

A metal-free, one-pot method for the oxidative cleavage of internal aliphatic alkenes into carboxylic acids

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Peter Spannring,^a Pieter C. A. Bruijninx,^b Bert. M. Weckhuysen^b and Robertus J. M. Klein Gebbink^{*a}

The oxidative cleavage of terpenes and unsaturated fatty acids into carbonyl compounds is an industrially interesting reaction. We have developed a metal-free protocol that can oxidatively cleave unsaturated fatty acids, terpenes and a variety of other alkenes into carboxylic acids in a synthetically straightforward, one-pot protocol. Near stoichiometric amounts of a combination of oxone and periodate are used in aqueous acetonitrile without additional additives, acids or emulsifiers. The solvent system and the reaction temperature have a profound influence on the reactivity of the substrates; conditions have been optimized for a broad scope of alkenes. The products can be isolated by simple extraction with an organic solvent without additional purification: the carboxylic acids are obtained in high yield (80–96%) as colourless solid or liquid products.

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Introduction

Terpenes and unsaturated fatty acids derived from vegetable oils and animal fats constitute natural resources of olefins. These renewable olefins may function as a feedstock for the production of a number of linear and branched functionalized hydrocarbons, *e.g.* after oxidative cleavage of the double bond(s). A large-scale industrial application involving an unsaturated fatty acid is the oxidative cleavage of the internal double bond of oleic acid by ozonolysis.¹ The products of this oxidative cleavage reaction are mono- or dicarbonyls (Scheme 1), *i.e.* aldehydes or carboxylic acids, which can be used for polymer, plasticizer and stabilizer production.^{1–3} A downside of this particular oxidative cleavage process is the use of the very hazardous oxidant ozone, which needs to be generated *in situ* for safety reasons and can cause explosions.⁴

Metal catalysts have been used for the catalytic oxidative cleavage of internal olefins. Expensive and often toxic transition-metal complexes of Ru,^{5–10} W^{11–17} or Os^{18–25} are known to catalyze the oxidative cleavage. From an economic and environmental perspective, it would be desirable to use catalysts based on cheaper, less toxic and more abundant metals, such as the first-row transition metals. However, catalyst systems based on these metals are only known to

cleave activated olefin substrates, such as styrene derivatives, cyclic olefins and relatively electron-poor alkenes. Typical catalysts for these transformations consist of salen-type^{26,27} and porphyrin-type^{28–30} ligands in combination with metals such as Fe or Mn. Permanganate is also commonly used for these reactions, albeit in stoichiometric amounts.^{31–39} Many different oxidants have been used with first-row transition metal catalysts for oxidative olefin cleavage. These include oxone, periodate and hydrogen peroxide. Yet, none of these metal-oxidant combinations brings about the activity and selectivity that is obtained with second- or third-row metal-oxidants or ozone.⁴⁰

The choice of solvent system has been shown to be another factor of crucial importance in metal-catalyzed olefin cleavage reactions. Oxone (2KHSO₅·KHSO₄·K₂SO₄, 1.5 eq.) has been used in aqueous acetonitrile (3 : 2, v/v) to cleave styrene derivatives and cyclic olefins to aldehydes with catalytic amounts of RuCl₃.⁸ Using trace amounts of OsO₄, oxone is known to cleave olefins in pure DMF, giving high yields of carboxylic acids (above 85%) for a variety of alkenes.²² The well-known Sharpless system uses periodate as the oxidant with RuCl₃ in different solvent mixtures, ranging from CCl₄ : MeCN : H₂O (2 : 2 : 3, v/v)⁵ to EtOAc : MeCN : H₂O

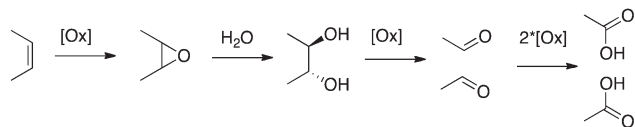
^aOrganic Chemistry & Catalysis, Debye Institute for Nanomaterials Science, Universiteit Utrecht, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands. E-mail: r.j.m.kleingebink@uu.nl; Fax: +31 30 2533120; Tel: +31 30 2523615

^bInorganic Chemistry & Catalysis, Debye Institute for Nanomaterials Science, Universiteit Utrecht, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands.

Fax: +31 30 2534328; Tel: +31 30 2511027



Scheme 1



Scheme 2

(2 : 2 : 3, v/v).^{41,42} Also, 1,2-dichloroethane : water (1 : 1, v/v),⁸ dioxane : H₂O (3 : 1, v/v),²⁵ pure 1,2-dichloroethane,⁴³ EtOAc : H₂O (3 : 5, v/v),⁴⁴ EtOAc : MeCN : H₂O⁴⁵ (1 : 1 : 1, v/v) or THF : H₂O (2 : 1, v/v)⁴⁶ can be applied to this system. It should be noted that neither periodate nor oxone is known to cleave alkenes directly without a catalyst.

Enzymes can also be used for oxidative cleavage reactions,⁴⁷ as can photochemolysis⁴⁸ and anodic oxidation,⁴⁹ yet the examples are scarce and have only a narrow substrate scope.

One could consider the oxidative cleavage of olefins to carboxylic acids to be the result of sequential oxidation steps, involving epoxide, diol and aldehyde intermediates (Scheme 2). Adaptation of systems known to catalyze epoxidation or dihydroxylation of internal olefins can therefore be of interest for the development of new catalytic systems for selective oxidative C=C bond scission.

Oxone is an attractive oxidant for alkene oxidation, as it is cheap and readily accessible. Epoxidations with oxone have been reported in water at neutral pH and without organic solvent, but the activity for electron-rich aliphatic olefins proved negligible under these conditions.⁵⁰ Other common solvents for epoxidations with oxone are aqueous MeCN or hexafluoroisopropanol. Ketones are commonly added in such olefin oxidations with oxone,^{51,52} to yield dioxirane intermediates, which are the active species in the epoxidation.^{53,54} Indeed, the epoxidation activity is very low without the ketone additive.⁵⁰ Oxone has also been reported to mediate the formation of *cis*-diols from alkenes with an Fe catalyst.⁵⁵ The use of tetraaza macrocyclic ligands in a MeCN : H₂O (1 : 1, v/v) mixture enables the *cis*-diol formation for a variety of electron-deficient alkenes, such as styrene derivatives. The activity and selectivity for electron-rich internal alkenes proved to be poor, however. Alternatively, alkenes can be transformed into diols with cyclobutane malonyl peroxide.⁵⁶ This system omits the use of an expensive or toxic transition metal. However, it needs the active oxidative species to be made *in situ* with an excess of hydrogen peroxide in the presence of an acid additive, and is primarily active for styrene derivatives. Eventually, the diol intermediates, which can be obtained by hydrolysis of the epoxide or directly formed by *cis*-dihydroxylation, can be cleaved by periodate to give the corresponding aldehydes.⁵⁷

Importantly, the nature of the olefin has a profound influence on the efficiency of a cleavage reaction and on the product outcome. Of the aliphatic alkenes, which are relatively electron-rich, the terminal alkenes are often more easily converted because of their lower steric demand and their higher electron deficiency compared to their internal counterparts.^{30,58} For styrene derivatives, a similar general trend can

be observed, *i.e.* more electron-deficient substrates give higher yields of the cleavage product with many metal-catalyzed procedures.^{59,60} On the other hand, some catalytic systems have been reported not to display a distinct difference between electron-rich and electron-poor styrene substrates.^{30,58}

In the course of an investigation aimed at the development of an oxidation catalyst based on first-row transition metals capable of oxidative olefin cleavage in renewable substrates, such as unsaturated fatty acids and terpenes, we have observed significant amounts of cleavage products in reactions with a combination of sacrificial oxidants only, *i.e.* without any metal complex. We have followed up on this observation and present a practical metal-free, one-pot method for the oxidative cleavage of olefins. Here, we provide details on the overall optimization and substrate scope of this approach and show that the combination of oxone and periodate in a MeCN : H₂O reaction mixture shows a preference for the cleavage of electron-rich internal olefins.

Results and discussion

Oxidative cleavage of *cis*-4-octene

In our initial reactivity tests *cis*-4-octene was selected as substrate to mimic the electron-rich internal double bond in unsaturated fatty acids. *cis*-4-Octene is a convenient model substrate as it is generally more soluble in organic media, does not contain a functional group that may interfere with reactivity, and leads to a single product upon cleavage as a result of its symmetric structure.

The reaction between *cis*-4-octene and a combination of oxone (2 eq., containing 4 oxidizing eq. of peroxomonosulfate) and sodium periodate (4 eq.) at ambient temperature shows no reaction in MeCN after 16 h (Table 1, entry 1) and only moderate activity in H₂O (entry 2). The introduction of an organic solvent in addition to H₂O shows the influence of solvent composition on activity and selectivity: hardly any activity is observed in DMF : H₂O (3 : 1, v/v) (entry 3), whereas

Table 1 Solvent optimization for the conversion of *cis*-4-octene to butyric acid^a

| Entry | Solvent (v/v) | Time (h) | Conversion (%) | Yield (%) ^b |
|----------------|-------------------------------|----------|----------------|------------------------|
| 1 ^c | MeCN | 16 | 0 | 0 |
| 2 ^c | H ₂ O | 26 | 30 | 10 |
| 3 | DMF : H ₂ O 3 : 1 | 16 | 6 | 2 |
| 4 | DMF : H ₂ O 1 : 3 | 16 | 67 | 35 |
| 5 | MeCN : H ₂ O 1 : 1 | 16 | 69 | 35 |
| 6 | MeCN : H ₂ O 1 : 3 | 16 | 74 | 51 |
| 7 | MeCN : H ₂ O 1 : 3 | 26 | 86 | 61 |
| 8 | MeCN : H ₂ O 1 : 3 | 72 | 100 | 95 |

^a Reaction conditions: 2 eq. oxone, 4 eq. periodate, 0.135 M *cis*-4-octene in 4 mL solvent, 16 h reaction time, ambient temperature.

^b Yield determined by GC analysis.

DMF : H₂O (1 : 3, v/v) shows a 67% substrate conversion and 35% butyric acid yield. When MeCN was used instead of DMF, similar results were obtained: in MeCN : H₂O (1 : 1, v/v) 69% conversion and 35% yield were observed (entry 5). Highest substrate conversions and butyric acid yields were obtained after 16 h using a MeCN : H₂O (1 : 3, v/v) mixture as the reaction medium (entry 6). Under these conditions, an increase in conversion to 86% and a yield in butyric acid of 61% can be achieved after 26 h (entry 7). Notably, product analysis by means of gas chromatography of all entries showed no or hardly any other products than butyric acid. When the reaction was run for 72 h with MeCN : H₂O (1 : 3, v/v), full conversion was obtained with a 95% butyric acid yield (entry 8). The reaction can also be scaled up tenfold (14.4 mmol), enabling the isolation of 84% cleavage product (see Experimental section). Based on this solvent screening, reactions were subsequently run in MeCN : H₂O (1 : 3, v/v) (method A). The incomplete mass balance at intermediate reaction times shows that reaction intermediates, such as, *e.g.*, iodate esters, must be present and are not detected by GC.

Next, the effect of the oxidant loading, the pH of the reaction medium, and the reaction temperature were investigated. It was anticipated that the initial oxidant loading of 2 eq. oxone and 4 eq. of periodate could be lowered without significant loss of reactivity, since 4 oxidizing equivalents should be sufficient for the full conversion of a double bond into carboxylic acids.

A decrease in periodate loading from 4 eq. to 2 eq. had almost no effect on the conversion (72% after 16 h; Table 2, entries 1,2), with the amount of butyric acid formed being almost the same (51–55%). Further decrease to 1 eq. of periodate gave similar results, with 79% conversion and 52% product yield (entry 3). Since the cleavage of diols towards aldehydes can be achieved with 1 eq. of periodate, over-oxidation to carboxylic acids seems to be carried out by oxone.

On the other hand, lowering the amount of oxone from 2 to 1 eq. does lead to a decrease of the conversion to 51% and of

the yield of butyric acid to 29%, but does not lead to the formation of butyraldehyde (entry 4). This shows that over-oxidation proceeds readily. Further decrease of the amount of oxone to 0.5 eq. gave a significant further decrease of these values (entry 5). The amount of periodate can therefore be decreased to 1 eq. without any loss in conversion or selectivity at ambient temperature for the oxidative cleavage of *cis*-4-octene, whereas 2 eq. of oxone are required to achieve high yields.

The pH of 1.4 that was recorded at the start of the reaction was not significantly changed at the end of the reaction. Increasing the pH to 6.0 by addition of NaHCO₃ (6 eq., entry 6), led to a drop in conversion from 74% to 52%. Further increase of the pH led to even lower conversions (entries 7,8), therefore the addition of NaHCO₃ was omitted in further experiments.

Next, the reaction was performed at 0 °C, which led to a drop in the conversion from 74% to 33%, yet the selectivity to butyric acid was quantitative (entry 9). The latter shows that most likely the rate-determining step is the substrate epoxidation at this temperature, unlike reactions performed at higher temperatures. At 60 °C the substrate was fully converted and the yield in butyric acid was 82% (entry 10).

Besides oxone, we also investigated *m*-chloroperbenzoic acid (*m*-CPBA) as a stoichiometric epoxidation agent. The use of *m*-CPBA enables the protocol to work under milder pH and the substrate is converted more rapidly. Additionally, small amounts of aldehyde are formed in this protocol, which are not observed with oxone. Yet, more oxidant is needed in order to arrive at reasonable amounts of cleavage product. Moreover, the epoxide remains as a byproduct in the reactions with *m*-CPBA.

The combination of periodate and oxone was therefore preferred for further studies exploring the substrate scope of the system optimized for *cis*-4-octene, *i.e.* with MeCN : H₂O (1 : 3, v/v) as solvent and an oxidant loading of oxone : NaIO₄ 2 : 1.5 eq. (method A). A slight excess of the NaIO₄ is used in the substrate scope reactions to maximize yields. Aliphatic olefins are good mimics of unsaturated fatty acids and therefore interesting to investigate in a substrate scope of our system. Styrenes and stilbenes are more electron-poor alkenes than aliphatic ones, yet are often used for oxidative cleavage to benzoic acid and have been included to compare our system with existing ones. Furthermore, the cleavages of the naturally occurring terpenes limonene (also being a diene) and pinene are investigated. Finally, we have investigated whether we could apply our protocol on the oxidative cleavage of unsaturated fatty acids.

Oxidative cleavage of aliphatic alkenes


















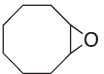
The terminal aliphatic olefin 1-decene hardly reacts under the standard conditions of method A nor at more elevated temperatures (91% substrate recovery, Table 3, entries 1,2). Therefore, a second method (method B) was developed that involves using a solvent composition of MeCN : H₂O (3 : 1, v/v) and heating to reflux first, in order to ensure dissolution of substrates not soluble under the conditions used in method A. After 16 h of reaction, the reaction mixture is then diluted with water to give again a MeCN : H₂O (1 : 3, v/v) mixture and is subsequently refluxed for 2 more hours, this is to ensure

Table 2 Optimization of the oxidant loading for the conversion of *cis*-4-octene into butyric acid^a

| Entry | Oxone : NaIO ₄ (eq.) | pH | T | Conversion (%) | Yield (%) ^b |
|----------------|---------------------------------|-----|-------|----------------|------------------------|
| 1 | 2 : 4 | 1.4 | RT | 74 | 51 |
| 2 | 2 : 2 | 1.4 | RT | 72 | 55 |
| 3 | 2 : 1 | 1.4 | RT | 79 | 52 |
| 4 | 1 : 4 | 1.9 | RT | 51 | 29 |
| 5 | 0.5 : 4 | 2.0 | RT | 29 | 16 |
| 6 ^c | 2 : 4 | 6.0 | RT | 52 | 34 |
| 7 ^d | 2 : 4 | 7.3 | RT | 51 | 0 |
| 8 ^e | 2 : 4 | 7.4 | RT | 39 | 0 |
| 9 | 2 : 4 | 1.4 | 0 °C | 33 | 33 |
| 10 | 2 : 4 | 1.4 | 50 °C | 100 | 82 |

^a Reaction conditions: 1–4 eq. of oxidant, 0.135 M *cis*-4-octene in MeCN : H₂O (1 : 3, v/v), ambient temperature, 16 h, measured pH of 1.4. ^b Yield determined by GC analysis. ^c 6 eq. NaHCO₃ added. ^d 12 eq. NaHCO₃ added. ^e 18 eq. NaHCO₃ added.

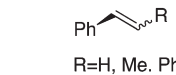








Table 3 Oxidative cleavage of aliphatic alkenes^a

| Entry | Substrate | Product | Time (h) | Method | Conv. (%) | Yield (%) ^b |
|-------|---|---|----------|----------------|-----------|------------------------|
| 1 |  | — | 16 | A | 0 | 0 ^c |
| 2 |  | — | 16 | A ^d | 0 | 0 |
| 3 |  |  | 18 | B | 47 | 42 |
| 4 |  |  | 18 | B | 100 | 88 |
| 5 |  |  | 120 | A | 100 | > 99 |
| 6 |  |  | 18 | B | 55 | 54 |
| 7 |  |  | 72 | A | 100 | 98 |
| 8 |  |  | 18 | B | 100 | 99 |
| 9 |  |  | 16 | A | 100 | 74 ^e |
| 10 |  |  | 16 | A | > 99 | 95 ^e |

^a Reaction conditions: Method A: 2 eq. oxone, 1.5 eq. periodate, 0.135 M olefin in MeCN : H₂O (1 : 3, v/v, 8 mL), ambient temperature, Method B: 0.135 M MeCN : H₂O (3 : 1, v/v, 8 mL), 16 h; then 2 h 0.07 M MeCN : H₂O (1 : 3, v/v, 16 mL). ^b Yield determined by GC. ^c 91% substrate retained by ether extraction. ^d Reflux. ^e Isolated yield.

complete dissolution and reaction of the periodate. With this method B, 47% substrate conversion of 1-decene can be achieved, yielding 42% nonanoic acid (entry 3). Method B was also applied to *cis*-4-octene, giving full substrate conversion and a high butyric acid yield after 18 h instead of the 3 days needed with method A (entry 4). *trans*-4-Octene, which showed a lower activity with method A than *cis*-4-octene (quantitative formation of butyric acid was only obtained after 5 days; entry 5), is also less reactive when method B is applied. Nonetheless, 55% conversion was observed after 18 h, with a 54% butyric acid yield (entry 6). On the other hand, with the more electron-rich trisubstituted alkene 2-methyl-2-hexene, the activity is relatively high: the substrate can be completely converted with method A in 3 days (entry 7) and with method B in 18 h (entry 8). Cyclohexene can be completely converted with method A after 16 h, isolating adipic acid in 74% yield as a white precipitate after extraction of the reaction mixture with ether (entry 9). The oxidation of *cis*-cyclooctene, on the other hand, stops at the cyclooctene oxide stage (95% yield; entry 10). When cyclooctene oxide itself was used as substrate under the same conditions, no reaction indeed occurred at room temperature, while at 60 °C the oxide completely converted overnight into a number of different products. A similar non-

Table 4 Oxidative cleavage of styrenes and stilbenes into benzoic acid and acetophenone^a

| Entry | Substrate | Time (h) | Method | Conv. (%) | Acid yield (%) ^b | Ketone yield (%) ^c |
|----------------|--|----------|----------------|-----------|-----------------------------|-------------------------------|
| 1 |  | 16 | A | 67 | 67 | — |
| 2 |  | 16 | A | 83 | 83 | — |
| 3 ^d |  | 16 | A | 4 | 4 | — |
| 4 ^d |  | 6 | A ^e | 61 | 61 | — |
| 5 ^d |  | 16 | A ^e | 100 | 95 | — |
| 6 |  | 16 | A | 5 | 5 | — |
| 7 |  | 16 | A ^e | 100 | 95 | — |
| 8 ^f |  | 120 | A | 10 | — | 9 |
| 9 |  | 18 | B | 100 | — | 99 |

^a For reaction conditions (methods A and B), see Table 3. ^b Yields determined by NMR. ^c GC yield. ^d In the dark. ^e Reflux. ^f 1.5 eq. periodate used.

selective conversion of substrate was also observed with 1-5-cyclooctadiene.

Oxidative cleavage of styrenes and stilbene

Styrene and *trans*- β -methyl-styrene (TBMS) give benzoic acid selectively at significantly higher conversions with method A after 16 h compared to *cis*-4-octene (Table 4, entries 1–2). After 2 days of reaction, moderate isolated yields of benzoic acid can be obtained from styrene (53%) and TBMS (59%) by simple extraction with ether. *cis*-Stilbene and *trans*-stilbene, on the other hand, show hardly any reactivity with method A (entry 3, 6). Conversion of these stilbenes can still be achieved though, simply by heating to reflux under the conditions of method A, without the need to resort to method B. *cis*-Stilbene is converted for 61% into benzoic acid within 6 h (entry 6), while *cis*- and *trans*-stilbenes are converted quantitatively to benzoic acid after 16 h (entries 5, 7). Trace amounts of aldehydes and ketones were observed in these reactions. α -Methyl styrene also shows poor reactivity with method A, even after 5 days of reaction (entry 8), yet can be converted completely to acetophenone after 16 h with method B (entry 9). Reactions performed with method A with 4-methyl styrene showed a variety of reaction products, including ones in which the methyl group is oxidized. 4-Methoxy styrene also showed a non-selective conversion, with the side reactions being attributed to the formation of radical intermediates.

Oxidative cleavage of terpenes

The terpene limonene contains two different types of double bonds. No regioselectivity was observed, however, in reactions with this substrate even at low oxidant loadings. The conditions chosen for this substrate, *i.e.* amount of oxidant used, were therefore intended to cleave both double bonds. This resulted in the formation of γ -acetyl-adipic acid rather than the anticipated acid-diketone. Complete conversion is obtained after 72 h and up to 76% γ -acetyl-adipic acid can be isolated (Table 5, entry 1). The over-oxidation of one of the initially formed ketones while the other one remains untouched is remarkable.

Additionally, the terpene α -pinene can be completely converted to give the diacid pinic acid in 68% yield after 108 h. Also in this case, the intermediate acid-ketone cleavage product was only observed at shorter reaction times. The formation of pinic acid is common for pinene derivatives such as pinocarveol.⁶¹ Pinocarveol is the product from allylic oxidation of β -pinene, therefore isomerization of α -pinene and allylic oxidation are possible pathways in our transformation. Method B is not suitable for the terpenes as at elevated temperatures non-selective conversion of the substrates into a variety of products is observed. These side reactions are the result of intramolecular rearrangements, tautomerizations and/or allylic oxidations that generally happen with these substrates.

Oxidative cleavage of unsaturated fatty acids

The oxidation of methyl oleate (Table 6, entries 1–3), oleic acid (entry 4), erucic acid methyl ester (entry 5), and elaidic acid (*trans*-isomer of oleic acid, entry 6) were investigated with the two methods. These substrates all give nonanoic acid upon cleavage. With method A, no reaction occurs at all with methyl oleate either at ambient temperature or at reflux (entry 1). In MeCN : H₂O (3 : 1, v/v) and at reflux methyl oleate is converted to the epoxide and diol products, but no cleavage products are observed. On the contrary, methyl oleate can be converted to nonanoic acid using method B, with 83% conversion and 70% yield obtained after 6 h. After 18 h, nonanoic acid formation is almost quantitative (entry 3). Methyl azelate was also observed by ¹H NMR in equal yields to nonanoic acid after extracting the mixture with ethyl acetate in a separate experiment. For practical reasons, only the yield of nonanoic acid is presented

Table 5 Oxidative cleavage of limonene and α -pinene^a

| Entry | Substrate | Time (h) | Product | Conv. (%) | Yield (%) ^b |
|-------|-----------|----------|---------|-----------|------------------------|
| 1 | | 72 | | 100 | 76 |
| 2 | | 108 | | 100 | 68 |

^a Reaction conditions: Method A. ^b Isolated yield.

Table 6 Oxidative cleavage of unsaturated fatty acids^a

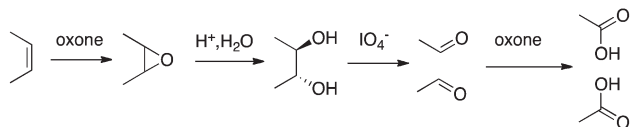
| Entry | <i>n</i> | R | Time (h) | Method | Conversion (%) | Yield (%) ^b |
|----------------|----------|----|----------|--------|----------------|------------------------|
| 1 | 6 | Me | 16 | A | 0 | 0 |
| 2 | 6 | Me | 6 | B | 83 | 70 |
| 3 | 6 | Me | 18 | B | 96 | 95 |
| 4 | 6 | H | 6 | B | 100 | 99 |
| 5 | 10 | Me | 18 | B | 65 | 52 |
| 6 ^c | 6 | H | 18 | B | 100 | 99 |

^a Reaction conditions: Method A, Method B. ^b Yield of the nonanoic acid determined by GC. ^c Elaidic acid used, containing a *trans*-double bond.

in Table 6, while the amount of the different difunctionalized products is assumed to be equal to this value for all substrates. The reaction with methyl oleate can be scaled up tenfold to give 75% isolated yield of the combined mono- and difunctionalized product (see Experimental section). Oleic acid was found to be more reactive under the applied conditions: full and selective conversion of the substrate to form the monoacid is achieved after 6 h (entry 4). The reactivity of erucic acid methyl ester is lower compared to methyl oleate, as only 52% of nonanoic acid is obtained at 65% conversion after 18 h (entry 5). The *trans*-alkene elaidic acid can be readily converted to quantitatively give nonanoic acid after 18 h (entry 6).

Conclusions

We have developed a synthetically straightforward, one-pot protocol for the formation of carboxylic acids from alkenes. The protocol does not require expensive or toxic transition metal reagents or catalysts. The carboxylic acid products can be isolated by simple solvent extraction and are obtained in high yield as colourless powders or oils that do not need further purification. All reagents can be added at the start and isolation of intermediate products is not required, which makes the procedure easy to carry out and broadly applicable. The protocol can be applied on a variety of alkenes. Aliphatic alkenes, including *cis*-, *trans*-, cyclic and trisubstituted double alkenes, can be cleaved in high yields. Additionally, styrenes and stilbenes can be transformed into benzoic acid. Moreover, industrially interesting unsaturated fatty acids can be oxidatively cleaved into mono- and diacids and a series of terpenes can be transformed into diacids. The nature of the substrate determines which of the two optimized methods is most suited. Method A is performed at ambient conditions for 72 h using a MeCN : H₂O (1 : 3, v/v) solvent mixture, while method B involves heating a MeCN : H₂O (3 : 1, v/v) solvent mixture to reflux temperature at the start, followed by dilution to



Scheme 3

MeCN : H₂O (3 : 9, v/v) after 16 h, and allowing the reaction to proceed for another 2 h.

The oxidative cleavage of alkenes by means of this protocol is believed to follow a number of sequential reaction steps (Scheme 3). First, oxone epoxidizes the alkene and the acidic nature of the oxidant in combination with water induces the hydrolysis of the resulting epoxide to give the diol. Subsequently, sodium periodate oxidatively cleaves the diol to the aldehydes,⁵⁷ which are finally further oxidized to the acids by oxone. The conversion of cyclic alkenes might involve anhydride intermediates, as postulated before in the case of cyclohexene.⁶² The over-oxidation of the aldehyde is more rapid than the epoxidation of the alkene and, accordingly, aldehydes cannot be isolated with this system. A protocol that uses *m*-CPBA rather than oxone does result in the formation of aldehydes, but large amounts of epoxide remain with this oxidant combination.

Compared to other conventional methods of oxidatively cleaving alkenes to carboxylic acids, our protocol shows a higher activity for more electron-rich double bonds. This is in contrast with the many systems using transition metal catalysts for the cleavage electron-poor alkenes.⁵⁵ The affinity of oxone to electron-rich double bonds is crucial in this case. Unlike protocols involving permanganate^{31–39} and Ru or Os,^{8,41,42} the products are colourless and need no column chromatography for additional purification. Moreover, our protocol can be applied to a broad scope of alkenes, which is not the case in other metal-free alkene oxidation systems.^{50–52,56}

We believe our protocol may find use in the utilization of vegetable oils in industrial manufacturing and recommend it as an easy tool for synthesizing carboxylic acids out of electron-rich alkenes on a research scale. Current efforts in our lab aim at further optimizing one or more reaction steps in the protocol, *e.g.* through the use of other oxidants, and at obtaining aldehydes from internal aliphatic alkenes.

Experimental section

General

Oxone (99%), sodium periodate (99%), (1*R*)-(+)- α -pinene (98%), cyclohexene (99%), *trans*- β -methyl styrene (97%), cyclooctene (95%), *trans*-stilbene (99%) 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. (*S*)-(–)-Limonene (99%)

and oleic acid (99%) were obtained from Fluka. *cis*-4-Octene (97%) was purchased from Alfa Aesar. 4-Methylstyrene (98%), 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, using distilled water, pro analysis DMF and MeCN, and technical grade ether, DCM or ethyl acetate. ¹H NMR and ¹³C NMR measurements were recorded at 298 K using a Varian 400 MHz NMR Spectrometer, using residual solvents peaks as reference. Gas chromatography was carried out on a PerkinElmer Clarus 500 Gas Chromatograph with a Nukol TM fused silica, 15 m \times 0.53 mm \times 0.5 μ m column supplied by Supelco and a PerkinElmer Autosystem XL. ESI-MS spectra were recorded using a Waters LCT Premier KE317 MT spectrometer using DCM as the solvent.

Method A

Alkene substrate (1.44 mmol), pentadecane (0.36 mmol; internal standard), oxone (2.88 mmol), and sodium periodate (2.16 mmol) were added to a mixture of MeCN (2 mL) and H₂O (6 mL) and vigorously stirred at ambient temperature for the duration of the experiment. Subsequently, the mixture was filtered and extracted with ether (3 \times 20 mL). The combined organic fractions were dried over MgSO₄ and filtered. The amount of carboxylic acid was determined with the Nukol column, the conversion (consumption of substrate) and formation of byproducts were determined with a polyethylene column. Reactions with the terpenes, cycloalkenes, styrene and stilbenes were done on a 14.4 mmol scale, and the isolated yield was determined after threefold extraction of the aqueous phase with ethyl acetate (terpenes) or ether (cycloalkenes, styrenes and stilbenes) and analyzed with ¹H and ¹³C NMR. The substrate conversion was determined in a separate experiment by GC analysis on a polyethylene column, using the same work-up procedure with internal standard present at start. Reactions using α -methyl styrene were subjected to GC analysis using a polyethylene column for determination of the formation of the ketone and the substrate conversion.

The conversion of *cis*-4-octene into butyric acid was performed at a preparative scale (1.62 g, 14.4 mmol alkene) without internal standard. After extraction of the reaction mixture with ethyl acetate (4 \times 50 mL), the isolated yield of butyric was determined with ¹H and ¹³C NMR confirmation (2.13 g, 24.2 mmol, 84%). In a similar way, the reaction of cyclohexene to form adipic acid was run on the same scale and provided 1.56 g (74%) isolated yield. Likewise, *trans*- β -methyl styrene (1.70 g, 14.4 mmol) afforded 82% benzoic acid (1.76 g, 11.81 mmol).

Method B

Alkene substrate (1.44 mmol), pentadecane (0.36 mmol; internal standard), oxone (2.88 mmol), and sodium periodate (2.16 mmol) were added to a mixture of MeCN (6 mL) and H₂O (2 mL) and refluxed until all of the alkene has been converted (2–26 h, depending on the substrate). Subsequently, 16 mL of H₂O was added and the reaction mixture was further refluxed for 2 h. After filtration, 10 mL of water was added and the aqueous phase was extracted with ether (3 \times 20 mL), the combined organic fractions dried with MgSO₄, filtered and

subjected to GC analysis. For unsaturated fatty acids and 1-decene, the aqueous phase was extracted with ethyl acetate (4×20 mL). The amount of aliphatic monoacid acid was determined with the Nukol column; the conversion (consumption of substrate) and formation of byproducts were determined with a polyethylene column. α -methyl styrene products were measured directly on the polyethylene column for determination of the formation of the ketone and substrate conversion. The conversion of methyl oleate into nonanoic acid and methyl azelate was performed at tenfold higher scale (4.27 g, 14.4 mmol alkene) without internal standard. Extraction of the reaction mixture with ethyl acetate (4×50 mL) gave a 1 : 1 mixture of nonanoic acid and methyl azelate in 75% isolated yield (3.89 g, 10.8 mmol), as determined by ^1H and ^{13}C NMR.

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