoxide (%)	Diol (%)	D/E
1	11	Me	1	2	0	89	50	12	0.2
2	11	Me	2	2	0	96	41[c]	48[c]	1.2
3	11	Me	2	2	15	54	18	29	1.6
4[d]	11	Me	2	2 × 1.2	15	63	21	38	1.8
5	7	Me	2	2	1	68	12	24	2.0
6	7	Me	2	2	0	98	32	56	1.8
7	7	Me	2	2	15	80	18	42	2.3
8[e]	7	Me	2	2	0	57	14	23	1.6
9[f]	7	Me	2	2	0	100	38	50	1.3
10	7	H	2	2	2	7[c]	7[c]	0	0
11	7	H	2	2	15	7[c]	7[c]	0	0

[a] Reaction conditions: alkene in MeCN, **1** or **2** (3 mol%), H_2O_2 added over 15 minutes, 0 °C, yields determined by GC. [b] Hydroxyl ketones detected as byproducts. [c] Determined by NMR. [d] More catalyst (3 mol%) and H_2O_2 (two times 1.2 eq.) added after 15 minutes, H_2O_2 added over 15 minutes. [e] Reaction carried out at −20 °C. [f] Catalyst and H_2O_2 added over 12 h.

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same reaction mixture in order to induce further oxidation. After completion of the dihydroxylation step (3 mol% **2**, 2 eq. H_2O_2, 0 °C, 15 minutes), 3 eq. of $NaIO_4$ were added at ambient temperature, followed by 150 eq. of H_2O to dissolve the periodate (yielding a 3 : 1 (v/v) MeCN : H_2O mixture).[35,46] This way, full substrate conversion and a 55% yield of nonanoic acid were obtained after 36 h of reaction (Table 3, entry 1, method A). Control experiments with lower amounts of added H_2O showed significantly lower yields of the cleavage products and incomplete dissolution of the periodate. The formation of carboxylic acids shows that the catalyst/oxidant combination is able to oxidize aldehydes into carboxylic acids, which was confirmed by control experiments. It should be noted that this aldehyde to carboxylic acid oxidation was not possible with the previously reported Fe-BPBP system.[35] The formation of the corresponding difunctionalized product, monomethyl azelate, was also observed, but reproducible quantification proved troublesome with our analytical protocol. Its formation is presumed to be equal to the formation of the monoacid,[35,46] as the mono- and difunctionalized aldehydes were observed in equal amounts as minor byproducts (10%). The major byproduct observed in this reaction was the epoxide with a 28% yield, which is similar to the amount of epoxide observed in the previously discussed *cis*-dihydroxylation reaction.

Alterations of this protocol involving shorter reaction times, additional amounts of water, and higher reaction temperatures all gave a lower carboxylic acid yield. As expected, the use of only H_2O_2 (5 or 10 eq.) in this two-step procedure resulted in low selectivity to the aldehydes (10–12% at 100% conversion) and no carboxylic acids were formed. The yields of methyl 9-oxononanoate were nearly identical to nonanal, indicating that the difunctionalized products form in equal yield as the monofunctionalized ones. In fact, a variety of oxidation products were obtained (data not shown).

On the other hand, the use of only $NaIO_4$ (4.5 eq.) did yield 50% of nonanoic acid and 33% of epoxide at full conversion in a reaction that was completely carried out at ambient temperatures for 48 h (entry 2). Here, shorter reaction times gave lower acid yields, which is consistent with the observation that the oxidation steps involving **2** and $NaIO_4$ are much slower than *cis*-dihydroxylations with H_2O_2.[47,53]

The similar epoxide yields in the *cis*-dihydroxylation and the one-pot cleavage reaction with methyl oleate indicate that the epoxides are inert under the conditions of the cleavage reaction. Notably, the use of only 1 eq. of $NaIO_4$ with **2** did not result in selective formation of the aldehyde, but into a mixture of hydroxyl ketones and aldehydes (data not shown). This observation suggests a competition between the direct oxidation of diols by $NaIO_4$ into aldehydes and the catalytic oxidation of diols by **2** and $NaIO_4$ into hydroxyl ketones (see Scheme 3). $NaIO_4$ does not mediate the oxidation of aldehydes into carboxylic acids by itself;[35,46] this reaction is therefore catalyzed by **2**. Accordingly, the catalytic oxidation of *cis*-diols into carboxylic acids with $NaIO_4$ is proposed to proceed *via* either hydroxyl ketone or aldehyde intermediates.

Oxidative cleavage in the presence of H_2SO_4

The significant amount of epoxides formed in the one-pot oxidative cleavage protocol of methyl oleate (method A) prompted us to investigate the addition of H_2SO_4 to the reaction mixture in order to hydrolyze these byproducts to *trans*-diols (Scheme 2).[35] The formed diols could then in turn be further oxidized to carboxylic acids (Scheme 3), which would add up to the total amount of cleavage product and thus lead to a higher selectivity of the overall oxidative cleavage reaction.

The oxidative cleavage of methyl oleate in the presence of H_2SO_4 was conducted using a protocol that involved the addition of the acid after both oxidants were added. Adding the acid at an earlier stage of the reaction led to lower substrate conversions (not shown).

In a protocol similar to method A and using 4.5 eq. $NaIO_4$ and 100 eq. H_2O (see Table 3, entry 2), the addition of H_2SO_4 (0.5 eq.) in H_2O (50 eq.) after 24 h resulted in complete substrate conversion and the formation of 50% of aldehydes and 42% of carboxylic acids (Table 4, entry 1, method B). Using this protocol, no epoxides were detected at the end of the reaction. A decrease of the catalyst loading from 3 to 1 mol% in this reaction resulted in incomplete conversion (73%), but rather selective aldehyde formation (60% yield, entry 2). Methyl 9-oxononanoate was formed in similar yield as nonanal.

However, the aldehyde yields obtained from methyl oleate with method B are lower than those obtained previously with our Fe-BPBP-based protocol,[35] and the carboxylic acid yields

Table 3 Oxidative cleavage of methyl oleate with **2** and $H_2O_2/NaIO_4$ into aldehydes and acids, forming epoxides as byproduct (method A)[a]
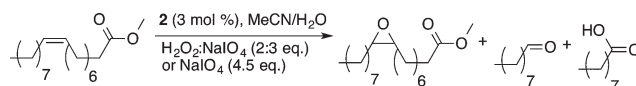
Ent.	H_2O_2 (eq.)	$NaIO_4$ (eq.)	Time (h)	Conv.[b] (%)	Epoxide (%)	Aldehyde (%)	Acid (%)
1	2	3	36	100	28	10[c]	55
2	0	4.5	48	100	33	8[d]	50

[a] Reaction conditions method A: methyl oleate and 3 mol% **2** in MeCN, i) H_2O_2 in MeCN added over 15 minutes at 0 °C, then 150 eq. H_2O and 3 eq. of $NaIO_4$ added and 36 h reaction at ambient temperature, or ii) 4.5 eq. $NaIO_4$ and 150 eq. H_2O added at the start, ambient temperature, 48 h. [b] Hydroxyl ketones as minor byproducts. [c] 10% methyl 9-oxononanoate detected. [d] 7% methyl 9-oxononanoate detected.

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Table 4 Oxidative cleavage of methyl oleate with H_2SO_4 into aldehydes and carboxylic acids (method B)[a]
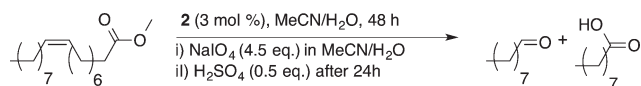
Entry	2 (%)	Conversion[b] (%)	Aldehyde (%)	Acid (%)
1	3	100	50[c]	42
2	1	73	60[d]	2

[a] Reaction conditions method B: methyl oleate in MeCN, 4.5 eq. $NaIO_4$, 100 eq. H_2O, 24 h, then 0.5 eq. H_2SO_4 in 50 eq. H_2O. [b] Hydroxyl ketones minor byproducts. [c] 44% methyl 9-oxononanoate detected. [d] 55% methyl 9-oxononanoate detected.

are lower than those in the protocol without H_2SO_4 (method A, Table 3). In order to arrive at improved carboxylic acid yields, we considered adding a mild base in the last stage of the protocol. While we postulated that **2** catalyzes the oxidation of aldehydes into carboxylic acids, the high aldehyde yields in the protocol using H_2SO_4 indicated deactivation of the catalyst, likely due to the acidic pH of the reaction medium. Therefore, we used a protocol similar to the one used for the reaction of Table 4, entry 1 (3 mol% **2**, 4.5 eq. $NaIO_4$, 48 h total reaction time, H_2SO_4 after 24 h), but now with the addition of $NaHCO_3$ after 36 h to neutralize the pH and an additional amount of **2** (1 mol%) to drive the oxidation of the remaining aldehydes into carboxylic acids (method C). Indeed, high carboxylic acid yields (82%) were observed in this way at full conversion of methyl oleate (Table 5, entry 1). This protocol was also successfully applied on oleic acid: in this case, full conversion and 85% formation of nonanoic acid were observed (entry 2). As observed with method A, H_2O_2:$NaIO_4$ (2:3 eq.) can be applied instead of $NaIO_4$ at a similar reactivity, giving rise to full conversion of methyl oleate into 80% carboxylic acid and 16% aldehyde (15% methyl 9-oxononanoate) after only 24 h. A high mass balance was observed in this case. Method C with H_2O_2–$NaIO_4$ was not applied on oleic acid, as the reactions with H_2O_2 only showed poor conversions

(see Table 2). In a separate experiment, low conversions of oleic acid were observed with 75 eq. H_2O compared with 150 eq., indicating solubility issues of periodate under these conditions, as also seen in our previous work.[46]

Conclusions

We have developed the first Fe-based catalytic system for the oxidative cleavage of unsaturated fatty acids and their esters into carboxylic acids. The system uses $[Fe(OTf)_2(6\text{-Me-PyTACN})]$ (**2**) as the catalyst, which was found to outperform the non-methyl substituted $[Fe(OTf)_2(PyTACN)]$ (**1**). **2** can be used in a number of different one-pot procedures, each of which uses a different combination of oxidants and additives, and each provides a different substrate conversion and product distribution.

Method A uses H_2O_2 (2 eq., 0 °C) for *cis*-dihydroxylation of methyl oleate (56%), after which the addition of $NaIO_4$ (3 eq.) at ambient reaction temperatures induces the subsequent over-oxidation steps towards the acids in good yields after 36 h (55%) with the epoxides being the major byproduct. The use of exclusively $NaIO_4$ (4.5 eq.) using this method for 48 h under ambient conditions allows one to obtain similar acid yields (50%). In method B, the addition of H_2SO_4 at intermediate reaction stages hydrolyzes the epoxide byproducts and eventually forms a mixture of aldehydes and carboxylic acids. Finally, a pH neutralization step with $NaHCO_3$ is incorporated in method C, followed by the addition of a small additional amount of catalyst to give almost exclusively carboxylic acids from both methyl oleate and oleic acid in high yields (>80–85%). Method C can again be run with a combination of H_2O_2 and $NaIO_4$ or only with $NaIO_4$.

The methods developed involve one-pot procedures with low catalyst loadings (3–4 mol%), small excess of oxidants (4.5–5 eq.), and convenient reaction temperatures (0–25 °C). The high selectivity to the carboxylic acids found with method C is complementary to the previously reported protocol based on Fe-BPBP systems, which is selective to the formation of the corresponding aldehydes.[35] Furthermore, these methods improve on our previous oxone–$NaIO_4$-based method[46] in the

Table 5 Oxidative cleavage of methyl oleate and oleic acid with **2** and H_2O_2/$NaIO_4$ into carboxylic acids with the aid of H_2SO_4 (method C)[a]
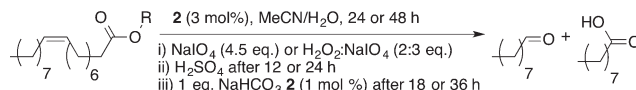
Entry	R	H_2O_2 (eq.)	$NaIO_4$ (eq.)	Time (h)	Conv.[b] (%)	Ald. (%)	Acid (%)
1	Me	0	4.5	48	100	9[c]	82
2	H	0	4.5	48	100	5	85
3	Me	2	3	24	100	16[d]	80

[a] Reaction conditions method C: substrate in MeCN, 3 mol% **2**, i) 4.5 eq. $NaIO_4$, 100 eq. H_2O, 24 h, then H_2SO_4 (0.5 eq.) in H_2O (50 eq.), 12 h, and $NaHCO_3$ (1 eq.) and **2** (1 mol%) or ii) 2 eq. H_2O_2 added over 15 minutes at 0 °C, then 3 eq. of $NaIO_4$ in 100 eq. H_2O added at RT, 12 h, H_2SO_4 (0.5 eq.) in H_2O (50 eq.), 6 h, then $NaHCO_3$ (1 eq.) and **2** (1 mol%), 6 h. [b] Hydroxyl ketones as minor byproducts. [c] 6% methyl 9-oxononanoate detected. [d] 15% methyl 9-oxononanoate detected.

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sense that ambient temperatures can be applied and significantly less waste is generated.

Overall, we believe that the new catalytic system is of general synthetic interest. More specifically, it represents an effective system for the production of medium length aliphatic aldehydes and carboxylic acids, as well as medium length α,ω-diacids and α,ω-aldehyde fatty acids from unsaturated fatty acids and esters. The system may accordingly find application in general organic systems as well as in the valorization of plant oils for the production of a number of interesting fine chemicals.

Experimental section

General

Sodium periodate (99%), *trans*-4-octene (90%), hydrogen peroxide (35% in H_2O) and methyl oleate (99%) were purchased from Aldrich. Oleic acid (99%) was obtained from Fluka. *cis*-4-Octene (97%) was purchased from Alfa Aesar. Erucic acid methyl ester (90%) was purchased from ABCR. All chemicals were used as received. The reactions were conducted under ambient conditions, using distilled water, pro analysis MeCN, and technical grade ethyl acetate. ^{1}H NMR and ^{13}C NMR measurements were recorded in CDCl₃ at 298 K on a Varian 400 MHz NMR spectrometer using residual solvent peaks as reference. Gas chromatography was carried out on an Agilent 7820A gas chromatograph (HP5 column, 30 m) and a flame ionization detector. The GC-FID was equipped with an Agilent J&W HP-5 column (30 m length, 0.32 mm internal diameter, 0.25 μm film thickness). Injector: 1 μl injection volume, split mode (ratio 100 : 1), temperature 275 °C; flow: constant at 2 mL min⁻¹, helium was used as the carrier gas; temperature program: initial temperature 75 °C for 0.5 min, first ramp to 190 °C at 10 °C min⁻¹, second ramp to 300 °C at 20 °C min⁻¹ and kept at 300 °C for 1 min; FID detector: temperature at 300 °C, hydrogen flow at 30 mL min⁻¹, air flow at 400 mL min⁻¹, and helium flow at 25 mL min⁻¹. The retention times (min) of the required products, the substrate and the internal standard were as follows: 4.81, nonanal; 6.70, nonanoic acid; 8.32, biphenyl (internal standard); 8.90, methyl 9-oxononanoate; 10.63, methyl azelate; 14.92, methyl oleate; 15.91, methyl oleate epoxide; 16.81, methyl oleate diol; 16.82, erucic acid methyl ester; 17.53, erucic acid methyl ester epoxide; and 18.44, erucic acid methyl ester diol.

The syntheses of [Fe(OTf)₂(PyTACN)] (**1**) and [Fe(OTf)₂(6-Me-PyTACN)] (**2**) were performed according to literature procedures.[47]

X-ray crystal structure determination of [Fe(OTf)₂(6-Me-PyTACN)] (2)

$C_{17}H_{26}F_6FeN_4O_4S_2$, Fw = 616.39, pale yellow needle, 0.38 × 0.11 × 0.05 mm³, orthorhombic, $P2_12_12_1$ (no. 19), a = 8.9413(6), b = 15.7005(10), c = 17.7436(11) Å, V = 2490.9(3) Å³, Z = 4, D_x = 1.644 g cm⁻³, μ = 0.86 mm⁻¹. 16 042 reflections were measured on a Bruker Kappa ApexII diffractometer with a sealed tube and a Triumph monochromator (λ = 0.71073 Å) at a

temperature of 150(2) K up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.60 Å⁻¹. Intensity data were integrated with the Saint software.[60] The absorption correction and scaling were performed using SADABS[61] (correction range 0.64–0.75). 4381 reflections were unique (R_{int} = 0.019), of which 4105 were observed [$I > 2\sigma(I)$]. The structure was solved using the program SHELXT.[62] The least-squares refinement was performed using SHELXL-97 (ref. 63) of F^2 against all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. All hydrogen atoms were located in difference Fourier maps and refined with a riding model. 329 parameters were refined with no restraints. R_1/wR_2 [$I > 2\sigma(I)$]: 0.0250/0.0559. R_1/wR_2 [all refl.]: 0.0290/0.0576. S = 1.096. Flack parameter[64] x = 0.007(13). The residual electron density was between −0.30 and 0.53 e Å⁻³. Geometry calculations and checking for higher symmetry were performed using the PLATON program.[65]

CCDC 951113 contains the supplementary crystallographic data for this paper.

cis-Dihydroxylation of alkenes

Alkene substrate (0.09 mmol), **1** or **2** (2.7 μmol), and H_2O (0–1.35 mmol) were dissolved in MeCN (1 ml) at 0 °C. Then, H_2O_2 in MeCN (90–180 μmol in 1.44 M) was added over 15 minutes. Biphenyl (22.5 μmol, internal standard) in MeCN (125 μL) and ethyl acetate (4 mL) were added, and the sample was filtered through a short silica column before being subjected to GC analysis. In a similar fashion, the reaction of erucic acid methyl ester with **2** and without addition of extra H_2O was analyzed by GC in order to determine the substrate conversion (Table 2, entry 2). The same sample was analyzed using ^{1}H NMR to determine the amount of epoxide and diol formed by comparing the aromatic signals of biphenyl (internal standard, 3'H signal of 1,1-biphenyl) with the $CH_2(CH(O)CH)CH_2$ signal of the epoxide and the $CH_2(CH(OH)CH(OH))CH_2$ of the diol. The conversion was determined from the decrease of the $CH_2CHCHCH_2$ signal of the double bond of erucic acid methyl ester with respect to the internal standard. In reactions with oleic acid, ^{1}H NMR was used to determine the amount of epoxide formed in a similar fashion as with erucic acid methyl ester and methyl oleate, using biphenyl as internal standard.

Oxidative cleavage of methyl oleate into epoxides and carboxylic acids (method A)

Alkene substrate (0.09 mmol), **2** (2.7 μmol), and H_2O (0–1.35 mmol) were dissolved in MeCN (1 mL) at 0 °C. Then, H_2O_2 in MeCN (180 μmol in 1.44 M) was added over 15 minutes. NaIO₄ (0.27 mmol) and H_2O (13.5 mmol) were added at ambient temperature and stirred for 36 h. In case no H_2O_2 was used, NaIO₄ (405 μmol) was added under ambient conditions and stirred for 48 h. Subsequently, biphenyl (22.5 μmol, internal standard) in MeCN (125 μL) and ethyl acetate (4 mL) were added and the sample was subjected to GC analysis. The catalyst precipitated under these conditions and needed no separation

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from the mixture. In the analytical protocol, monomethyl azelate was observed as well, but quantification proved not to be reproducible with the applied GC method. As the yields of nonanal and methyl 9-oxononanoate match, only the yields of nonanal, nonanoic acid and methyl 9-oxononanoate are given in Table 3.

Oxidative cleavage of methyl oleate and oleic acid into aldehydes and carboxylic acids (method B)

Alkene substrate (0.09 mmol), **2** (2.7 µmol), sodium periodate (0.405 mmol) and H_2O (75 eq.) were stirred in MeCN (1 mL) for 24 h. Then, H_2SO_4 (0.5 eq.) in H_2O (75 eq.) was added and stirred for additional 24 h. Subsequently, biphenyl (22.5 µmol, internal standard) in MeCN (125 µL) and ethyl acetate (4 mL) were added and the sample was subjected to GC analysis. The catalyst precipitated under these conditions and needed no separation from the mixture. In the analytical protocol, monomethyl azelate was observed as well, but quantification proved not to be reproducible with the applied GC method. As the yields of nonanal and methyl 9-oxononanoate match, only the yields of nonanal, nonanoic acid and methyl 9-oxononanoate are given in Table 4.

Oxidative cleavage of methyl oleate into carboxylic acids (method C)

Alkene substrate (0.09 mmol), **2** (2.7 µmol), sodium periodate (0.405 mmol) and H_2O (100 eq.) were stirred in MeCN (1 mL) for 24 h. Then, H_2SO_4 (0.045 mmol) in H_2O (75 eq.) was added and stirred for an additional 12 h. Subsequently, NaHCO$_3$ (0.09 mmol) and **2** were added (0.9 µmol) and stirred for additional 12 h. Biphenyl (22.5 µmol, internal standard) in MeCN (125 µL) and ethyl acetate (4 mL) were added and the sample was subjected to GC analysis. The catalyst precipitated under these conditions and needed no separation from the mixture. In the analytic protocol, monomethyl azelate was observed as well in reactions with methyl oleate, but quantification proved not to be reproducible with the applied GC method. Azelaic acid was not observed at all in the reaction with oleic acid. As the yields of nonanal and methyl 9-oxononanoate match, only the yields of nonanal, nonanoic acid and methyl 9-oxononanoate are given in Table 5.

In reactions performed using methods A, B, and C with H_2O_2, the same conditions as for *cis*-dihydroxylations are applied at the start. After 15 minutes of reaction, NaIO$_4$ (0.27 mmol) and H_2O (100 eq.) were added and stirred for 12 h. In a similar fashion as for reactions with 4.5 eq. NaIO$_4$, H_2SO_4 was added and stirred for 6 h, and NaHCO$_3$ and NaIO$_4$ were added and reacted for an additional 6 h.

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