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Fe-Catalyzed One-Pot Oxidative Cleavage of Unsaturated Fatty Acids into Aldehydes with Hydrogen Peroxide and Sodium Periodate

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Abstract: A one-pot method has been developed for the oxidative cleavage of internal alkenes into aldehydes by using 0.5 mol% of the nonheme iron complex [Fe(OTf)$_2$(mix-bpbp)] (bpbp = *N*,*N*′-bis(2-picolyl)-2,2′-bipyrrolidine) as catalyst and 1.5 equivalents of hydrogen peroxide and 1 equivalent of sodium periodate as oxidants. A mixture of diastereomers of the chiral bpbp ligand can be used, thereby omitting the need for resolution of its optically active components. The cleavage reaction can be performed in one pot within 20 h and under ambient conditions. Addition of water after the epoxidation, acidification and subsequent pH neutralization are crucial to perform the epoxidation, hydrolysis, and subsequent diol cleavage in one pot. High aldehyde yields can be obtained for the cleavage of internal aliphatic double bonds with *cis* and *trans* configuration (86–98%) and unsaturated fatty acids and esters (69–96%). Good aldehyde yields are obtained in reactions of trisubstituted and terminal alkenes (62–63%). The products can be easily isolated by a simple extraction step with an organic solvent. The presented protocol involves a lower catalyst loading than conventional methods based on Ru or Os. Also, hydrogen peroxide can be used as the oxidant in this case, which is often disproportionated by second- and third-row metals. By using only mild oxidants, overoxidation of the aldehyde to the carboxylic acid is prevented.

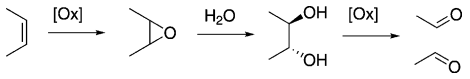
Keywords: aldehydes · alkenes · cleavage reactions · fatty acids · hydrogen peroxide · iron

Introduction

The oxidative cleavage of unsaturated fatty acids into either aldehydes or carboxylic acids is a reaction of considerable practical interest.[1–3] This conversion is nowadays mostly performed with second- and third-row transition-metal catalysts based on Os,[4–12] Ru,[13–18] or W,[19–25] on the lab scale, or with ozone in an industrial process.[3,26] More benign methods for these processes are clearly desired. Recently, we reported on the nonmetal-mediated oxidative cleavage of internal alkenes and unsaturated fatty acids into carboxylic acids with a combination of the oxidants oxone and sodium periodate.[27] This oxidative cleavage involves a cascade of reactions starting with epoxidation of an alkene with oxone, acid-catalyzed ring-opening of the epoxide to give a diol intermediate (oxone solutions are slightly acidic), periodate-mediated cleavage of the diol into aldehydes in the same pot, and finally oxidation of the aldehyde with oxone to give the carboxylic acids. The oxone/periodate combination is very useful for the preparation of fatty-acid-derived carboxylic acids, but does not allow for the isolation of products at the aldehyde oxidation level.

To allow selective aldehyde formation in such a one-pot protocol, alternatives for oxone need to be sought for the epoxidation step, because this oxidant readily overoxidizes the aldehydes formed into the corresponding carboxylic acids. Additionally, an alternative oxidant should preferably produce less waste than oxone. The use of periodate as the oxidizing agent of diols can be considered acceptable from a sustainability viewpoint, as this oxidant can be regenerated electrochemically.[28,29] Any alternative for oxone should be compatible with sodium periodate to maintain the facile, one-pot conversion approach. For these reasons, catalytic systems that involve first-row transition-metal systems and benign oxidants were considered to replace oxone and to arrive at a one-pot protocol to form aldehydes out of internal, electron-rich alkenes (Scheme 1).

Hydrogen peroxide is widely used in epoxidation reactions and does not overoxidize aldehydes into carboxylic acids by itself. First-row transition-metal-catalyzed epoxida-



Scheme 1. Reaction sequence for the formation of aldehydes from internal alkenes.

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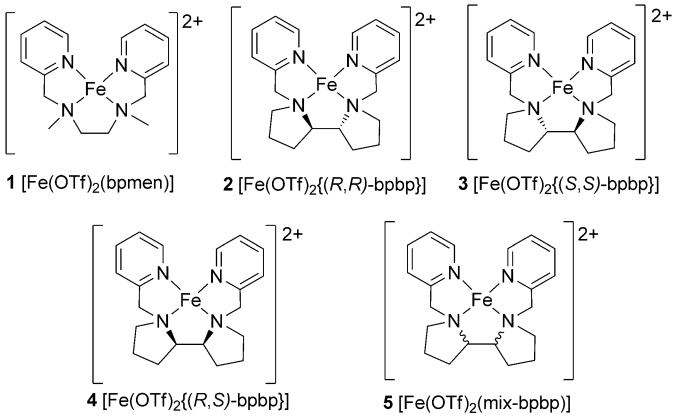
tions with H_2O_2 typically involve nonheme Fe and Mn complexes derived from ligands such as tris(2-picolylamine) (tpa), *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-1,2-diaminoethane) (bpmen),[30] tetraalkylcyclam (Me_2EBC = 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane),[31] bispidine ligands,[32] or *N*,*N*′-bis(2-picolyl)-2,2′-bipyrrolidine (bpbp).[33–35] Commonly, alkene epoxidation reactions catalyzed by such systems are optimized for *cis*-cyclooctene or styrene derivatives. When it comes to the epoxidation of internal, aliphatic alkenes, examples based on these nonheme complexes are rather limited: *cis*-2-heptene can be oxidized with Fe–Me_2EBC complexes under oxidant-limiting conditions, yet the epoxides are only a minor product under the applied conditions, as *cis*-diols are primarily formed in pure CH_3CN.[31] Ligands that mimic the active site of a group of nonheme iron oxygenases characterized by the so-called 2-His-1-carboxylate triad show similar results.[36,37] Under substrate-limiting conditions, significantly higher epoxide yields can be obtained: the oxidation of *cis*-2-heptene by using Fe–tpa complexes affords 44% of 2,3-epoxyheptane,[38] whereas Fe–bpmen complexes yield up to 77% of the epoxide.[38] Nevertheless, high efficiencies (>90% yield) in the epoxidation of acyclic, internal aliphatic *cis*-alkenes with H_2O_2 are still only obtained with methods based on Re catalysts.[12,39–41] In addition, some V-, Mo-, and W-based catalysts give high epoxide yields of the *trans*-internal aliphatic alkenes[42] and *cis*-2-heptene[43] (90%) as substrate when using H_2O_2 as the oxidant.[43] Acyclic, internal aliphatic *cis*-alkenes were not investigated with these catalysts, however. Also, Mo catalysts have been shown to give internal aliphatic epoxides in high yield, but with *tert*-butyl hydroperoxide as oxidant rather than H_2O_2.[44]

In our search for a suitable system for the epoxidation of internal aliphatic alkenes, the recently reported catalytic performance of a Fe–bpbp catalyst stood out, given its low catalyst loading, high selectivity toward the epoxide, and its significant activity, also in the absence of additives such as MeCOOH, which are often required for high activity with similar catalysts.[34] In addition, Fe–bpbp-catalyzed epoxidation reactions typically result in high mass balances in pure acetonitrile, with only some minor amounts of *cis*-diol observed as byproduct.[35] So far, the bpbp system has been applied in its enantiomerically pure form ((*S*,*S*)-bpbp) for asymmetric epoxidations,[33] which raises the costs involved because of the need for chiral resolution. A chiral catalyst is not necessary for oxidative cleavage, and a cheaper, diastereomerically impure form of the Fe–bpbp catalyst can in principle be used.

Herein we present our results on the sequential Fe/H_2O_2-catalyzed epoxidation, acid-catalyzed hydrolysis, and periodate-mediated diol cleavage for the one-pot oxidative cleavage of alkenes and unsaturated fatty acids into aldehydes. On the basis of the promising results previously reported, we explored in detail the activity and selectivity of the iron complexes [Fe(OTf)$_2$(bpmen)] (**1**), [Fe(OTf)$_2${(*R*,*R*)-bpbp}] (**2**), [Fe(OTf)$_2${(*S*,*S*)-bpbp}] (**3**), [Fe(OTf)$_2${(*R*,*S*)-bpbp}] (**4**), and the complex with an isomeric mixture of bpbp ligands, [Fe(OTf)$_2$(mix-bpbp)] (**5**) (Scheme 2). The optimization of the individual steps in the oxidative cleavage sequence is discussed as well as the substrate scope. Aldehyde cleavage products were obtained in excellent yields with a particular preference for the cleavage of electron-rich internal olefins.



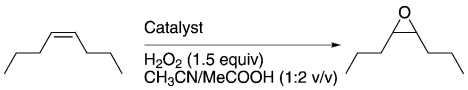
Scheme 2. Nonheme Fe^{II} complexes used in this study (coordinating triflate ions are not drawn for clarity).

Results and Discussion

The epoxidation activity toward internal alkenes was initially screened with *cis*-4-octene as substrate by adding 1.5 equivalents of H_2O_2 dropwise to a CH_3CN/MeCOOH (1:2 v/v) solution that contained 0.5 mol% [Fe(OTf)$_2$(bpmen)] (**1**). After 45 min, near complete conversion (98%) was achieved with an 89% yield of 4,5-epoxyoctane (Table 1, entry 1). Performing the reaction at 0°C improved the yield of the epoxide to 95% (Table 1, entry 2). The higher epoxide yields at lower temperature can be attributed to lower H_2O_2 disproportionation rates under such conditions, as also observed with epoxidations of *cis*-cyclooctene and **1** reported by Mas-Balleste et al.[38] Identical epoxide yields were obtained whether the oxidant was added with a syringe pump or manually, which prompted us to manually add the oxidant in a dropwise fashion in all further experiments. When the loading of **1** was decreased to 0.1 mol%, the substrate conversion dropped significantly to 39% (Table 1, entry 4). On the other hand, using 0.1 mol% of [Fe(OTf)$_2${(*R*,*R*)-bpbp}] (**2**) quantitatively converted the substrate into 4,5-epoxyoctane within 45 min, even at ambient temperature (Table 1, entry 5). Further lowering of the loading of **2** to 0.05 mol% gave 78% of the epoxide after 45 min (Table 1, entry 6), thereby resulting in a turnover number (TON) of 1560. The use of [Fe(OTf)$_2${(*S*,*S*)-bpbp}] (**3**) gave almost identical results to **2**, with full substrate conversion and 97% epoxide yield (Table 1, entry 7). On the contrary, *meso*-complex [Fe(OTf)$_2${(*R*,*S*)-bpbp}] (**4**) showed no activity at all, not even at 0°C (Table 1, entry 8). Importantly, the latter complex seems rather innocent, as no side products are observed either. Therefore, a mixture of Fe

complexes [Fe(OTf)$_2$(mix-bpbp)] (**5**) generated from a mixture of the different diastereomers of bpbp, that is, by using a nonresolved mixture of bpbp ligands that contained around 60% of *R*,*R* and *S*,*S* and 40% of *R*,*S* diastereoisomers, was tested. Such a mixture would represent a much cheaper source of the bpbp ligand, because the time-consuming synthetic step of ligand resolution is omitted. The use of 0.25 mol% of **5** gave quantitative *cis*-4-octene conversion to 4,5-epoxyoctane at RT after 45 min (Table 1, entry 9). Lower loadings of 0.1 and 0.05 mol% gave conversions of 90 and 59% of the substrate, respectively (Table 1, entries 10 and 11). Since an excess amount of water is required for the subsequent epoxide hydrolysis step, we also investigated the stability of the catalysts in the presence of water. The addition of only 0.25 mL water significantly decreased the conversion when using 0.5 mol% **1** from 99 to 35%, and the epoxide yield from 95 to 26% (Table 1, entry 12). On the other hand, 0.5 mol% of **2** quantitatively converted the substrate in the presence of up to 1 mL of water, thus forming 88% of the epoxide (Table 1, entry 13).

Table 1. *cis*-4-Octene epoxidation with H_2O_2 in a CH_3CN/MeCOOH mixture.[a]

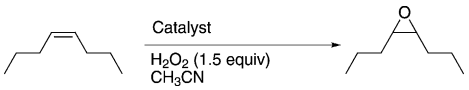


Entry	Catalyst	Loading [mol%]	*T* [°C]	*t* [min]	Conv. [%][b]	Yield [%][b]
1	**1**	0.5	25	45	98	89
2	**1**	0.5	0	45	99	95
3[c]	**1**	0.5	0	90	100	95
4	**1**	0.1	0	90	39	33
5	**2**	0.1	25	45	100	99
6	**2**	0.05	25	45	78	78
7	**3**	0.1	25	45	100	97
8	**4**	0.5	0	45	0	0
9	**5**	0.25	25	45	100	99
10	**5**	0.1	25	45	90	89
11	**5**	0.05	25	45	59	56
12[d]	**1**	0.5	0	90	35	26
13[e]	**2**	0.5	0	90	100	88

[a] Reaction conditions: catalyst (0.05–0.5 mol%), *cis*-4-octene (0.18 M) in CH_3CN/MeCOOH (1:2 v/v, 3 mL), H_2O_2 (1.5 equiv) added dropwise. [b] Yields and conversions (Conv.) determined by GC. [c] H_2O_2 added over 1 h. [d] H_2O added: 0.25 mL. [e] H_2O added: 1 mL.

Subsequently, the possibility to omit acetic acid from the reaction mixture was explored, as this would facilitate product separation. Reactions were performed at low temperature to limit oxidant disproportionation.[35] Using 0.5 mol% of **1** in CH_3CN as the sole solvent component gave only 35% conversion of the substrate after 90 min at 0°C, with 2% of *meso*-4,5-octanediol (*cis*-dihydroxylation product) and 27% of the epoxide as products (Table 2, entry 1). On the other hand, 0.5 mol% of either **2** or **3** gave full substrate conversion, thereby yielding 92% epoxide and 6% diol (Table 2, entry 2 for **2**). Identical results are obtained when the catalyst loading was decreased to 0.25 mol% (Table 2, entry 3). Because complex **4** proved inactive in this protocol

Table 2. *cis*-4-Octene epoxidation with H_2O_2 in the absence of MeCOOH.[a]



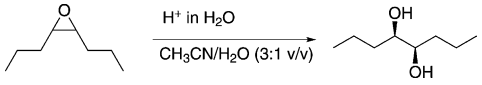
Entry	Catalyst	Loading [mol%]	Conv. [%][b]	Diol yield [%][c]	Epoxide yield [%]
1	**1**	0.5	35	2	27
2	**2**	0.5	100	6	92
3	**2**	0.25	100	6	92
4	**4**	0.5	0	0	0
5	**5**	0.25	42	4	37
6	**5**	0.5	100	5	92

[a] Reaction conditions: catalyst (0.25–0.5 mol%), H_2O_2 (1.5 equiv) added dropwise, *cis*-4-octene (0.18 M) in CH_3CN (3 mL), 0°C, 1.5 h. [b] Yields and conversions determined by GC. [c] *meso*-4,5-Octadiol.

as well (Table 2, entry 4), the reaction could again be performed with 0.5 mol% of racemic **5** to give 92% epoxide and 5% diol at full substrate conversion (Table 2, entry 6). The latter conditions were taken as optimal for the epoxidation of internal alkenes.

The epoxide ring opening can be performed by a variety of strong acids in aqueous organic solvent, but isomerization, dehydration, or halohydrin formation are common side reactions.[45] With the one-pot sequence in mind, the ring opening of 4,5-epoxyoctane was optimized in CH_3CN with some added water. Reactions of the epoxide with 1 equivalent of tartaric acid with respect to the substrate in CH_3CN/H_2O (3:1, v/v) gave only 5% substrate conversion after 30 min at ambient temperature (Table 3, entry 1). Increasing the amount of acid (6 equiv) and extending the reaction time to 90 min led to 96% substrate conversion, but with only 39% diol being formed (Table 3, entry 2). Complete conversion of the epoxide was observed with 1 equivalent of *p*-toluene sulfonic acid (*p*-TSA; Table 3, entry 3). Using this acid also gave only 45% of the diol, whereas HCl converted only 50% of the epoxide and gave considerable amounts of byproducts (Table 3, entry 4). Rewardingly, the use of H_2SO_4 (1 equiv of H^+) in CH_3CN/H_2O (3:1 v/v) gave *rac*-4,5-octanediol in 96% isolated yield after 30 min, with full conversion and no detectable byproducts (Table 3, entry 6).

Table 3. Acid-catalyzed hydrolysis of 4,5-epoxyoctane into *rac*-4,5-octanediol.[a]

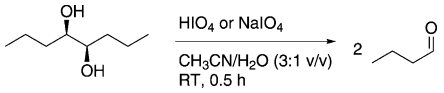


Entry	Acid	H^+ [equiv]	*t* [min]	Conv. [%][b]	Yield [%][b]
1	tartaric	1	30	5	0
2	tartaric	6	90	96	39[c]
3	*p*-TSA	1	30	100	45[c]
4	HCl	1	30	50	25[c]
5	H_2SO_4	0.1	30	28	23
6	H_2SO_4	1	30	100	96[d]

[a] Reaction conditions: 4,5-epoxyoctane (0.135 M) in CH_3CN/H_2O (3:1 v/v; 4 mL), RT. [b] Determined by GC. [c] By-products observed. [d] Isolated yield.

Optimization of the final step in the sequence, that is, periodate-mediated oxidative cleavage of *rac*-4,5-octanediol into butanal, was carried out in CH_3CN/H_2O 3:1 (v/v), the same solvent system as was used for the epoxidation and hydrolysis reactions. Complete conversion was obtained with 3 equivalents of HIO_4 within 2 h, but byproducts were formed in addition to the 75% of yield of butanal (Table 4, entry 1). Byproduct formation could be attributed to the use of periodic acid rather than a periodate salt. Indeed, the conversion into butanal was quantitative after 30 min with 3 or even 1 equivalent of $NaIO_4$ (Table 4, entries 2 and 3). Notably, oxidation of the diol did not occur in the absence of H_2O (Table 4, entry 4).

Table 4. Oxidation of *rac*-4,5-octanediol into butanal.[a]



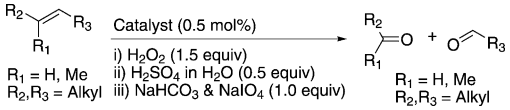
Entry	Oxidant	[Equiv]	CH_3CN/H_2O (v/v)	Conv. [%][b]	Yield [%][c]
1	HIO_4	3	3:1	100	75[d]
2	$NaIO_4$	3	3:1	100	99
3	$NaIO_4$	1	3:1	100	99
4	$NaIO_4$	1	1:0	0	0

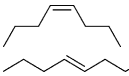
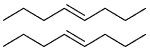
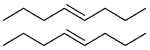
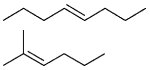
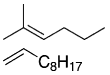
[a] Reaction conditions: *rac*-4,5-octanediol (0.135 M) in CH_3CN/H_2O (3:1 v/v; 4 mL), RT, 30 min, oxidant. [b] Determined by GC. [c] Maximum amount of butanal set to 100%. [d] Side products observed, 2 h.

Having optimized the individual steps of alkene epoxidation, epoxide ring opening, and diol oxidation into aldehydes with our model substrate *cis*-4-octene, we intended to combine the individual protocols for a procedure to convert *cis*-4-octene into butanal in one pot. To maximize the yield, the reaction time was increased to 2.5 h for the epoxidation reaction and to 1 h for the epoxide hydrolysis. The procedure was as follows (method A): Epoxidation with 0.5 mol% of catalyst **2** or **5** at 0°C with 1.5 equivalents of H_2O_2 in CH_3CN for 2.5 h, subsequent hydrolysis by addition of 0.5 equivalents of H_2SO_4 in H_2O to give a 0.135 M solution in CH_3CN/H_2O (3:1 v/v), which was stirred for 1 h at ambient temperature. Finally, 1 equivalent of $NaHCO_3$ (neutralizing the pH) and 1 equivalent of $NaIO_4$ were added, and the mixture was stirred for an additional 0.5 h. To our delight, the presence of all reagents did not cause side reactions in the protocol: *cis*-4-octene was completely converted after 4 h with catalyst **2**, which yielded 94% of butanal (Table 5, entry 1), whereas the use of **5** even resulted in an aldehyde yield of 98% at full substrate conversion (Table 5, entry 2). The presence of the catalyst in the mixture did not cause side reactions upon the introduction of either the acid or the base, nor did overoxidation of the aldehyde take place when $NaIO_4$ was introduced.

The substrate scope of this one-pot procedure was subsequently explored with various aliphatic alkenes using catalyst **5**. Reactions with *trans*-4-octene gave 90% conversion but only 40% aldehyde (Table 5, entry 3). As remaining traces of both epoxide and *meso*-4,5-diol suggested that the initial steps in the sequence were incomplete, reaction times were extended for the hydrolysis from 1 to 16 h, and for the diol oxidation from 0.5 to 1.5 h (method B). This did not result in any major improvement, however, as the diol cleavage step was still found to be incomplete (95% substrate conversion with 41% aldehydes; Table 5, entry 4). On the basis of our observations in the previously reported metal-free one-pot protocol[27] that transformation of diols into aldehydes works especially well once the reaction mixture is diluted with water to an CH_3CN/H_2O ratio of 1:3 (v/v), we applied the same strategy here (method C). Notably, 96% of *trans*-4-octene was converted into 86% of butanal with method C and only 9% of diol remained (Table 5, entry 5). Method C also allowed for 70% conversion of 2-methyl-2-hexene to yield 63% of butanal (Table 5, entry 6). The terminal alkene 1-decene was also converted by 70%, thus generating 63% of nonanal (Table 5, entry 7). Moreover, 93% of adipaldehyde was isolated from cyclohexene at complete substrate conversion with this method. The isolation of the dialdehyde was straightforward and could be conducted by simple extraction of the reaction mixture with ether and subsequent evaporation. Likewise, the reaction of the terpene α-pinene yielded the ketoaldehyde by oxidative cleavage in 60% isolated yield (Table 5, entry 9). On the other hand, reactions with *trans*-β-methyl styrene gave only

Table 5. One-pot oxidative cleavage of aliphatic alkenes.[a]



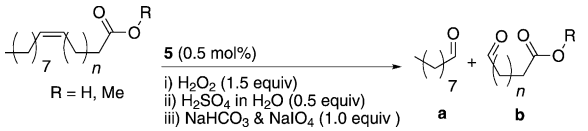
Entry	Substrate	Catalyst	t [h]	CH_3CN/H_2O (v/v)	Method	Conv. [%][b]	Yield [%][c]
1		**2**	4	3:1	A	100	94
2		**5**	4	3:1	A	100	98
3		**5**	4	3:1	A	90	40
4		**5**	20	3:1	B	95	41
5		**5**	20	3:1→3:9	C	96	86
6		**5**	20	3:1→3:9	C	73	62
7		**5**	20	3:1→3:9	C	70	63
8		**5**	20	3:1→3:9	C	100	93[d]
9		**5**	20	3:1→3:9	C	100	60[d]
10		**5**	20	3:1	B	60	44

[a] Reaction conditions: method A: i) alkene (0.18 M) in CH_3CN (3 mL), **5** ([Fe(OTf)$_2$(mix-bpbp)], 0.5 mol%), H_2O_2 (1.5 equiv) in CH_3CN (1.08 M) added dropwise, 0°C, 2.5 h; ii) alkene (0.135 M) in CH_3CN/H_2O (3:1 v/v, 4 mL), RT, 1 h; iii) $NaHCO_3$ (1 equiv), $NaIO_4$ (1 equiv), 0.5 h. Method B: ii) 16 h; iii) 1.5 h. Method C: ii) 16 h; iii) addition of H_2O (8 mL), CH_3CN/H_2O (0.07 M, 3:9 v/v), 1.5 h. [b] Determined by GC. [c] Maximum aldehyde yield set to 100 %. [d] Isolated yield.

60% conversion and yielded 44% benzaldehyde (Table 5, entry 10). Styrenes and stilbenes generally showed poor yields, and increasing the catalyst loading was not found to be beneficial (not shown).

Next we turned our attention to the application of the one-pot method in the oxidative cleavage of unsaturated fatty acids and esters. In the oxidative cleavage of nonsymmetric substrates such as the unsaturated fatty acids, both a linear aldehyde as well as an ω-1 aldocarboxylic acid are formed. For analytical reasons, the conversion and selectivity of the fatty acid cleavage reactions were determined by monitoring the amounts of linear aldehyde being produced, with the yield of the corresponding ω-1 aldocarboxylic acid assumed to be equal. The difunctionalized molecules are more water soluble at high temperatures than the monofunctionalized ones and can therefore be separated in hot water. We initially applied method A for the oxidation of the fatty acid ester methyl oleate, as *cis*-4-octene is readily converted under these conditions into the aldehyde in high yields. Methyl oleate was converted in 93% after 4 h with this method, and 78% of nonanal was obtained (Table 6, entry 1). As product analysis by ^{1}H NMR spectroscopic measurements showed that diols were still present at the end of the reaction, the reaction time was extended (method B) to give excellent yields of nonanal (92%) after 20 h at 94% substrate conversion (Table 6, entry 2). In a similar fashion, we conducted the reaction with methyl oleate on a preparative scale, that is, using a tenfold larger substrate amount, and obtained a 75% isolated yield of the mono- and difunctionalized product in an equal molar ratio. The reaction of the fatty acid oleic acid in pure CH_3CN resulted in 95% substrate conversion and 90% yield of nonanal (Table 6, entry 3). To illustrate the influence of MeCOOH in the conversion of fatty acid substrates, some reactions were performed in a mixture of MeCOOH and CH_3CN (1:2 v/v). In the case of methyl oleate, full substrate conversion and 96% yield of nonanal was achieved, which showed a small beneficial effect of the use of acetic acid (Table 6, entry 4). On the other hand, MeCOOH is required for the efficient conversion of elaidic acid (*trans* isomer of oleic acid), erucic acid (C11 fatty acid), and the methyl ester of erucic acid, as reactions in pure CH_3CN resulted in mediocre amounts of nonanal. The higher solubility of these substrates in the MeCOOH/CH_3CN medium is considered to be a crucial factor. The somewhat sluggish reactivity of these three substrates required that the epoxidation, hydrolysis, and diol cleavage were performed for 24 h each. In this way, elaidic acid was completely converted to form 69% of nonanal (Table 6, entry 5). Likewise, erucic acid and its methyl ester gave yields of 73 and 70% of nonanal, respectively, at full substrate conversion (Table 6, entries 6 and 7). The developed protocol therefore proved to be very efficient for the one-pot oxidative cleavage of various fatty acids and their esters.

Table 6. Oxidative cleavage of unsaturated fatty acids and esters.[a]



Entry	*n*	R	MeCOOH [equiv]	Method	Conv. [%][b]	Yield **a** [%][b]	Yield **b** %][b]
1	6	Me	0	A	93	78	73
2	6	Me	0	B	94	92	86
3	6	H	0	B	95	90	n.d.[e]
4	6	Me	50	B	100	96	89
5[c]	6	H	50	B[d]	100	69	n.d.[e]
6	10	H	50	B[d]	100	73	n.d.[e]
7	10	Me	50	B[d]	100	70	n.d.[e]

[a] Reaction conditions: method A: i) alkene (0.18 M) in organic solvent (CH_3CN, 3 mL or CH_3CN/MeCOOH 2:1, v/v, 3 mL), **5** ([Fe(OTf)$_2$(mix-bpbp)], 0.5 mol%), H_2O_2 (1.5 equiv) in CH_3CN (1.08 M) added dropwise, 0 °C, 2.5 h; ii) H_2SO_4 (0.5 equiv, 0.18 M in H_2O, 1 mL), 1 h, RT; iii) $NaHCO_3$ (1 equiv), $NaIO_4$ (1 equiv), 0.5 h. Method B: ii) 16 h; iii) 1.5 h. [b] Determined by GC. [c] Elaidic acid used, *trans* double bond. [d] Reaction steps i), ii), and iii) all performed for 24 h. [e] Not determined.

Conclusion

A straightforward one-pot protocol for the transformation of internal alkenes into aldehydes has been developed. The protocol relies on the use of iron as the transition metal and a combination of the benign oxidants H_2O_2 (1.5 equiv) and $NaIO_4$ (1 equiv) in CH_3CN as the sole solvent. The reaction sequence involves the initial epoxidation of the alkene with hydrogen peroxide, mediated by a mixture of iron complexes obtained from an unresolved mixture of isomers of the bpbp ligand. This [Fe(OTf)$_2$(mix-bpbp)] catalyst is a cheap and synthetically more straightforward alternative to optically pure Fe–bpbp complexes, which need chiral resolution of the ligand. Subsequently, epoxide ring opening with diluted sulfuric acid and finally cleavage of the resulting diol into aldehydes by stoichiometric amounts of $NaIO_4$ occur in the same pot. High yields of the cleavage products can be obtained with catalyst loadings as low as 0.5% and without the need for acetic acid. The reaction sequence is not hampered by the epoxidation catalyst that remains in the reaction mixture, and no overoxidation of the aldehydes towards carboxylic acids occurs in this system despite the presence of $NaIO_4$ and the catalyst. In this way, the subsequent intermediates do not need to be isolated and the reaction can occur in pot. The use of a limited number of reactants, the omission of MeCOOH, and the fact that acid and base neutralize each other enables the aldehydes to be obtained by direct extraction in organic solvent from the reaction mixture without the need for column chromatography. Cyclic, internal, terminal, and trisubstituted aliphatic alkenes as well as terpenes can all be cleaved in high yields within 4–20 h.

Furthermore, we have shown that a variety of unsaturated fatty acids and esters can be cleaved into nonanal and an ω-1 aldocarboxylic acid. The former is an industrially interesting product, nowadays typically produced by hydroformyla-

tion of 1-octene, for which this system can be regarded as an alternate process. However, the latter product could serve as a valuable monomer of a variety of biobased polymers. Our protocol is an alternative to similar processes that involve Ru-, Os-, and W-mediated systems that use additives and less benign oxidants for the oxidative cleavage of unsaturated fatty acids into aldehydes. Furthermore, this system might serve as a substitute for the ozonolysis of oleic acid carried out on a large scale in industry.

Experimental Section

General: Sodium periodate (99%), (1*R*)-(+)-α-pinene (98%), cyclohexene (99%), *trans*-β-methyl styrene (97 %), hydrogen peroxide (35 wt% in H_2O), and α-methyl styrene (99%) were purchased from Acros Organics. *trans*-4-Octene (90%), 1-decene (94%), styrene (99%, stabilized with 10–15 ppm *p-tert*-butylcatechol), *cis*-stilbene (96%), and methyl oleate (99%) were purchased from Aldrich. Oleic acid (99%) was obtained from Fluka. *cis*-4-Octene (97%) was purchased from Alfa Aesar. 2-Methyl-2-hexene (98%), elaidic acid (98%), and erucic acid methyl ester (90%) were purchased from ABCR. All chemicals were used as received. The reactions were conducted under ambient conditions unless stated otherwise by using demineralized water, pro analysis CH_3CN, and technical-grade ether or CH_2Cl_2. Gas chromatography was carried out using a PerkinElmer Clarus 500 Gas Chromatograph with a Nukol TM fused-silica 15 m × 0.53 mm × 0.5 μm column supplied by Supelco and a Perkin–Elmer Autosystem XL. Compounds **1**–**3** were synthesized according to literature procedures.[30,35] Compound **4** was prepared by using a similar procedure to that for the synthesis of **2** and **3**, starting from the commercially available (*R*,*S*)-bpbp ligand. The synthesis and characterization of compound **5** will be published elsewhere.

Method A: Alkene substrate (0.72 mmol), pentadecane (0.18 mmol; internal standard), and [Fe(OTf)$_2$(mix-bpbp)] (3.6 mmol, [Fe(OTf)$_2${(*R*,*R*)-bpbp}] or [Fe(OTf)$_2${(*S*,*S*)-bpbp}] can also be used) were dissolved in CH_3CN (3 mL) at 0°C. Subsequently, H_2O_2 (1.08 mmol) in CH_3CN (0.75 mL) was added dropwise to the mixture. After 2.5 h, H_2SO_4 in H_2O (0.72 mmol, 1 mL) was added, and the reaction mixture was stirred at RT for 1 h. Next $NaHCO_3$ (0.72 mmol) and $NaIO_4$ were added consecutively, and the solution was stirred for an additional 0.5 h. For analysis, ether (20 mL) was added to the solution to precipitate the remnants of the catalyst after which a sample was subjected to GC analysis. The conversion was determined by the consumption of substrate, and the product yields were compared with authentic samples of aldehydes. Quantification of aldehydes was based on the partition coefficient in the organic solvent, as the products show a very slight solubility in the water phase, and we intended to omit extraction on such small scale. Similar results were obtained when the reaction was performed on a tenfold larger scale and extracted with diethyl ether (3 × 40 mL) prior to analysis with GC.

Method B: Alkene substrate (0.72 mmol), pentadecane (0.18 mmol; internal standard), and [Fe(OTf)$_2$(mix-bpbp)] (3.6 μmol, [Fe(OTf)$_2${(*R*,*R*)-bpbp}] or [Fe(OTf)$_2${(*S*,*S*)-bpbp}] can also be used) were dissolved in CH_3CN (3 mL) at 0°C. Subsequently, H_2O_2 (1.08 mmol) in CH_3CN (0.75 mL) was added dropwise to the mixture. After 2.5 h, H_2SO_4 in H_2O (0.72 mmol, 1 mL) was added and it was reacted at RT for 16 h. Next, $NaHCO_3$ (0.72 mmol) and $NaIO_4$ were added consecutively, and the solution was stirred for an additional 1.5 h. For analysis, diethyl ether (20 mL) was added to precipitate the remnants of the catalyst, after which a sample was subjected to GC analysis. The conversion was determined by the consumption of substrate, and the product yields were compared with authentic samples of aldehydes. Quantification of the aldehydes was based on the partition coefficient in the organic solvent, as the products are slightly soluble in the water phase. In this way, small-scale extractions were omitted. The reaction conducted with methyl oleate on a larger scale (7.2 mmol) was done in a similar fashion. After extraction with diethyl ether (3 × 40 mL), a combined yield of 75% of the mono- and difunctionalized aldehydes was obtained (1.77 g, 5.4 mmol).

Method C: Alkene substrate (0.72 mmol), pentadecane (0.18 mmol; internal standard), and [Fe(OTf)$_2$(mix-bpbp)] (3.6 μmol, [Fe(OTf)$_2${(*R*,*R*)-bpbp}] or [Fe(OTf)$_2${(*S*,*S*)-bpbp}] can also be used) were dissolved in CH_3CN (3 mL) at 0°C. Subsequently, H_2O_2 (1.08 mmol) in CH_3CN (0.75 mL) was added dropwise to the mixture. After 2.5 h, H_2SO_4 in H_2O (0.72 mmol, 1 mL) was added, and it was reacted at RT for 16 h. Next $NaHCO_3$ (0.72 mmol), $NaIO_4$ (0.72 mmol), and H_2O (8 mL) were added consecutively, and the solution was stirred for an additional 1.5 h. The reaction mixture was filtered and extracted three times with diethyl ether (15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and subjected to GC analysis. Product yields were compared with authentic samples of aldehydes. Reactions with α-pinene and cyclohexene were carried out on a larger scale (2.16 mmol), and the isolated yield was determined by extraction with diethyl ether (4 × 40 mL) in a similar procedure by omitting the internal standard. The isolated products were characterized with ^{1}H and ^{13}C NMR spectroscopy. The substrate conversion with the latter alkenes was determined in a separate experiment by GC analysis and by using the same workup procedure with the internal standard present from the start of the reaction.

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