Straightforward radical organic chemistry in neat conditions and "on water"†‡

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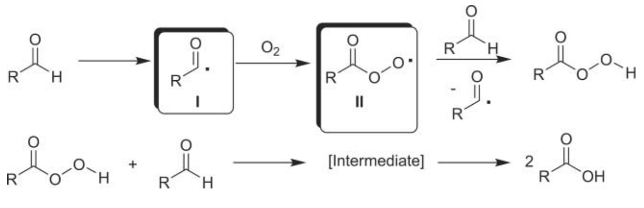
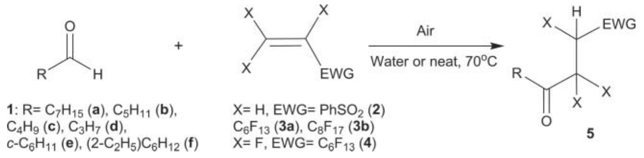
Radicals generated during aldehyde oxidation to carboxylic acids can be efficiently trapped under environmentally friendly conditions, either in neat conditions or "on water".

Organic solvents represent the biggest pollution problem of many synthetic organic processes[1] and the development of efficient synthetic methodologies for organic reactions, in the absence of organic solvents, is an important challenge toward reducing the amount of waste.[2] An ideal organic reaction would proceed in neat substrate(s)[3] or an environmentally benign solvent, such as water.[4,5] The major problem of a wider use of water instead of organic solvents is the very low solubility of most organic compounds in aqueous media. Use of additives, such as surfactants, helps to increase the solubility of organic compounds,[6] however, the reaction protocols become more complicated. It has been noted many years ago that certain organic reactions are greatly accelerated when performed in an aqueous suspension rather than solution.[7] These "on water" reactions have received a great deal of attention in recent years, yet their scope is still limited.[8,9] In particular, organic synthesis involving free radicals under the "on water" conditions remains largely unexplored.[10] Interestingly, it was often found that many organic reactions that proceed well "on water" also work well under solvent-free conditions, neat reactions being next in line or on par with reactions in aqueous suspensions.[8a] Herein we report several selective and efficient radical organic reactions that take place in neat reactants and "on water".

We recently showed that simple hydrophobic aldehydes undergo rapid oxidation reactions when stirred with water in air.[11] The reactions also take place without water, albeit large amounts of by-products were observed under water-free conditions. Generally, the uncatalyzed aldehyde oxidation reaction proceeds *via* a radical mechanism with the acyl radical **I** formed in the first step followed by the formation of the peroxo radical **II** (Scheme 1).[12] The facile formation of these radicals under the reported conditions prompted us to investigate their applications in organic synthesis. The first reaction tested was alkene hydroacylation, which had already been reported back in 1949.[13] It is established that aldehydes can react with terminal alkenes in the presence of a radical initiator to give products of the anti-Markovnikov hydroacylation.[14] The reaction was significantly improved with the introduction of polarity-reversal catalysts, such as N-hydroxyphthalemide (NHPI) or thiols.[15,16] However, there are still several limitations for this reaction, such as the necessity to use primary aldehydes to prevent undesired radical side reactions. Also, in nearly all cases, organic solvents and radical initiators have been used to facilitate the radical addition.[17] We reasoned that the radical hydroacylation might proceed well when the reactants are stirred in air with water. To verify this, we treated a series of hydrophobic aldehydes **1** with phenyl vinyl sulfone **2** under the "on water" conditions. Heating aldehydes **1a-c** (six-fold excess) with **2** at 70 °C resulted in the formation of the corresponding ketones **5** in very high yields (Scheme 2, Table 1). The regioselectivity of the anti-Markovnikov addition supports the radical mechanism proposed earlier,[12,13] although the detailed mechanistic studies are still underway. The remaining aldehyde was cleanly converted to the corresponding carboxylic acid. Importantly, the reaction also worked well with α-branched aldehydes (**1e**,**f**) which usually give mixtures of products when reacted in organic media. The hydrophobicity of the aldehydes was essential to achieve a high alkene conversion, as smaller, less hydrophobic aldehyde **1d**, gave the hydroacylation product in a low yield. The reactions could easily be scaled up to obtain hundreds of milligrams of the desired product. Thus, the "on water" hydroacylation reaction provides a simple access to various γ-ketosulfones **5**, most of which are unreported in the literature.[18] Furthermore, considering that RSO_2 is a good leaving group, compounds **5**



Scheme 1



Scheme 2

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† Electronic supplementary information (ESI) available: Detailed description of the experimental procedures and X-ray data for heptyl 2-(perfluorohexyl)ethyl ketone. CCDC reference number 734004. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b922475k

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Table 1 Aldehyde addition to alkenes[a]

Aldehyde	Alkene	Yield of **5**, % [b]	Aldehyde	Alkene	Yield of **5** (%)
1a	**2**	100 [c](100)	**1b**	**3a**	70 [d](82)
1b	**2**	97 [c](91)	**1e**	**3a**	69[d]
1c	**2**	90 [c](69)	**1a**	**3b**	77[d]
1d	**2**	5 [d](91)	**1b**	**3b**	79[d]
1e	**2**	77 [d](99)	**1e**	**3b**	37 [d](69)
1f	**2**	50 [d](69)	**1a**	**4**	59[d]
1a	**3a**	71[d]	**1b**	**4**	37 [d](82)

[a] General procedure: aldehyde (1.07 mmol) and **2** (0.178 mmol, 6 : 1 ratio) were stirred with 3 ml of water at 70 °C in a 50 cc glass reactor in air. For alkenes **3-4**, the amounts of the aldehyde and alkene were 2.4 and 0.4 mmol, respectively. [b] In parentheses, yields in the solvent-free reactions. [c] After 3 h. [d] After 16 h.

Table 2 Aldehyde–alkenes co-oxidation "on water"[a]

Alkene	Aldehyde/ alkene ratio	Conversion to **9**
1-Octene (**8a**)	4 : 1	62
Styrene (**8b**)	6 : 1	90
Cyclohexene (**8c**)	6 : 1	88
Cyclooctene (**8d**)[b]	6 : 1	87 (mixture of *cis*- and *trans*-isomers)
1-Decene (**8e**)[b]	6 : 1	91
Propene (**8f**)	5 : 1	36 (isolated yield)

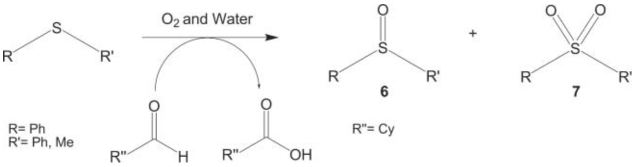
[a] General procedure: aldehyde (11.5 mmol) and alkene (8.9 mmol) were stirred with 100 ml of water (pH 1) at 60 °C under an oxygen atmosphere for 1 h. The remaining aldehyde was slowly added within the course of 4 h and the mixture stirred for 16 h under a slow flow of O_2. [b] After 48 h. See ESI for more detail.

can be used for the preparation of α,β-unsaturated ketones,[19] important building blocks in synthetic organic chemistry.

To further verify the importance of "on water" rather than "in water" conditions, we studied the "ultimate" hydrophobic substrates, polyfluoroalkenes, in the hydroacylation reaction. The reaction between the 1*H*,1*H*,2*H*-perfluoro-1-octene **3a** and a series of organic aldehydes under the "on water" conditions gave the corresponding semi-fluorinated ketones **7** in high yields (Scheme 2, Table 2). Such ketones can serve as new precursors to semi-fluorinated alkanes, which are valuable compounds with a number of applications in medicine.[20] Similar reactivity was also observed for 1*H*,1*H*,2*H*-perfluoro-1-decene **3b**, as well as perfluorooctene **5**.

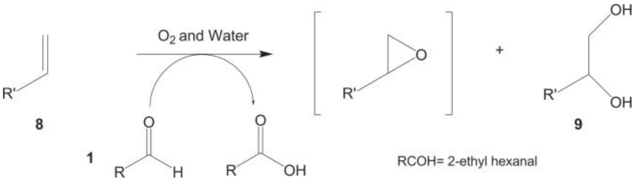
Importantly, in most cases, the reactions performed "on water" proceeded similarly well or even better in the absence of any solvent. Furthermore, excellent yields of the hydroacylation product were obtained with the water-soluble **1d** (Table 1). On the downside, performing the reactions in neat conditions often gave decarbonylation products reducing the yields of the carboxylic acids.

Having established that radical **I** (Scheme 1) can be utilized in synthesis under the organic solvent free conditions, we explored the possibility of also utilizing the radical **II**, which was proposed as a reactive intermediate in the non-catalyzed co-oxidation of aldehydes with various organic substrates.[21] Preliminary results showed that the simple stirring of aldehydes with organic sulfides under an oxygen atmosphere resulted in the complete conversion of both substrates after several hours. While the aldehydes were cleanly oxidized to the corresponding carboxylic acids, the sulfides gave mixtures of sulfoxides and sulfones (Scheme 3).[22] For example, stirring Ph_2S with 3 equiv. of **1e** for 4 h gave a 77%:23% mixture of the sulfoxide (**6**) and sulfone (**7**) in 100% overall yield (per sulfide). The same reaction gave a 55%:45% ratio of the products after 4 h but with 5 equiv. of **1e**. Shorter reaction times resulted in a higher **6**:**7** ratio; reaction between Ph_2S and 5 equiv. of **1e** gave 89% of **6** and only 3% of **7** after 1 h. Thioanisol reacted similarly to diphenyl sulfide giving **7** as the major product as rapidly as within 4 h, while dialkyl sulfides reacted somewhat sluggishly under the same conditions. The aldehyde–sulfide co-oxidation reactions "on water" gave lower yields of the products.



Scheme 3

Alkenes represent perhaps the most important substrates for a radical co-oxidation with aldehydes under the "on water" conditions. While such co-oxidation in organic solvents or *neat* aldehyde is well known,[21,23] the resulting products, carboxylic acid and epoxide, are difficult to separate making the whole process unattractive for practical applications. As most of the epoxides prepared on the industrial scale serve as intermediates in the conversion of alkenes to the corresponding 1,2-diols,[24] it would be important to develop a convenient route to such diols directly from alkenes. We hypothesized that performing the co-oxidation, industrially-relevant alkenes and aldehydes "on water" under acidic conditions would result in the direct conversion of alkenes to 1,2-diols with the simultaneous production of carboxylic acids in a 2-in-1 process.[25] A particularly attractive process would result in a hydrophobic acid and hydrophilic diol, which would remain in the aqueous phase. As a starting point, we studied the co-oxidation of various liquid alkenes with 2-ethylhexanal **1f**, which is used industrially as a precursor to 2-ethylhexanoic acid. We found that at pH 1, most of the alkene is converted to the corresponding 1,2-diol at one atmosphere of dioxygen (Scheme 4, Table 2), while the aldehyde is oxidized to the carboxylic acid with over 90% selectivity in all cases. Small amounts of byproducts originating from the aldehyde were also obtained, while the alkenes were converted exclusively to 1,2-diols. Although excess of the aldehyde is required to obtain diols in high yields, this excess is converted to 2-ethylhexanoic acid which is a valuable chemical product. Importantly, in all reported reactions, the aqueous phase could be re-used in the same synthesis without purification, which is essential for designing truly "green" synthetic protocols.[26] Addition of



Scheme 4

various transition metal ions (Cu^{2+}, Fe^{3+}, Co^{3+}) to the reaction mixture resulted in a significant decrease in activity.

Encouraged by these results, we next targeted propene—a gaseous alkene which, upon oxidation, gives water-soluble diol. Interestingly, using propene in combination with 2-ethylhexanal resulted in the clean oxidation of both substrates to 1,2-propanediol and 2-ethylhexanoic acid, respectively. The two products remained in different phases allowing for their easy separation. The reactions were performed in glass reactors at a low gas pressure to avoid the possible interference from the metal parts of stainless steel reactors.[27] The mild reaction conditions represent an advantage over the two-step alkene oxidation/epoxide hydrolysis process. Performing the reaction in D_2O and following it up by ^1H NMR spectroscopy showed that only 1,2-propanediol is formed in the aqueous phase. Furthermore, 2-ethylhexanoic acid obtained in the organic phase contained a significantly smaller amount of impurities than when liquid alkenes were used as co-substrates. It is worth noting that, in industry, 1,2-propanediol is prepared in an aqueous solution, thus its isolation does not present additional challenges.[24]

In conclusion, aldehyde oxidation by molecular oxygen under "on water" or in neat conditions generates a sequence of radicals that can be efficiently trapped by reactions with various organic substrates. These reactions open new possibilities in the synthesis of organic compounds without the utilization of organic solvents.

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