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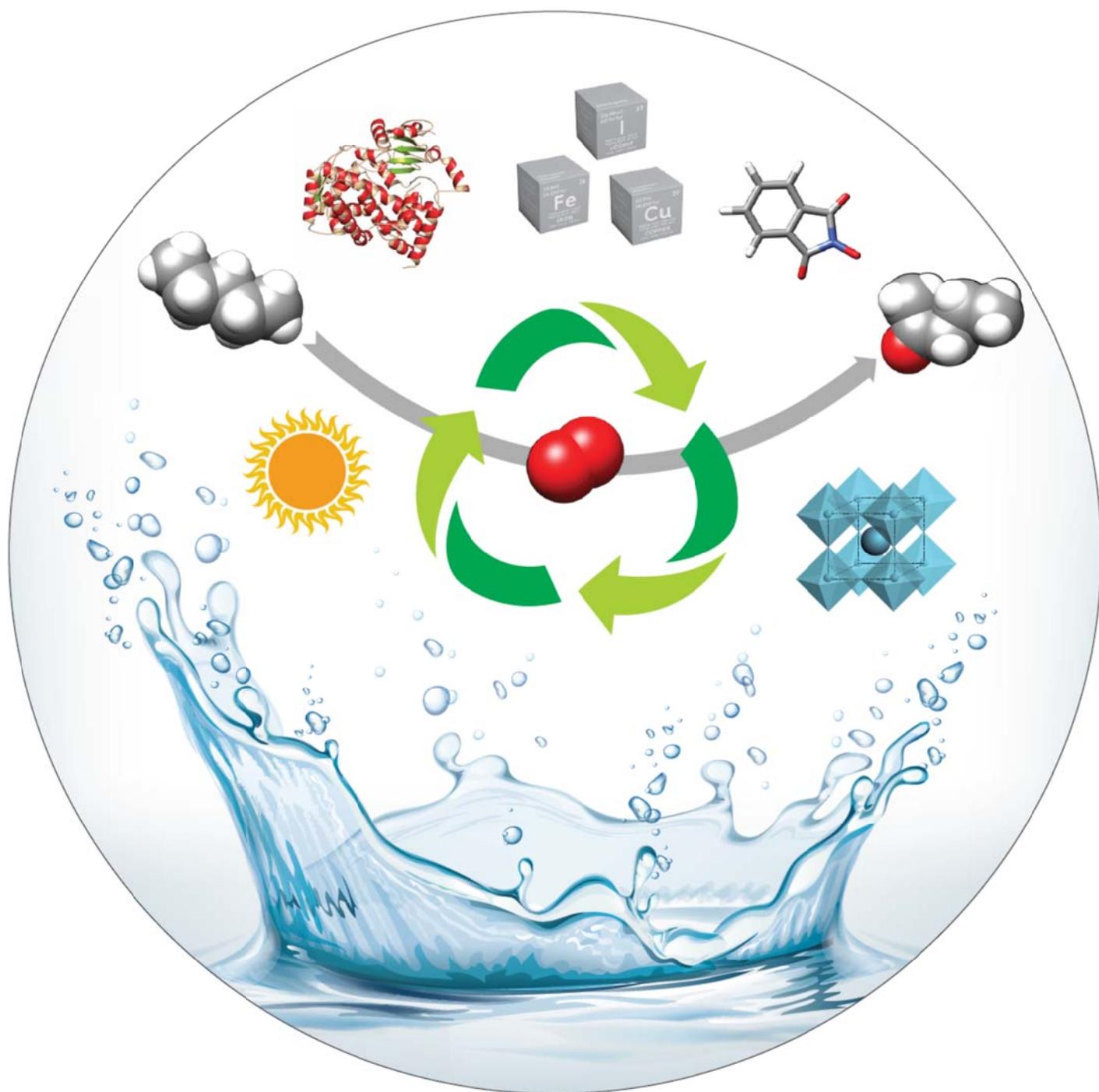
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Recent advances in catalytic aerobic oxidation of C(sp³)-H bonds

Hans Sterckx, Bénédicte Morel and Bert U.W. Maes*

Dedicated to the memory of Prof. István Markó (1956-2017)



Abstract: Oxidation reactions are a key technology to transform hydrocarbons from petroleum feedstock into chemicals of a higher oxidation state, allowing further chemical transformations. These bulk scale oxidation processes usually employ molecular oxygen as the terminal oxidant as at this scale it is typically the only economically viable oxidant. The produced commodity chemicals possess limited functionality and usually show a high degree of symmetry thereby avoiding selectivity issues. In sharp contrast in the production of fine chemicals preference is still given to classical oxidants. Considering the strive for greener production processes the use of O₂, the most abundant and greenest oxidant, is a logical choice. Given the rich functionality and complexity of fine chemicals achieving regio/chemoselectivity is a major challenge. This review presents an overview of the most important catalytic systems recently described for aerobic oxidation, and the current insight in their reaction mechanism.

1. Introduction

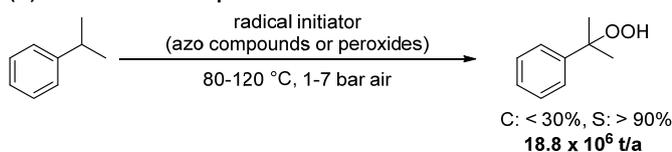
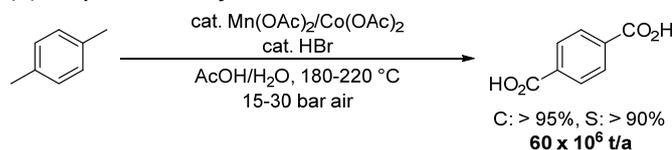
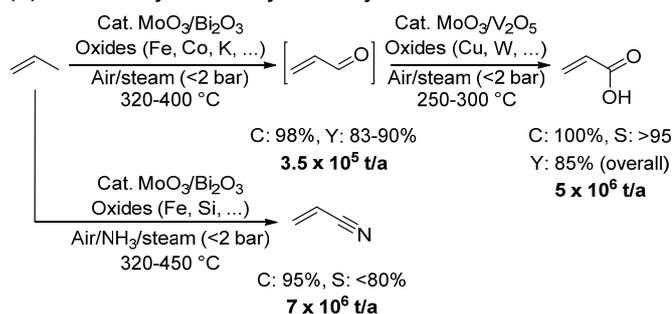
Autoxidation, the oxidation of organic compounds by molecular oxygen, can be initiated spontaneously but is a very slow process at ambient temperature. At high temperature it is highly unselective and usually leads to combustion with formation of CO₂ and water. Control of autoxidation can be achieved by using a suitable catalyst. Nature has mastered selective oxidation of organic substrates using specialized enzymes that usually contain a transition metal (TM) catalyst, the most important being iron and copper. It is therefore not surprising that they are the most used chemocatalysts for aerobic oxidation.

The field of aerobic oxidation has grown exponentially since the early 90s. This evolution coincides with the emergence of green chemistry, as O₂ is the greenest and cheapest oxidant available. Its versatility as a reagent/reactant is shown by its two distinct oxidation modes, oxidase and oxygenase, named in accordance with the enzymes with similar modes of action. In oxidase type reactions O₂ is used as an electron acceptor, which can potentially take up four electrons, and is sequentially reduced to water.¹ O₂ reduction is typically accompanied by reoxidation of a catalyst which generates turnover. This type of oxidation is used in the formation of both C-C and C-X σ as well as π bonds. In this review, for dehydrogenations we limit ourselves to aerobic alcohol oxidation into aldehydes and ketones, which is hitherto the most studied system. In oxygenase reactions, one or both O-atoms are incorporated in the final product. While this is usually accompanied by an electron transfer to O₂, it is not strictly necessary, as sometimes co-oxidants are used for this purpose.

Organic molecules typically possess many C-H bonds which are similar in terms of reactivity, yet certain trends, largely independent of the oxidant used, can be observed with respect to their innate reactivity. Considering the vast majority of oxidation catalysts are electrophilic in nature, the reactivity trend of unactivated C-H bonds is: tertiary > secondary >> primary, in accordance with an increased electron density on the reactive center through inductive donating effects.² This trend is also reflected in the homolytic bond dissociation energy (BDE) of these C-H bonds (see section 3.3), where tertiary C-H bonds have the lowest BDE. Despite being less reactive, selectivity for secondary positions can be achieved by using very bulky catalysts.³ Although heteroatoms usually exert an inductive withdrawing effect reducing reactivity, the nonbonding electrons may donate electron density into the neighbouring σ^* orbital of the C-H bond, effectively activating this position and imparting regioselectivity through stereoelectronic effects.⁴ The majority of published aerobic oxidation protocols deals however with activated C-H bonds such as benzylic and allylic positions.

The reduction of O₂ to H₂O is highly exothermic, giving a thermodynamic driving force for aerobic oxidations. Triplet, ground-state O₂ however neither readily reacts with organic molecules at ambient pressure and temperature nor forms oligomers, as sulfur does.⁵ When it is activated by means of catalysis, heating or by adding a stoichiometric reductant ("Mukaiyama trick", *vide infra*), the exothermic reaction is harder to control and might lead to hot spots and runaway reactions, causing fire or explosions. Efficient heat transfer as well as controlling the O₂ concentration in the reactor headspace to avoid combustion is therefore crucial. These safety hazards made the fine chemicals industry very reluctant to adopt new protocols making use of this oxidant. In fact oxidation in general is not a very common reaction in fine chemicals production, where readily available building blocks in higher oxidation state are typically purchased and reductions are common practice. This is in sharp contrast with the commodity chemicals industry, where oxidation is omnipresent. This might look strange at first glance but is related to the way scale up is typically performed in these sectors, multipurpose batch (fine chemicals) versus dedicated plants (commodity). The scale of fine chemicals required and time for market introduction justify the production approach chosen. Furthermore, bulk chemicals are typically very simple molecules which avoid chemoselectivity issues, and the sheer volume of oxidant needed for their transformation makes O₂ the only economically viable candidate. According to Ullmann's Encyclopedia of Industrial Chemistry, the limit above which O₂ economically outperforms other oxidants such as HNO₃, H₂SO₄ and SO₃/H₂SO₄ (oleum), Cl₂, MnO₂, CrO₃, and H₂O₂ currently lies between 10⁴-10⁵ tonnes per annum (t/a) depending on the product.⁶ Of the 109 industrial oxidation processes listed in Ullmann's Encyclopedia with a capacity of >1000 t/a, 61% use O₂ as oxidant.⁷ The majority concern the oxidation of C(sp³)-H bonds (49 examples) (C(sp²)-H only 8 examples).

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(A) Cumene oxidation process:**(B) Terephthalic acid synthesis:****(C) Acrolein/acrylic acid/acrylonitrile synthesis:**

Scheme 1. Selected examples of industrial aerobic oxidation processes, C = conversion; S = selectivity; Y = yield.

A prominent example of such a large-scale process delivering one of the most important bulk chemicals is the autoxidation of cumene, which is produced by Friedel-Crafts alkylation of benzene and propene, to cumene hydroperoxide (CHP) (Scheme 1A). CHP can then be converted to phenol and acetone by treatment with acid in a follow-up Hock rearrangement reaction. The oxidation reaction of cumene is quite slow and is typically performed in large bubble columns operated at high air pressures (1-7 bar).⁸ Given the exothermicity of the oxidation (117 kJ/mol) and the subsequent decomposition of CHP (270 kJ/mol), great attention is given to the removal of excess heat. Furthermore, the O₂ conversion throughout the reactor is optimized so the residual O₂-concentration in the headspace is below the limiting oxygen concentration (LOC) to avoid the formation of explosive/combustible gas mixtures. New developments currently focus mostly on process intensification through improvements of reaction and process design, although there is a large body of academic research on the use of various catalysts and additives to enhance conversion and selectivity of the oxidation. The major drawback with these additives is safety, as they increase the rate of decomposition of CHP and thus the risk for uncontrolled reactions. Their influence on downstream processes is usually not examined, making the industry reluctant to adopt such new protocols.

The oxidation of *p*-xylene to terephthalic acid (TA) using a Co-Br-Mn catalytic system, also known as the Mid-Century (MC) catalyst, is the largest homogeneously catalyzed oxidation reaction performed in industry (Scheme 1B).⁹ TA has an estimated annual demand of 60 million tons and is mainly used in the production of polyethylene terephthalate (PET) which is used in numerous applications such as plastic water bottles.¹⁰ The MC catalyst has been extensively studied and is now

relatively well understood despite its complex nature. A boiling mixture of AcOH/H₂O is used as solvent to solubilize the catalysts with the added advantage that TA is insoluble in this mixture and precipitates out. Excess reaction heat from this highly exothermic reaction is removed by the evaporation of solvent and can be recovered as low-pressure steam which can be utilized in other parts of the process such as the recycling of solvent by dehydration of AcOH.¹¹ Although the process has been around since 1955, innovations are still being patented. These deal mostly with optimizing reactor design in terms of minimizing byproduct formation¹², maximizing safety¹³ or making the process more energy and cost effective¹⁴. A few modified protocols were also patented like the use of ionic liquids or using substitutes for bromine, as it is corrosive to the reactor wall over time.¹⁵ Finally, the development of protocols and reactors for the purification and subsequent oxidation/polymerization of *p*-xylene from bio-renewable sources are a rich new source of intellectual property.¹⁶

The gas phase oxidation of propene was developed in 1957 by the Standard Oil of Ohio Company (SOHIO) and is now the major production process for acrolein, acrylic acid and acrylonitrile (Scheme 1C).¹⁷ In the production of acrolein a mixture of air, steam and propene is passed through a tubular fixed bed reactor containing a Mo/Bi based catalyst. Over the years many refinements have been made to this catalyst system and a large variety of metal oxides are usually added to optimize conversion and selectivity. Most of the produced acrolein is not isolated but is used directly in follow up chemistry such as the production of methionine. The majority is oxidized to acrylic acid, requiring a different catalyst system and conditions to achieve optimal conversion and selectivity. For this step a Mo/V catalyst system is used, again in combination with various metal oxides to increase performance. Alternatively, when ammonia is added to the reagent stream, ammoxidation of propene occurs leading to acrylonitrile. Acrylonitrile is used in the synthesis of many (co)polymers such as styrene acrylonitrile (SAN) and acrylonitrile butadiene styrene (ABS).

As already stated above, the use of O₂ in the fine chemicals industry is rare. H₂O₂ is currently preferred over O₂ despite its higher cost, as this is mainly compensated by its simplicity of operation.¹⁸ This is exemplified for instance by the S-oxidation in the synthesis of Armodafinil, a reaction that could also be performed using O₂ as oxidant.¹⁹ While H₂O₂ possesses its own unique reactivity patterns, often distinct from O₂ (epoxidations, Baeyer-Villiger oxidations), it can often also replace O₂ in many reactions as it is a reduced form of O₂ (*vide infra*). Its availability in dilute aqueous solution limits usability, though stable adducts such as urea-H₂O₂ can sometimes also be used. Considering H₂O₂ is produced from O₂ via the anthraquinone oxidation process, its use adds extra cost to any process.²⁰

With the introduction of flow chemistry in the fine chemicals industry, new solutions (dedicated low-volume reactors, minimizing risk and guaranteeing productivity by numbering-up, enhanced gas-liquid mass/heat transfer, easy pressurization limiting/omitting combustible headspace) for hitherto generally considered 'unaccessible' chemistry such as aerobic oxidations arose.²¹ Efficient and selective oxidation protocols, involving (partial) O₂ atmosphere, are now expected from academia to subsequently resolve the technical and safety aspects of the continuous production of fine chemicals intermediates applying these protocols.

Hans Sterckx was born in 1988 in Belgium. After finishing his M.Sc. in Chemistry at the UAntwerp he joined the Maes group where he obtained his Ph.D in 2018. His doctoral work mainly focused on the development of novel aerobic oxidation protocols and the unravelling of their reaction mechanism. He is currently employed as a post-doctoral fellow at The Janssen Pharmaceutical companies of Johnson & Johnson in Beerse (Belgium).



Bénédicte Morel was born in Rennes (France) in 1986. After completing her M.Sc. in Organic Chemistry at the University of Versailles Saint-Quentin-en-Yvelines (France), she joined the research group of professor Maes at UAntwerp (Belgium) where she obtained her Ph.D. degree in 2018. Her research focused mainly on novel synthetic methodologies employing oxygen as the terminal oxidant. She is currently working in medical affairs at Archemin.



Bert Maes obtained his Ph.D. at UAntwerp in 2001 and subsequently received a Post-Doctoral Fellowship of the National Science Foundation (FWO-Flanders) in Belgium. He performed postdoctoral work at the *École Normale Supérieure* in Paris with Prof. Anny Jutand (CNRS) studying reaction mechanisms in catalysis. Maes currently is full professor of Organic Chemistry at UAntwerp and since 2009 he holds a position as a Research Professor. His research interests include heterocyclic, organometallic, and sustainable chemistry and homogeneous catalysis.



With this review we provide an overview of the most important advances made in the different types of catalyst systems developed since 2013 for aerobic C(sp³)-H oxidations. Catalysts are either homo- or heterogeneous but even within one class majorly differ in their structure (organic, inorganic, hybrid). Furthermore, there are specific modes of activation (thermal, photoredox, electrochemical), so dividing them into different sections is not self-evident and open to discussion. The sections organo-, photoredox-, and biocatalysis are selected based on their specific importance, and can contain examples that can be either homo- or heterogeneous in nature. Remaining examples, which are mostly TM based, are divided on whether they fall under the larger classes of homo- or heterogeneous catalysis. However, several examples include a combination of transition metals and organic catalysts. In these cases, section allocation has been done on the basis of the catalyst type assumed essential for the reaction to proceed.

2. Working with oxygen: important parameters

When using gaseous O₂ in liquid-gas phase reactions some important parameters need to be considered. O₂ is a gas which can form combustible mixtures with organic vapors. Under air (20.95% O₂) one can work safely with organic solvents below their flash point (fp). However, the actual fp of mixtures is often not known and even small amounts of low boiling impurities may lower the fp significantly. Many solvents typically used in organic chemistry have a very low fp, with the exception of several dipolar aprotic solvents like DMSO, but these have a very low O₂ solubility or are undesired because of environmental concerns.²² Therefore, O₂/N₂ mixtures (typically between 5-10% O₂) are used in batch, and the limiting oxygen concentration (LOC) value of the solvent (below which combustion does not happen) has to be taken into account (Table 1).^{21b} Though N₂ is typically used, other gases such as CO₂ are inherently more interesting as higher concentrations of O₂ are allowed based on the higher heat capacity.²³ This can be clearly seen in Table 1: the LOC in CO₂-air mixtures is 19-26% higher than in N₂-air mixtures. It is important to note that care should be taken in adopting these parameters as they are determined under standard conditions. Pressure, temperature and O₂ concentration are often significantly different in the actual process conditions. The latter two parameters mainly impact the explosion limits.

Mass transfer limitation is a second point of attention, as the rate can be greatly affected by gas solubility.^{21a, 24} While the solubility of O₂ in most organic solvents is higher than in water, it is still extremely low compared to typical concentrations of chemical reactants. Furthermore, it is noteworthy that, for many organic solvents with the exception of alcohols, O₂ solubility can be larger at higher temperature as in the cases of MeOAc at 40°C, benzene at 60°C, and DMSO at 80°C versus 25°C (Table 1). Gas solubility in function of temperature can, depending on the gas and the solvent, increase, decrease or even pass through a minimum with increasing temperature.²⁵ This is because the enthalpy of dissolution leads to an exponential increase in solubility with rising temperature, while entropy leads to a linear decrease. Initially solubility will appear to go down but this trend is quickly reversed and solubility will increase. As the concentration of O₂ often directly influences the overall rate of the reaction, poor solubility has a direct negative effect on the reaction rate. Considering this is a major concern in every aerobic oxidation reaction it is therefore of vital importance to check whether the reaction is O₂ diffusion controlled. This can be done in the reaction development by measuring the reaction rate at different stirring rates, if the stirring affects the rate of the reaction it is diffusion controlled.²⁶ This limits the turnover frequency but can also lead to undesired products, for instance, side products formed by unwanted radical termination in autoxidation reactions.²⁷ To counterbalance this, a higher gas pressure can be applied, which will increase the gas solubility in correspondence to Henry's law which states that the amount of dissolved gas is proportional to its partial pressure in the headspace. Increasing the surface area between gas and liquid phases is another well-used trick which is for instance used in gas-liquid segmented or annular flow.²⁸ To intensify gas-liquid contact, O₂/N₂ mixtures can also be bubbled through the liquid phase, using bubble columns.²⁹ The size and velocity of the bubbles depend on the temperature and pressure applied, and the interfacial area can be increased up to 17 times compared to classical round-bottom flasks.^{28b}

Table 1. Flash point (fp), limiting oxygen concentration (LOC) and O₂ solubility in organic solvents^a

Solvent	Fp (°C) ^b	LOC (vol% O ₂) for N ₂ at 25°C, 1 atm	LOC (vol% O ₂) for N ₂ at higher T and/or P	LOC (vol% O ₂) for CO ₂ mixture at 25°C, 1 atm	O ₂ solubility at 25°C, 1 atm (mM) ⁱ	O ₂ solubility at 25°C, 1 atm (10 ⁴ x ₁) ^c	O ₂ solubility at higher T, 1 atm (10 ⁴ x ₁) ^c
Water	NA	NA	NA	NA	1.27	0.229	0.159 (60°C) 0.149 (120°C)
Alcohols							
MeOH	9.7	10.0 ^d 8.6 ^e	7.6 (100°C, 1 bar) ^f 6.9 (100°C, 20 bar) ^f	12.0 ^d	10.25	4.15 ^g	4.06 (40°C)
EtOH	14	10.5 ^d 9.8 ^e	8.7 (60°C, 1 atm) ^d	13.0 ^d	10.0 9.80	5.83 5.71 ^g	5.70 (40°C) 5.57 (60°C)
<i>i</i> -PrOH	12	UNK	9.5 (60°C, 1 atm) ^d	UNK	10.24 10.18	7.82 7.78 ^g	7.66 (40°C)
<i>t</i> -BuOH	11	UNK	UNK	16.5 (150°C) ^d	UNK	UNK	UNK
<i>t</i> -Amyl alcohol	20	UNK	9.6 (100°C, 1 bar) ^f 10.1 (100°C, 20 bar) ^f	UNK	UNK	UNK	UNK
Ketones							
Acetone	-17	11.5 ^d	UNK	14.0 ^d	11.44 11.86	8.40 8.71 ^g	8.61 (40°C)
Cyclohexanone	44	UNK	UNK	UNK	6.15	6.36	UNK
Esters							
MeOAc	-13	11.0 ^d	UNK	13.5 ^d	11.22	8.91	9.17 (40°C)
EtOAc	-3	UNK	9.4 (100°C, 1 bar) ^f 9.9 (100°C, 20 bar) ^f	UNK	8.86	8.7 ^h	UNK
<i>n</i> -BuOAc	23	UNK	9.0 (60°C, 1 atm) ^d	UNK	UNK	UNK	UNK
Ethers							
Et ₂ O	-40	10.5 ^d	UNK	13.0 ^d	18.69	19.37	UNK
THF	-17	UNK	UNK	UNK	10.07	8.16	UNK
2-Me-THF	-10	UNK	9.4 (100°C, 1 bar) ^f 9.1 (100°C, 20 bar) ^f	UNK	UNK	UNK	UNK
1,4-Dioxane	12	UNK	UNK	UNK	6.31	5.38	UNK
Hydrocarbons							
<i>n</i> -Pentane	-49	12.1 ^d	UNK	14.4 ^d	17.82 23.05	20.5 26.5 ^g	UNK
<i>n</i> -Heptane	22	11.5 ^d	UNK	14.5 ^d	13.96 14.88	20.55 21.9 ^g	22.24 (40°C)

Cyclohexane	-18	UNK	UNK	UNK	11.42	12.34	12.39 (40°C)
					11.85	12.8 ^g	
Benzene	-11	11.4 ^d	UNK	13.9 ^d	9.10	8.10	8.80 (60°C)
					9.21	8.20 ^g	
			9.5 (60°C, 1 atm) ^d				
Toluene	4	11.6 ^e	10.4 (100°C, 1 bar) ^f	UNK	8.72	9.23	9.38 (40°C)
			10.3 (100°C, 10 bar) ^f		9.27	9.81	
Halogenated							
DCM	NA ^k	NA	NA	NA	11.08	7.09 ^g	UNK
CCl ₄	NA ^k	NA	NA	NA	12.39	12.00	12.05 (60°C)
Perfluoroheptane	UNK	UNK	UNK	UNK	24.74	55.5	UNK
Hexafluorobenzene	10	UNK	UNK	UNK	21.00	24.18	UNK
PhI	77	UNK	UNK	UNK	4.56	5.10	UNK
Dipolar aprotic							
MeCN	2	12.7 ^e	12.1 (100°C, 10 bar) ^f	UNK	8.10	4.23 ⁱ	UNK
			11.9 (100°C, 20 bar) ^f				
DMA	69.5	UNK	UNK	UNK	5.19	4.82 ^g	UNK
DMF	58	UNK	UNK	UNK	5.05	3.89 ^g	UNK
DMSO	89	UNK	6.4 (100°C, 1 bar) ^f	UNK	2.21	1.57	2.39 ^j (80°C)
			3.9 (200°C, 1 bar) ^f				
NMP	91	UNK	8.1 (200°C, 1 bar) ^f	UNK	UNK	UNK	UNK
			7.6 (200°C, 20 bar) ^f				
Acids							
AcOH	UNK	UNK	10.6 (200°C, 1 bar) ^f	UNK	UNK	UNK	UNK
			9.6 (200°C, 20 bar) ^f				
Amines							
Aniline	70	UNK	UNK	UNK	2.48	2.26	UNK
Pyridine	17	UNK	UNK	UNK	5.68	4.58	UNK

^aNA: not applicable. UNK: unknown. ^bClosed cup. ^cMole fraction solubility of O₂. ^dref³¹. ^eref³². ^fref³³. ^gref³⁴. ^hAt 20°C. ⁱref³⁵. ^jref²⁴. ^kflash point is higher than boiling point ^lcalculated from O₂ solubility at 25°C, 1 atm (10⁴x₁).

3. Aerobic C(sp³)-H oxidation reactions

3.1. Homogeneous transition metal based catalysis

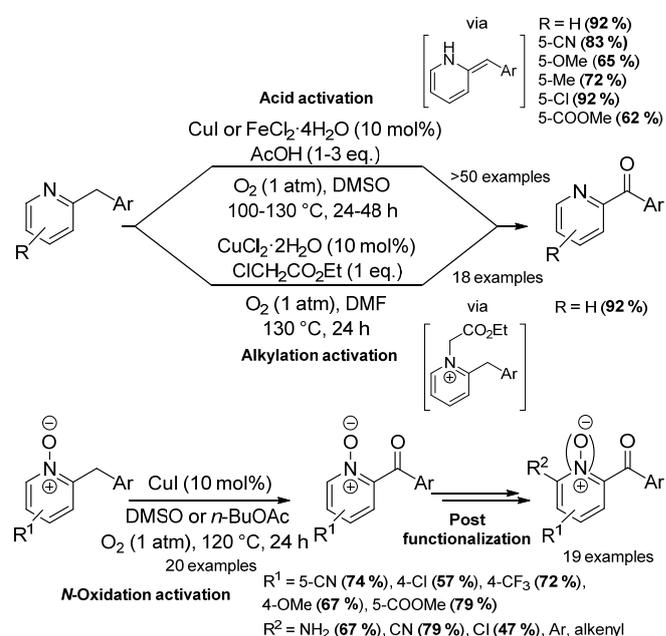
Activation can occur either by reaction of the organic substrate with transition metal catalyst or by an initial electron-transfer from the catalyst to O₂ resulting in a metal bound superoxide (O₂^{•-}) species, which subsequently reacts with substrate. These relatively stable complexes modulate the reactivity and can thereby induce selectivity. The stability is highly dependent on the metal and ligands used. Earth abundant TMs such as Fe, Cu, Co and Mn are nowadays most commonly employed, in combination with a large variety of N-, O- and P-containing ligands such as: Salen, heme- and non-heme N4-, and phosphine ligands.³⁶

In 2012 the Maes group reported the chemoselective benzylic oxidation of benzylpyridines (Scheme 2, top).^{37a} The addition of acetic acid promotes imine-enamine tautomerization, which is a vital step in the reaction mechanism. Reaction of the enamine tautomer with *in situ* formed CuX₂ yields a C-Cu bond which then reacts with O₂.³⁸ This tautomerization is the basis for the chemoselectivity observed for 2- and 4-benzylpyridines (oxidizable) versus 3-benzylpyridines or diphenylmethanes (not-oxidizable). The method could be extended towards other benzyl heterocycles featuring a nitrogen in the α - or γ - position, such as diazines and azoles, and was used in the formal synthesis of the active pharmaceutical ingredients (API) Mefloquine and Acrivastine.^{37a, 38b}

Zhuo and Lei reported a similar oxidation protocol using ethyl chloroacetate rather than acid as stoichiometric promotor (Scheme 2, middle).³⁹ In the first step ethyl chloroacetate alkylates the pyridine forming a pyridinium salt. Through consecutive CuCl₂-catalyzed electron- and proton transfer, a benzylic radical is formed which is consequently trapped by O₂. After the oxidation the activator is spontaneously cleaved and the hydroperoxide of the substrate decomposes via O-O cleavage into the desired ketone and water. This remarkable difference in mechanism between the two activation modes, protonation versus alkylation, provides a degree of orthogonality as the latter method is also able to oxidize alkyipyridines, including 3-alkylpyridines. Alternatively, the oxidation of picolines was also reported by Sato and Itoh using CuCl₂·2H₂O as catalyst with seemingly no extra additive required. However, HCl is formed *in situ* from the catalyst which activates the substrates via protonation as in the Maes protocol.⁴⁰ Although present in catalytic amounts, HCl is a significantly stronger acid than AcOH explaining the increased reactivity towards 2- and 4-alkylpyridines. After all, strength and amount of acid have a large influence on the tautomerization rate and thus on the overall oxidation protocol.^{38b}

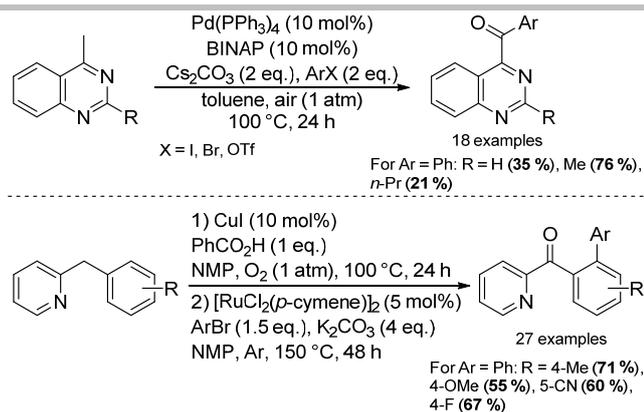
The high sensitivity of the methylene oxidation protocols on the substitution pattern of the azine requires post functionalization for application in synthesis. However, the acylpyridine reaction products do not allow this. Activation of the pyridine ring for oxidation by means of *N*-oxidation was evaluated to solve this problem, considering the acylpyridine *N*-oxides allow reaction with both nucleo- and electrophiles (Scheme 2, bottom).⁴¹ Substrates can be easily obtained via direct Pd-catalyzed arylation or benzylation of commercially available picoline- or pyridine *N*-oxide, respectively.⁴² Interestingly, the reaction could be executed without acid mediator, indicating that activation by

the *N*-oxide moiety is sufficient on its own. The reaction products were successfully post functionalized in α position via cine substitution, such as amination, cyanation, and chlorination, with concomitant loss of the *N*-oxide moiety. Direct Pd-catalyzed arylation or oxidative Heck reactions can also be executed, in this case keeping the *N*-oxide moiety intact, allowing even further transformations.⁴¹



Scheme 2. Three different substrate activations used in the Cu-catalyzed oxidation of benzylpyridines

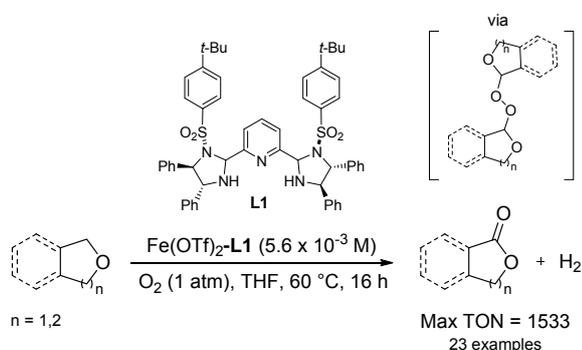
Noble metals are still used when another step in a cascade reaction requires its utilization. An example is the domino direct arylation/oxidation of 4-methylquinazolines reported by Li (Scheme 3, top).⁴³ Pd catalysis allows direct arylation using aryl bromides, careful tuning of the reaction conditions gives a further Pd-catalyzed aerobic oxidation of the benzylic position of the initially formed 4-benzylquinazolines. Water is presumed to deliver the oxygen atom and not O₂, which is assumed to fulfil an oxidase role. In 2016 a related one-pot example is found in the oxidation/direct arylation of 2-benzylpyridines reported by Gramage-Doria. In this case each step involves a different transition metal (Scheme 3, bottom).⁴⁴ In the first step 2-benzylpyridines are oxidized to 2-benzoylpyridines with O₂ by means of CuI and benzoic acid additive. The reaction is subsequently brought under an Ar atmosphere and then Ru catalyst and aryl bromide are added. Interestingly, the picolinoyl moiety formed in the oxygenation step acts as a directing group (DG) to promote the *ortho* C(sp²)-H arylation of the phenyl ring.⁴⁵



Scheme 3. One-pot direct arylation and oxidations

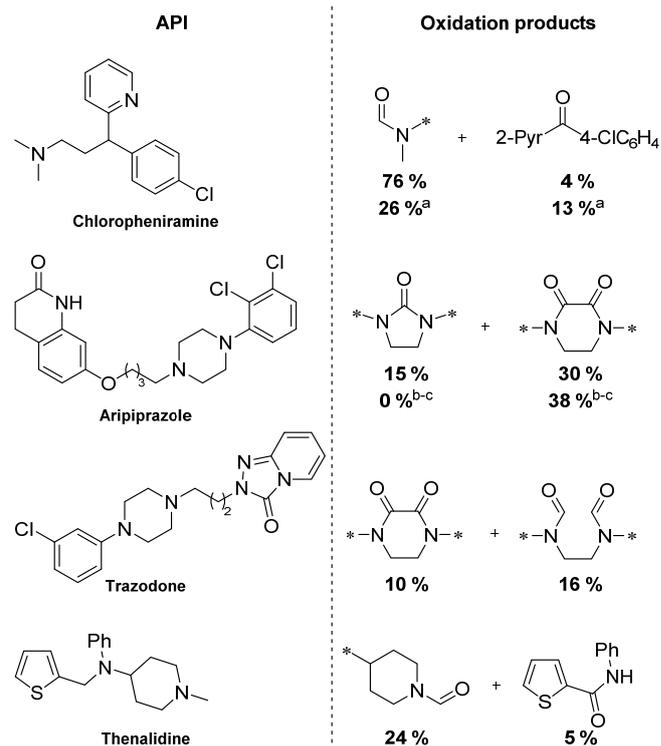
The formation of esters, amides or carboxylic acids can be achieved by oxidation of activated methyl groups (or primary alcohols)⁴⁶ in the presence of alcohols, amines or water.⁴⁷ The mechanism of these transformations is thought to proceed via initial oxidation to aldehyde followed by *in situ* formation of a hemi-aminal, -acetal or a hydrate followed by a second oxidase reaction.

Despite the inductive electron withdrawing effect of heteroatoms, methylenes α to heteroatoms are activated for oxidation, since the nonbonding electrons can donate electron density into the antibonding σ^* of neighbouring C-H bonds.⁴ Cyclic ethers are transformed into lactones using a PyBisulidine (L1) based Fe catalyst as reported by Xiao (Scheme 4).⁴⁸ Though a chiral ligand is involved no asymmetric synthesis is performed. This catalyst system is used to oxidize substituted tetrahydrofurans, isochromans and phthalans with excellent mass balance. Mechanistic experiments reveal a peroxide dimer of the substrate to be the crucial intermediate for this reaction. This dimer is formed with release of one equivalent of H₂ gas (GC identification). Subsequent O-O bond cleavage and dehydrogenation, possibly mediated by the same catalyst, releases a second equivalent of H₂ and two product molecules, meaning no water is formed in this reaction. Although it is usually only considered as a background reaction, the evolution of this second equivalent of H₂ gas could arise through a concerted retro [2+2+2] cycloaddition which is a preferred reaction for bis-peracetals and bis-perketals bearing a hydrogen atom on each α -carbon.⁴⁹



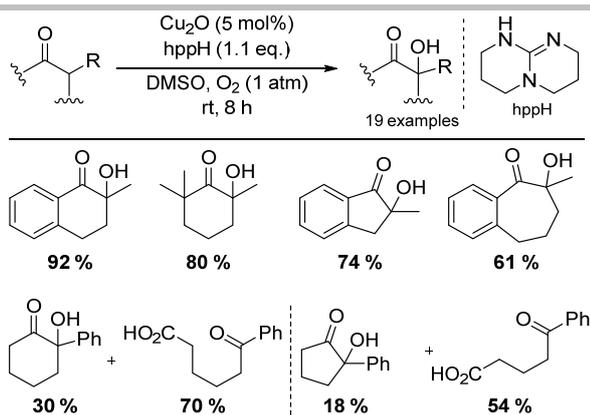
Scheme 4. Fe-catalyzed oxidation of cyclic ethers

Touré identified a CuI/air system to oxidize tertiary amines α to the nitrogen.⁵⁰ Model APIs were selected as substrates aiming to access putative metabolites in sufficient quantities for structural elucidation and further studies (Scheme 5). In this way a mimic of cytochrome P450s and alcohol/aldehyde dehydrogenases was achieved.⁵¹ Lactam/amide formation and *N*-dealkylation via subsequent hydrolysis were the main reactions observed, but C-C bond cleavage in oxalimide fragments and on tertiary carbons, initiated via benzylic oxidation, were also seen depending on the substrate. Though selectivity was not an aim it nicely illustrates chemoselectivity to be one of the big challenges in aerobic oxidations.



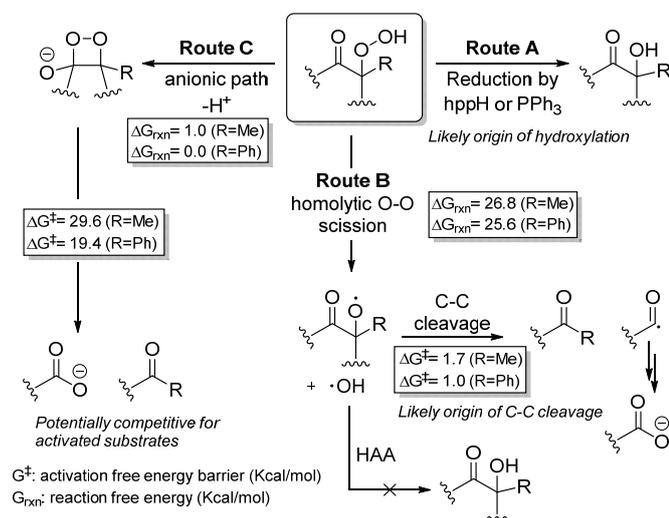
Scheme 5. Cu-catalyzed oxidation of tertiary amines in selected APIs. * indicates that the substituent is the same as in the parent API. Conditions: drug 0.1 M, CuI (20 mol%), air or O₂ (balloon), DMSO, 120 °C, 16h. ^awith AcOH (1 eq.) ^bwith TEMPO (2 eq.) ^cCuI (1 eq.)

Aerobic oxidation of substituted methylene positions α to a carbonyl ($\text{pK}_{\text{a,DMSO}} \approx 26$)⁵² or azomethine ($\text{pK}_{\text{a,DMSO}} \approx 30$)⁵³ are well known.⁵⁴ As these C-H bonds are acidic and prone to deprotonation this is a likely first step in the mechanism, explaining the typical use of a base in these reactions. The tertiary hydroperoxide intermediates can undergo either O-O bond cleavage, leading to hydroxylation, or C-C bond cleavage.⁵⁵ The factors controlling C-H hydroxylation versus C-C cleavage were studied in detail for ketones by Schoenebeck.⁵⁶ Several cyclic ketones were oxidized with O₂ using Cu₂O as catalyst and hppH as a base in DMSO (Scheme 6). Next to a catalyst and solvent effect on the selectivity, a pronounced substrate dependence was seen. α -Methylated ketones only provided the α -hydroxylated products, while the more activated α -phenyl derivatives provided a mixture of both. This could be generalized towards acyclic ketones as well.



Scheme 6. Selected scope of Cu-catalyzed oxidation of ketones

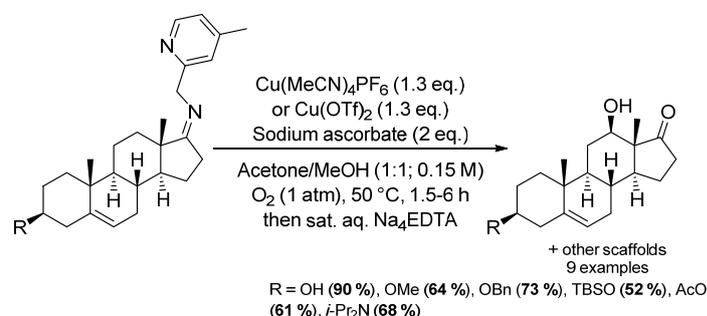
Mechanistic studies revealed a common precursor for the two pathways and that C-C bond cleavage does not occur through product overoxidation. The tertiary α -hydroperoxide precursor can undergo either reduction leading to alcohol (Route A), homolytic O-O scission (route B) or an anionic pathway (route C), both producing ketone and carboxylate (Scheme 7). Route B is likely the major pathway by which C-C cleavage occurs and is thought to be facilitated by the catalyst, explaining the large differences in selectivity for different Cu-salts. Given the low activation barrier for α -oxy radical fragmentation, no time for competitive intermolecular hydrogen abstraction is left, which could otherwise also be a pathway for hydroxylation. Route C is slightly higher in energy than the radical pathway but could be competitive for activated substrates (R=Ph). It does not however account for differences in selectivity observed for different catalysts.



Scheme 7. Overview of different mechanistic pathways for the α -hydroxylation versus C-C bond cleavage of ketones

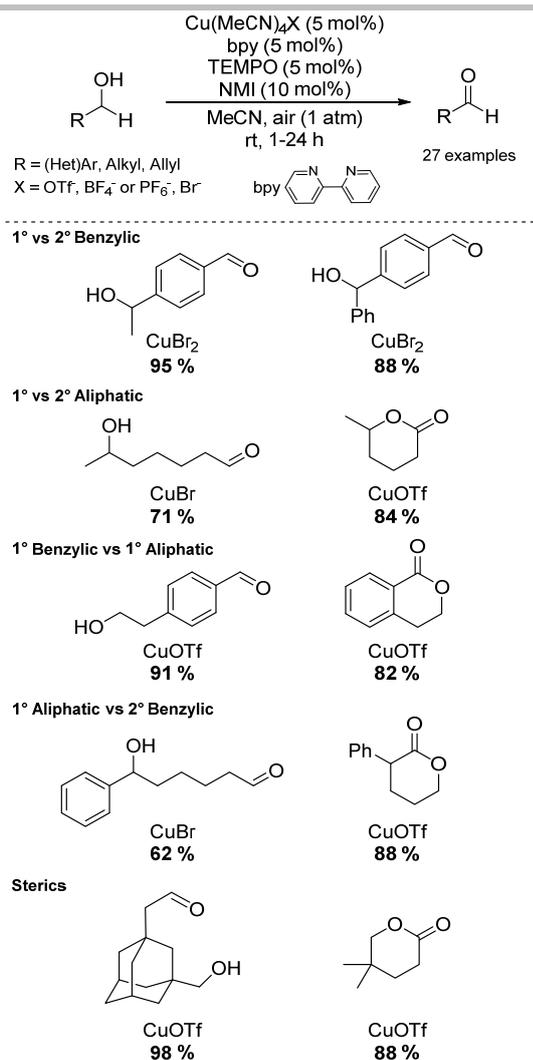
Examples of the use of unactivated C-H are still rare. When a DG is present this is possible.⁴⁵ In 2003, Schönecker reported the diastereoselective C12 hydroxylation of steroids using a *N*-(pyridin-2-ylmethyl)imine DG and superstoichiometric Cu(OTf)₂.⁵⁷ This method suffered from several shortcomings

including a max. yield of 50%. Building on this seminal work, the Baran group proposed sodium ascorbate as a key reducing agent to cross 50% yield (Scheme 8).⁵⁸ Furthermore, the addition of MeOH as cosolvent and optimization of the DG, i.e. *N*-(4-methylpyridin-2-ylmethyl)imine, increased conversions significantly. While the procedure still employs superstoichiometric Cu, the complexity of the substrates and selectivity of oxidation make it a rather remarkable transformation. The addition of (super)stoichiometric reductants to aid in the activation of O₂ is a common strategy in aerobic oxidation chemistry. While sodium ascorbate is used to reduce copper from oxidation state II to I, other additives, such as aldehydes⁵⁹ or cumene⁶⁰, are commonly employed to react directly with O₂ delivering another oxidant. This method of O₂ reduction is referred to as the “Mukaiyama trick” and results in a more reactive peracid or peroxy species that acts as the active oxidizing agent.⁶¹ Using this trick, otherwise difficult aerobic oxidations, such as Baeyer-Villiger oxidations and alkene epoxidation, become feasible.⁶²



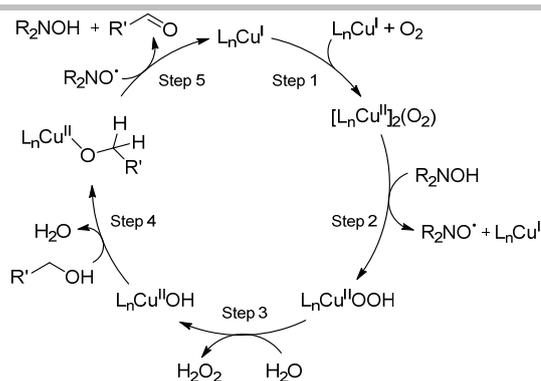
Scheme 8. Directed diastereoselective Cu-mediated C12 oxidation of steroids

Achieving chemoselectivity in aerobic alcohol oxidation is generally less troublesome in comparison to C-H oxygenation (alcohols are more reactive) and typically hinges around avoiding overoxidation. When multiple alcohols are present in a substrate distinction can usually be made by careful selection of the catalyst.⁶³ A frequently used, and very potent catalyst system is the combination of copper and TEMPO cocatalyst, which was first described by Semmelhack and later refined by many others, though other cocatalysts such as di-*t*-butyl azodicarboxylate (DBAD) have also been used.^{61, 64} Stahl reported a (bpy)Cu^I/TEMPO catalytic system using *N*-methylimidazole (NMI) as base that enables the oxidation of benzylic, allylic and aliphatic primary alcohols with excellent chemoselectivity (Scheme 9).⁶³ Replacing TEMPO with 9-azabicyclo[3.3.1]nonane (ABNO) in combination with a (^{MeO}bpy)Cu^I catalyst enhances the reaction rate significantly and allows the procedure to be compatible with secondary alcohols and to lower ABNO loading (1 mol%).⁶⁵ The increased reactivity can be explained by the decreased one-electron redox potential and less sterical encumbrance of ABNO (Figure 2). The (^{MeO}bpy)Cu^I/ABNO-catalyzed oxidation strategy was also recently applied to the synthesis of amides via oxidative coupling of primary alcohols and amines involving an aldehyde and hemiaminal intermediate.⁴⁶

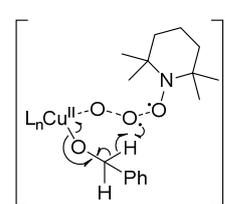


Scheme 9. Selected scope of chemoselective Cu/TEMPO-catalyzed aerobic oxidation of alcohols

The mechanism of this transformation starts with the oxidation of Cu^I to form a peroxo-bridged binuclear Cu^{II}-complex, followed by oxidation of the *N*-hydroxylamine cocatalyst forming the nitroxyl radical species and a Cu^{II}-OOH (Scheme 10).⁶⁶ Exchange with H₂O yields Cu^{II}-OH and H₂O₂ (step 3). Ligand exchange with alcohol gives Cu^{II}-OCH₂R' from which the nitroxyl radical is able to abstract a hydrogen atom, with concomitant formation of product and regeneration of the Cu^I and *N*-hydroxyl species. In the case of TEMPO, aliphatic alcohols undergo rate limiting C-H cleavage (step 5) while activated alcohols (weaker α-C-H bonds) undergo rate limiting catalyst reoxidation (step 1). In the case of ABNO, catalyst reoxidation seems to be rate limiting for all substrates. Operado EPR/UV-Vis/ATR-IR spectroscopy was later used by Brückner to further elucidate mechanistic details and shed light on the role of TEMPO. The results suggest that TEMPO stabilizes the superoxo complex L_nCu^{II}OO[•], which will then perform hydrogen atom abstraction from the substrate (Scheme 11).⁶⁷



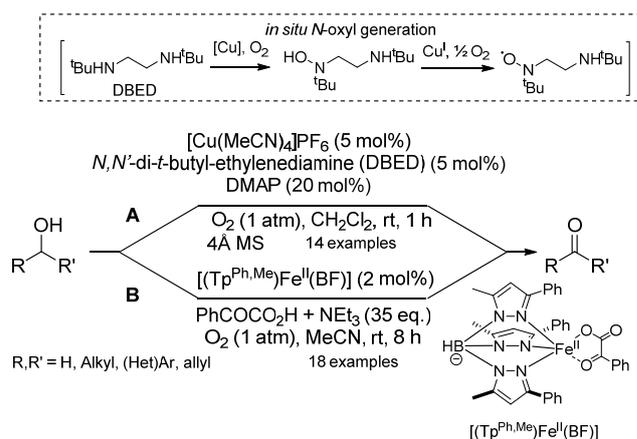
Scheme 10. Simplified catalytic cycle for Cu^I/nitroxyl radical catalyzed alcohol oxidation



Scheme 11. Proposed alternative role of TEMPO

Nitroxyl radicals can also be generated *in situ*, as exemplified by Lumb, Arndtsen and Stahl (Scheme 12, A). In this Cu-catalyzed alcohol oxidation inspired by oxo-tyrosinase, the ligand, DBED, undergoes *N*-hydroxylation under the reaction conditions and subsequently acts as a hydrogen abstracting agent.⁶⁸ The overall mechanism is thus similar as presented in Scheme 10. Interestingly, in this protocol secondary alcohols are preferred over primary.

Nitroxyl radicals are not always required however as exemplified by Paine who demonstrated the use of an *in-situ* formed high-valent iron-oxo-complex as catalyst (Scheme 12, B).⁶⁹



Scheme 12. Base metal-catalyzed alcohol oxidation with nitroxyl radical generated *in situ* (A) or omission (B).

Interestingly, various procedures for alcohol oxidation were investigated in continuous flow. Favre-Réguillon developed a methodology based on gas-liquid segmented flows in PFA (Perfluoroalkoxy) tubing.^{28a} Additionally, Stahl studied

continuous flow with a PTFE (poly(tetrafluoroethylene) membrane flow reactor.⁷⁰ PTFE tubing is permeable to O₂ and compatible with elevated pressures and temperatures, making it very attractive for biphasic gas/liquid systems, as the phases are separated with a polymer through which only the gas can permeate. This tubing runs through a stainless steel shell which is brought under pressure of O₂ and can be heated as desired.

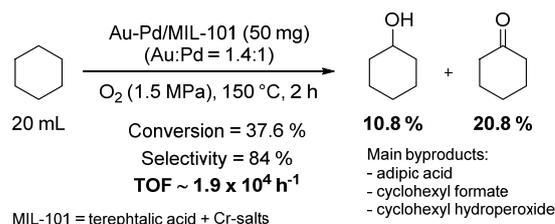
3.2 Heterogeneous catalysis

In heterogeneous catalysis the phase of the catalyst differs from that of the reactants. This allows easy recovery and reusability of the catalyst, which is the major advantage and preferred for commodity chemicals. Therefore, the number of times a heterogeneous catalyst can be reused without significant loss of activity is an often reported parameter in literature. This value should always be interpreted in the right context as often operations, e.g. washing and drying, are performed before reuse. A true measure of robustness can only be attained by immediate reuse after separation or ideally by performing the reaction in flow.

All classes of solid materials can be tailored to act as heterogeneous catalysts including metal oxides, metals and alloys, carbides and nitrides, metal organic frameworks (MOFs) and allotropes of carbons such as carbon nanotubes (CNT).⁷¹ While some materials have the ability to perform the desired catalysis on their own, others need to be decorated with transition metals, organocatalysts or enzymes. Design of new heterogeneous catalysts is typically focused on increasing the productivity (TON), activity (TOF) and selectivity of the catalyst and less on broadening of the substrate scope. Screening is generally performed on structurally simple and rather unfunctionalized model substrates that are important feedstock for commodity chemicals, except for heterogeneous biocatalysis (see section 3.5). In fact, heterogeneous catalysis in fine chemicals synthesis is still limited, though easy catalyst removal and use in continuous production (packed bed) are very attractive features. In this section a few representative model reactions are discussed. This allows getting an overview of the various catalysts that are used in heterogeneous aerobic oxidation with indication of their activity and selectivity. Care should however be taken in the direct comparison of different methods as they may vary largely on important parameters such as temperature, O₂ pressure and reaction scale. The same mechanistic principles identified for homogeneous can be used to rationalize the reaction mechanism of heterogeneous catalysis. Nonetheless, adsorption of substrate and desorption of product are very important additional steps to consider. In addition, the unique porous nature of some catalyst, for instance zeolites, permits shape-selective catalysis that is akin to the macromolecular nature of enzymes. A unique mode of catalysis specific for heterogeneous catalysts is the exploitation of semiconductive properties to create a reactive center; examples can be found in the section on photoredox catalysis.⁷² Semiconductivity is a bulk property and cannot be achieved via homogeneous catalysis.

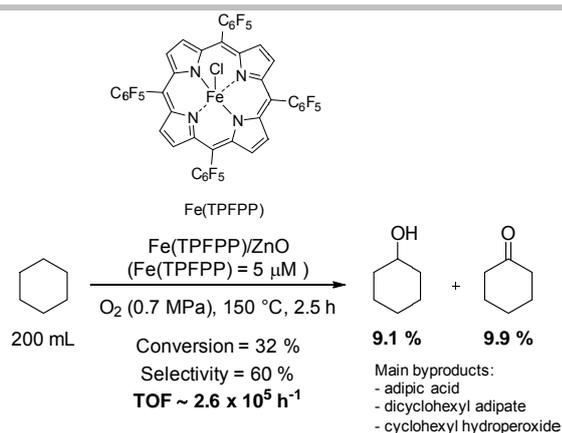
MOFs are made from organic linkers and inorganic building blocks. While hundreds of different MOFs are known, their application in catalysis is still limited.⁷³ A large advantage of MOFs is their easy preparation and the ease of modification of the organic fragment, allowing fine-tuning of the catalyst structure and its activity. Furthermore they are excellent supports for metal nanoparticles due to their high surface area

and porosity. Li illustrated that Au-Pd bimetallic alloy nanoparticles deposited on MIL-101, comprised out of Cr-salts and TA as the organic linker, acted as a highly active and selective catalyst in the oxidation of cyclohexane (cyHex) (Scheme 13), a good model compound for alkane oxidation.⁷⁴ Due to its symmetry no regioselectivity issues can arise. In its industrial oxidation, using homogeneous (Co) catalysis and air, conversion is usually kept low (<5%) to avoid overoxidation and formation of byproducts.⁷⁵ Reports where high selectivity is achieved at high conversions are therefore doubtful. The mixture of cyclohexanone/cyclohexanol that is typically produced in this reaction is known as KA oil and is the main feedstock for the synthesis of adipic acid, a precursor in the production of Nylon 6,6. Interestingly, using the Au-Pd/MIL-101 catalyst a high selectivity (>80%) is still observed at conversions >35%. This high selectivity is due to a synergistic alloying effect of the bimetallic Au-Pd nanoparticles. While these results are promising, only high catalyst productivity will make this catalyst economically viable, considering the cost and low abundance of the noble metals involved. Furthermore, the high selectivity claimed is remarkable but should be complemented by a complete mass balance. Reusability up to 4 cycles was shown without loss of any activity or selectivity but required the catalyst to be washed and dried at 80 °C between each run.



Scheme 13. Oxidation of cyclohexane using Au-Pd/MIL-101

Metal porphyrins act as biomimetics for cytochrome P450 and are able to perform oxygenation of cyHex without the addition of coreductants or solvents. Their applicability on multiton scale (125 kt) has already been demonstrated using a homogeneous Co-tetrakis(phenyl)porphyrin catalyst (TON value of 3.1x10⁵).⁷⁶ Porphyrins often suffer from oxidative degradation but their stability and activity can be increased by halogenation of the ring.⁷⁷ These degraded Co-salts formed are usually still catalytically active. By immobilizing homogeneous Fe-tetrakis(pentafluorophenyl)porphyrin (Fe(TPFPP)) on a biocompatible ZnO support, Huang showed that the high turnovers of homogeneous catalysis can be combined with easy reusability (Scheme 14).⁷⁸ Immobilization further protected the catalyst against oxidative degradation which allowed the catalyst to be recycled, after washing and air drying, for a total of 11 runs and provided an average TOF value of 2.6x10⁵ h⁻¹ over 2.5 hours. A rather low selectivity and sub-optimal ketone/alcohol ratio (a high ratio is desired for KA oxidation to adipic acid) leave room for improvement.



Scheme 14. Oxidation of cyclohexene using Fe(TPFPP)@ZnO

Oxidation of cyclohexene functions as a representative example of allylic oxidations and can be performed using a large variety of catalysts and supports such as MOFs⁷⁹, CNTs⁸⁰, metal oxides⁸¹ and mesoporous materials⁸². Next to the allylic alcohol and ketone products, epoxides and vicinal diols can be formed. CNTs and their doped variants have seen large application as catalysts or as a support material due to their high mechanical strength and resistance to abrasion, combined with high accessibility of active sites.⁸³ Despite their carbon based skeleton, CNTs are generally considered as inorganic entities due to the lack of C-H bonds. In a metal free cyclohexene oxidation Yu and Peng employed a N-doped CNT (NCNT) that competes with the state-of-the-art metal catalysts (Table 2).^{80a} Uncatalyzed autoxidation gave about 13 % conversion after 4 hours, while the addition of activated carbon (AC) or CNT raised this marginally to 17 % and 21 % respectively. In each case hydroperoxide is the major product, next to smaller amounts of ketone and alcohol. It is noteworthy that only minor amounts of epoxide are formed, usually not the case when metal catalysts are involved. The NCNT drastically raised the conversion (59%) with ketone as the major product. This indicates that the catalyst acts on the hydroperoxide decomposition, which is the rate determining step in the autoxidation mechanism. A clear correlation could be seen between the N-content in the NCNT and the activity of the catalyst, more active and selective towards alcohol and ketone with higher N-content (Figure 1). Reusability after washing and drying at 110 °C of the catalyst was tested up to 5 cycles without loss in activity or selectivity, making this a cheap oxidation protocol.

Table 2. Catalytic performances of different carbon materials in cyclohexene oxidation

Catalyst	BET (m ² /g)	Conversion (%)	Selectivity (%)				
			A	B	C	D	E
Blank (uncatalyzed)	-	13.5	15.5	9.9	67.9	3.0	0.8
Activated Carbon (AC)	731.5	17.0	5.9	7.5	73.0	3.0	2.3
Carbon Nanotube (CNT)	127.8	21.0	7.1	8.1	62.9	2.2	1.2
Nitrogen doped CNT (NCNT) (4.36% N-content)	155.1	59.0	11.2	41.1	27.3	5.9	0.18

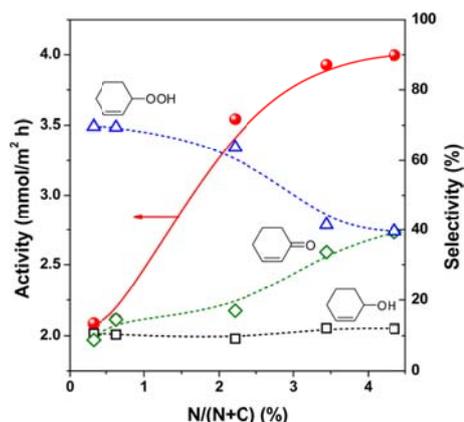


Figure 1. Dependence of activity and selectivity on the nitrogen content in NCNTs at ~20% conversion. Adapted with permission from Cao, Y.; Yu, H.; Peng, F.; Wang, H.; *ACS Catal.* **2014**, *4*, 1617-1625. Copyright 2014 American Chemical Society.

Hutchings studied the effect of support, metal and method of catalyst preparation on the oxidation of cyclic alkenes of different ring sizes using catalytic amounts of ^tBuOOH as initiator in air.⁸⁴ The results for 1%Au@SiO₂ and benchmark SiO₂ are listed in Table 3. The authors found that Au was superior to Pd or a Au-Pd alloy and that oxides provide a better support than graphite. Other oxides tested were TiO₂ and CeO₂. At higher temperatures the support itself can catalyze oxidation. In terms of the preparation method it was found that the procedure which provides the smallest particles (sol-immobilization) gave the best results. In general, smaller rings are more reactive towards oxidation, hence higher temperatures were used for the larger ones. This effect is caused by the degree of reorganization required to form a planar allyl radical and is independent of the catalyst system.⁸⁵ A selectivity shift from ketone and alcohol

towards epoxide was observed when the ring size increases. This shift in selectivity can be attributed to the inherent reactivity of the different rings.⁸⁶

Table 3. 1%Au@SiO₂-catalyzed oxidation of cyclic alkenes

n	T (°C)	Catalyst	Conv. (%)	Selectivity (%)		
				A	B	C
1	26	SiO ₂	0.2	25	49	20
1	26	1%Au/SiO ₂	5.2	44.8	11.5	9
2	50	SiO ₂	0	0	0	0
2	50	1%Au/SiO ₂	7.9	51.1	41.8	6.2
3	60	SiO ₂	2.5	44	34	21
3	60	1%Au/SiO ₂	14.1	40.5	41.5	18
4	80	SiO ₂	0.1	20	30	50
4	80	1%Au/SiO ₂	4.6	5	7.7	87.4
8	120	SiO ₂	7.4	6.9	-	93
8	120	1%Au/SiO ₂	8.6	35	-	60.9

The oxidation of alcohols is a frequently used reaction to test the potential of new heterogeneous catalysts. Its importance resulted in many reports covering basically all areas of solid materials such as polyoxometalates⁸⁷, metal oxides⁸⁸, clays⁸⁹ and deposited transition metals⁹⁰ as catalysts. Perovskites are porous mineral structures with a general formula ABO₃, A and B being respectively a small high-charged and a large low-charged cation. Their low cost and stability make them interesting for use in catalysis, as exemplified by SrMnO₃.⁹¹ Although they are typically employed at high temperatures, for example in exhaust gas purification, they can also be employed at mild temperatures. A porous perovskite-type catalyst for the oxidation of alcohols, La_{0.9}Ce_{0.1}CoO₃, was recently developed by Zhu and Carabineiro.⁹² Reusability was effective after calcining the catalyst at 500°C in an air oven. The choice of Ce⁴⁺ cation lays on its strong affinity to oxygen, and is supposed to enhance the mobility of surface oxygen participating in the reaction.

3.3 Organocatalysis

The area of organocatalyzed aerobic oxidation is dominated by *N*-hydroxyphthalimide (NHPI) with typical loadings starting from 20%. NHPI was first used by Masui as an electron carrier for the electrochemical oxidation of alcohols⁹³ and later adopted by Ishii for the oxidation of alkanes. While the majority of reactions employing NHPI are in combination with TM cocatalysts (e.g. Co⁹⁴, Mn⁹⁵, Cu⁹⁶ and Fe⁹⁷) or heterogeneous catalysts,⁹⁸ also other additives have been used as NHPI activator (e.g. peroxides,⁹⁹ SET reagents and light¹⁰⁰ or just thermal activation¹⁰¹) (Scheme 15). NHPI in aerobic oxidations has been reviewed extensively, the last one appeared in 2014.¹⁰² Its unique reactivity stems from the bond dissociation energy (BDE)

of the O-H bond (88.1 kcal/mol) which matches well with the C-H BDE in most organic molecules (85 – 100 kcal/mol), allowing for hydrogen atom abstraction (HAA) (Figure 2).¹⁰³ In contrast, the O-H BDE of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPOH) is only 69.6 kcal/mol. HAA of common C-H bonds by TEMPO is therefore unlikely, as the reaction is too endothermic to occur. Examples involving activated C-H, such as a benzylic oxidation using a recyclable TEMPO catalyst, have been reported.¹⁰⁴ TEMPO is more commonly used as cocatalyst in the oxidation of alcohols as the α-Hs feature a significantly lower BDE (see section 3.1).

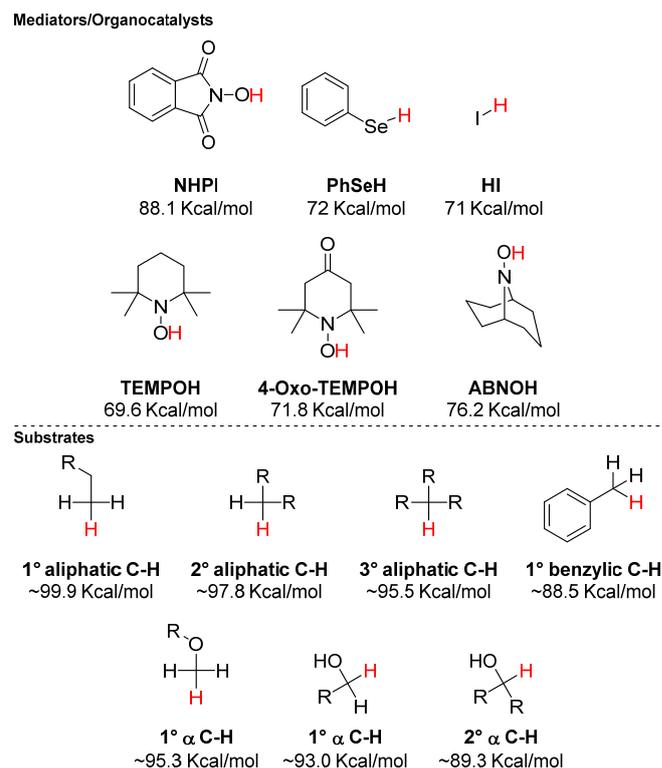
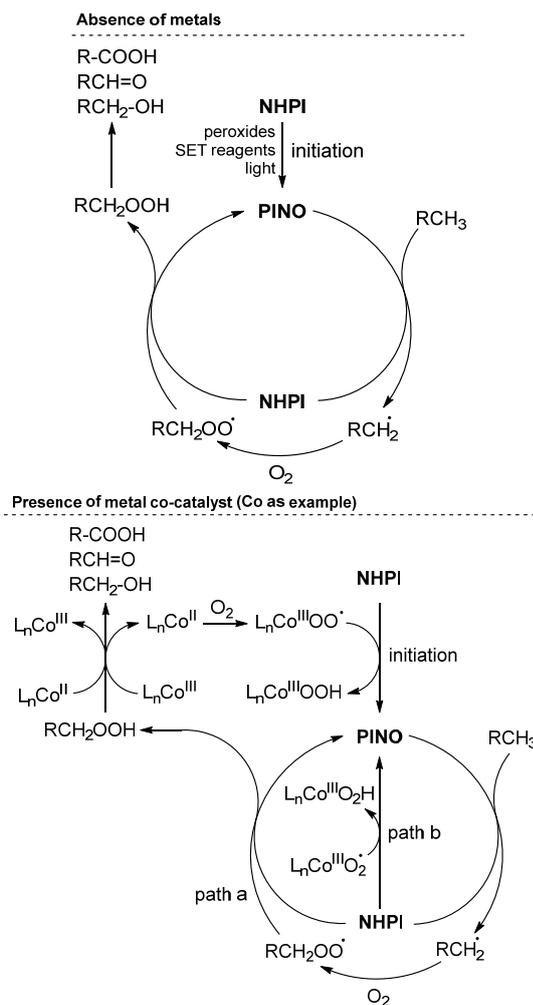


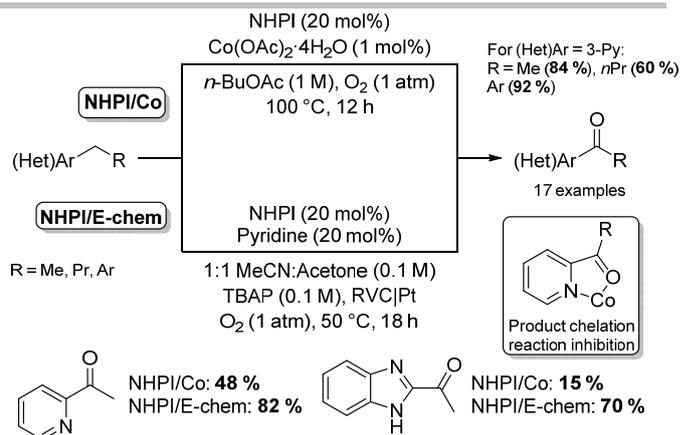
Figure 2. Homolytic BDEs of commonly used mediators/organocatalysts and substrate C-H's¹⁰⁵

Typical catalytic cycles for NHPI-catalyzed aerobic oxidation in the absence or presence of a TM are depicted in Scheme 15.¹⁰⁶ An initiation process converts NHPI to phthalimide *N*-oxyl radical (PINO). This step can be mediated by radical initiators or by TM/O₂. PINO is able to abstract a hydrogen atom from an organic substrate and is thus transformed back into NHPI. The formed organic radical will be trapped by O₂, generating a peroxy radical species, regenerating PINO by hydrogen abstraction from NHPI (path a). Alternatively, a TM can also be involved in the PINO regeneration (path b). The formed hydroperoxide is sometimes sufficiently stable to be isolated but when α-Hs are present usually *in situ* transformed into ketones/aldehydes via homo- or heterolytic O-O bond scission. TMs additionally catalyze the decomposition of the hydroperoxide.



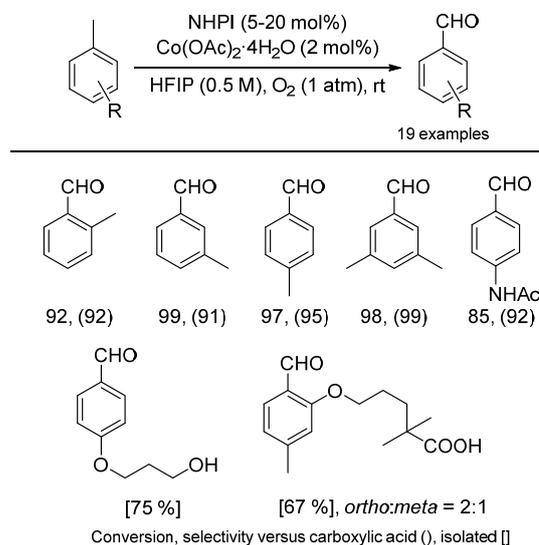
Scheme 15. General catalytic cycle of the NHPI-catalyzed C-H oxidation in the absence (top) or presence (bottom) of cocatalyst (Co as example)

A recent contribution from Stahl deals with benzylic oxidation using NHPI with a Co cocatalyst.¹⁰ Interestingly, due to the coordinating ability of some of the heteroarylketone products with Co, product inhibition was seen. Inspired by the original paper of Masui, electrochemical oxidation of NHPI was employed to overcome this problem (Scheme 16). Improved yields were achieved with this method for several chelating products, but this was not general, making the two methods somewhat complementary.



Scheme 16. Co(OAc)₂/O₂ vs. electrochemical activation of NHPI

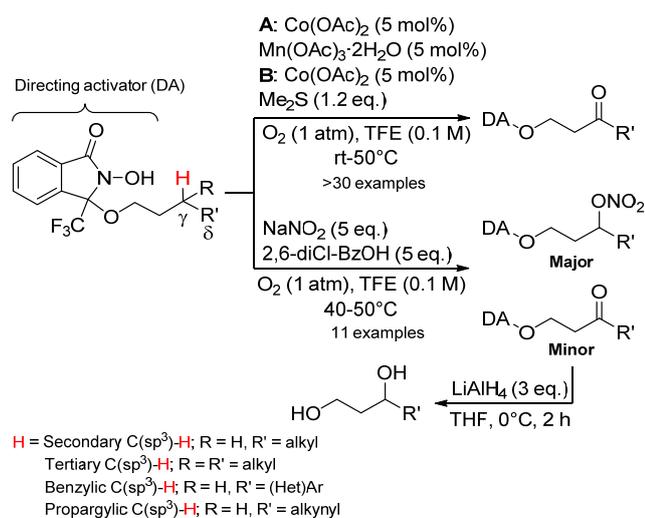
As benzaldehyde oxidizes more easily than toluene under aerobic conditions, problems with overoxidation often arise in the oxidation of methyl(hetero)arenes. The use of 1,1,1-3,3,3-hexafluoropropan-2-ol (HFIP) as solvent was shown by Pappo to allow high conversions with excellent selectivity towards the aldehyde (Scheme 17).¹⁰⁷ HFIP forms a strong hydrogen bond with the aldehyde product, thereby making the aldehyde hydrogen less susceptible to hydrogen atom abstraction, hereby preventing overoxidation.¹⁰⁸ Remarkably, when multiple methyl substituents were present the oxidation reaction also stopped after one oxidation. This resulted in a single product in the case of symmetrical methylarenes or in regioisomers in asymmetric substrates.



Scheme 17. Selected scope of the NHPI-catalyzed Co-cocatalyzed benzylic oxidation in HFIP

Due to the abundance of unactivated C(sp³)-H bonds with similar reactivity, chemo- and regioselectivity problems are generally expected in oxygenation through intermolecular activation. Moreover, low conversions are typically observed.¹⁰⁹ An elegant solution was devised by Oisaki and Kanai. A covalently bound NHPI analog acts as a directing activator (DA), allowing easier

and selective intramolecular activation of a specific C-H (Scheme 18).¹¹⁰ Oxygenation of benzylic, propargylic, tertiary and secondary C-H bonds with good regioselectivity for the γ and δ position depending on the substrate was possible. $\text{Co}(\text{OAc})_2$ was used as a cocatalyst either in combination with catalytic $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ or, in the case of tertiary C-H bonds, stoichiometric Me_2S , which acts as a reductant for the initially formed hydroperoxides. In a follow-up paper they proposed a metal-free alternative using superstoichiometric NaNO_2 in combination with an acid activator.¹¹¹ This method provided predominantly the nitrate esters with significant amounts of ketone present. The DA can be removed by reduction with LiAlH_4 , with concomitant reduction of the ketone, resulting in the formation of 1,3-diols.



Scheme 18. Intramolecular activation of $\text{C}(\text{sp}^3)\text{-H}$ bonds using an NHPI derived DA

While NHPI oxidations usually show good conversion and selectivity, they have not found their way to industrial application in commodity chemicals. Major drawbacks are low solubility in non-polar solvents, requiring acetonitrile or acetic acid as solvent. NHPI and PINO are unstable above 80°C and decompose into phthalimide, phthalic anhydride or form inactive trimers.¹¹² Recently, Punta examined the use of PINO in cumene oxidation.¹¹³ Addition of 1% of a polar solvent (MeCN) to 'neat' cumene was sufficient to get good conversions (>30%) and selectivity (>90%). The catalyst could be recovered by solvent evaporation, which caused 60-80% of the NHPI to precipitate. Treatment of the filtrate with Amberlyst basic supports (quaternary ammonium hydroxide) removes another ~80% of the remaining NHPI by physical interaction. The high cost of NHPI warrants full recovery to be economically competitive, leaving room for further research. Considering the high added value of fine chemicals and Intellectual Property on the application of the molecule, there are besides the safety aspects of working with O_2 principally no aspects preventing take up of this methodology in this sector.

Catalyst immobilization is another technique that can be applied to increase the stability and recoverability of NHPI. The support can also act as an initiator often avoiding the need of a cocatalyst as recently exemplified by García. Immobilization of NHPI on diamond nanoparticles (DH) allowed metal-free oxidation of benzylic hydrocarbons and cyclic alkenes (Table

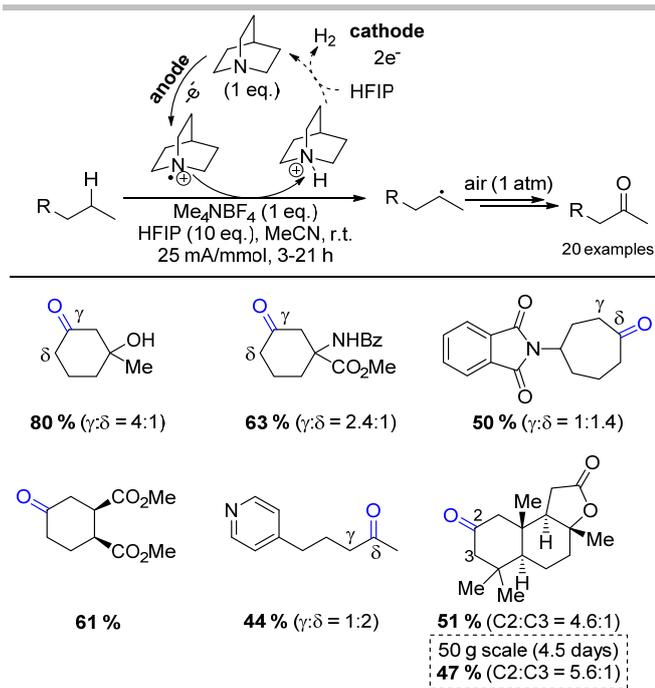
4).^{98b} Linkage was achieved by covalently anchoring 4-carboxy-NHPI to the DH, functionalized through Fenton hydroxylation, via esterification. The main advantage of the DH support is the inertness of its surface towards reactive oxygen species, in theory ensuring catalytic activity over many cycles. Reusability of the catalyst, after washing and drying, was shown up to three cycles, where in the third cycle a loss of activity was noticed due to leaching/degradation of NHPI. This could be deduced by a decrease of the characteristic band of the ester linkage (1735 cm^{-1}) in the IR spectra of the catalyst. An interesting aspect of this study is the very low NHPI loading versus substrate required (around 0.05 mol%).

Table 4. Conversion and selectivity for benzylic NHPI@DH-catalyzed oxidation^a

Substrate	Conversion (%)	Time (h)	Main reaction products	Selectivity (%)
Ph-CH ₂ -CH ₂ -CH ₃	97	24	Ph-C(=O)-CH ₂ -CH ₂ -CH ₃	95
			Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -OH	5
Ph-CH ₂ -CH ₂ -CH ₂ -CH ₃	83	5	Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₃	76
			Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -OH	17
Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	80	72	Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	80
			Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -OH	6
Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	55	24	Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	66
			Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -OH	29

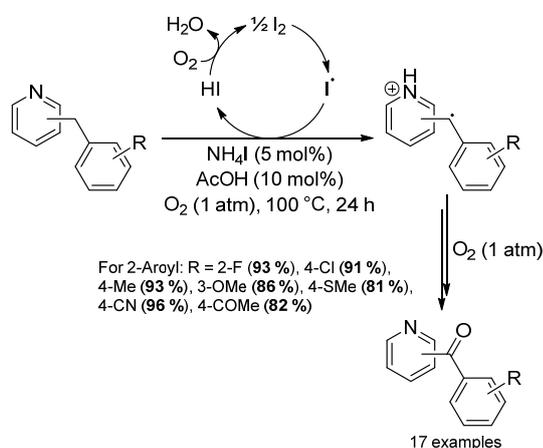
^aConditions: Catalyst (~4 wt% NHPI) (40 mg), substrate (20 mmol), O_2 (1 atm), 140 °C. NHPI/substrate = 5×10^{-4}

Selective intermolecular unactivated $\text{C}(\text{sp}^3)\text{-H}$ bond oxygenation featuring high conversion is very rare. Baran reported a remarkable electrochemical aerobic oxidation of unactivated $\text{C}(\text{sp}^3)\text{-H}$ bonds (Scheme 19), making use of a simple set-up based on inexpensive C and Ni electrodes.¹¹⁴ Electrochemical activation of the quinuclidine mediator allowed for very selective radical generation of unactivated $\text{C}(\text{sp}^3)\text{-H}$ bonds, often in the presence of more active positions. HFIP was identified as essential additive, proposed to serve as an electron acceptor to generate H_2 in the cathodic process. However, quinuclidine was added stoichiometrically to achieve high conversions and yields. Easy batch scalability was shown, exemplified by the oxidation of scalareolide, without any decrease in yield or selectivity. Considering the safety hazards of working with O_2 in MeCN (Table 1), electrochemical oxidations in flow would be the method of choice for larger scales.¹¹⁵



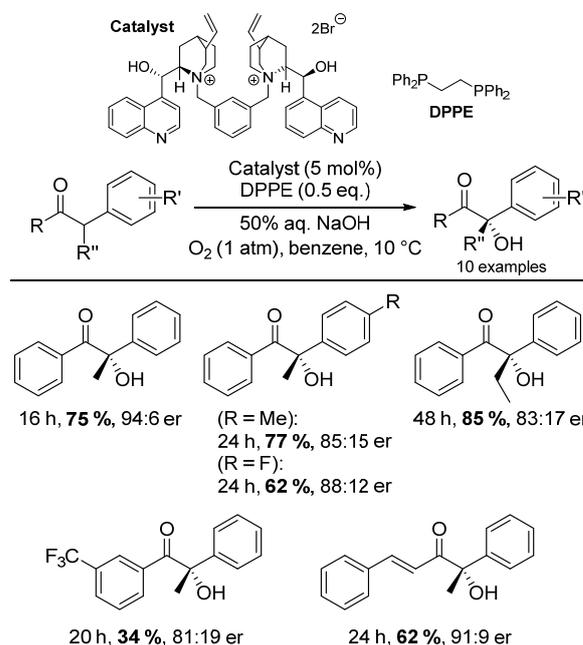
Scheme 19. Selected examples of the electrochemical oxidation of unactivated C(sp³)-H bonds with quinuclidine mediator

Iodine is an environment friendly and relatively inexpensive element making it interesting for use in catalysis. Although strictly not being an organocatalyst, it will be treated in this section due to the mechanistic similarities. As the BDE of HI is similar to TEMPOH (Figure 2), a similar HAA tendency can be expected.¹¹⁶ Oxidations making use of iodine as catalyst in combination with O₂ are therefore limited to activated C-H bonds.¹¹⁷ *In-situ* generated I₂ oxidizes a broad range of substituted benzylpyridines to the corresponding benzoylpyridines under solvent free conditions in excellent yields as reported by Gao (Scheme 20).^{117b} Electron paramagnetic resonance (EPR) studies confirm the involvement of a benzylic radical. In this case O₂ has a dual role, reoxidation of I⁻ and trapping of the radical. A similar set of substrates was subjected to oxidation using a Se organocatalyst (PhSeBr), thermally producing PhSe radical.¹¹⁸ PhSeH has a similar BDE (72 kcal/mol) as HI and TEMPOH (Figure 2).¹⁰⁵



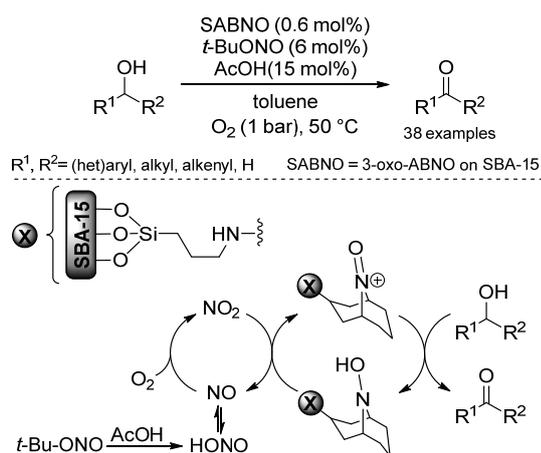
Scheme 20. I₂-catalyzed oxidation of benzylpyridines

Sufficiently acidic methylenes can be activated by an initial deprotonation, similarly to what has been described for oxygenations with TMs (Scheme 6).¹¹⁹ The mechanism by which these reactions proceed is obscure, and many articles propose a direct nucleophilic attack of the carbanion to O₂. This is unlikely due to the spin forbidden nature of this transformation at ambient temperature. Interestingly, the combination of a base and a chiral phase transfer catalyst allow enantioselective oxidation. Zhao reported enantioselective α -hydroxylation of both cyclic and acyclic ketones (Scheme 21).¹²⁰ The chiral induction occurs via ion pair interaction between the enolate of the substrate and the chiral organocatalyst. In order to avoid regioselectivity issues, only one α position of the ketone should be enolizable. A comprehensive review concerning enantioselective aerobic oxygenations appeared recently, giving a more detailed overview of this type of reactions.¹²¹



Scheme 21. Selected scope of the enantioselective phase transfer-catalyzed α -hydroxylation of acyclic ketones involving base

As mentioned above nitroxyl radical based TEMPO¹²² or ABNO¹²³ cocatalyst can be used in combination with Cu catalysts for aerobic oxidation of alcohols. They can also be used as organocatalysts in combination with other cocatalysts. Usually a nitrous acid (derivative) is added to generate NO cocatalyst (Scheme 22), however, it can also be generated *in-situ* by the reaction of alcohol with a mixture of NO and O₂.¹²⁴ A good example is the mesoporous silica supported 3-oxo-ABNO catalyst (SABNO) which interestingly showed similar reactivity compared to homogeneous 3-oxo-ABNO in the oxidation of alcohols as reported by Karimi. O₂ is involved in the NO reoxidation. Furthermore, catalyst was shown to be recyclable, after washing, up to 12 times with only a limited (~20%) loss in catalytic performance (Scheme 22).¹²⁵

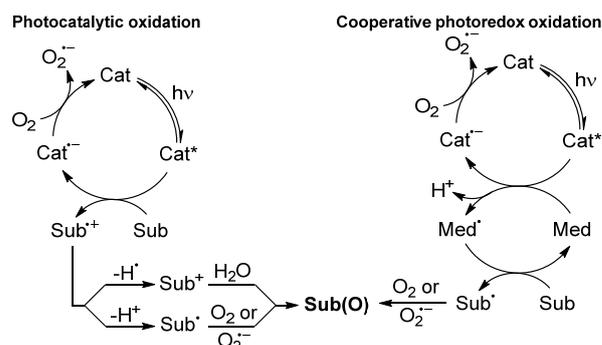


Scheme 22. Oxidation of alcohols using an immobilized 3-oxo-ABNO catalyst and NO cocatalyst

3.4 Photoredox catalysis

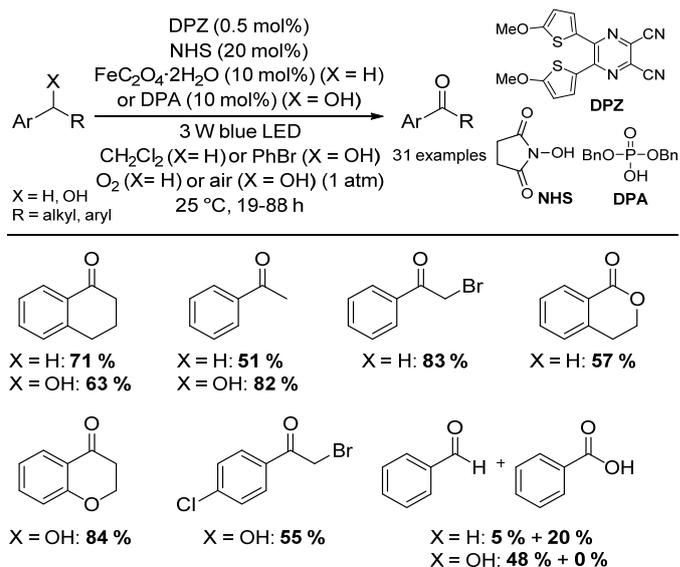
Light, and especially visible light, is the zenith of 'green' reagents as it generates no waste, is non-toxic and can be obtained from renewable sources. The combination of light with O_2 looks like a match made in heaven.¹²⁶ In its ground state, oxygen is in a triplet, denoted as $^3\text{O}_2$ (typically written as O_2),⁵ its singlet state ($^1\text{O}_2$) lies 95 kJ/mol higher in energy and can be formed through a combination of light and a photosensitizer. While $^1\text{O}_2$ possesses a very rich and distinct chemistry compared to $^3\text{O}_2$, we will not deal with these reactions here as they have been recently reviewed.¹²⁷ In the past, the activation of organic substrates was performed directly using high-energy UV radiation, which is less attractive.¹²⁸ The recent emergence of commercial UV LEDs will foster new innovations in this field.¹²⁹ However, there has been a major shift towards visible light photocatalysis. This term might be somewhat misleading, as the photons themselves are not catalytic, but are used to bring a catalyst to an excited state (called photocatalyst), which in turn activates the target substrate. Catalysts, either organic¹³⁰ or metal based,¹³¹ are designed to absorb at wavelengths in the visible range of the spectrum. A general mechanism for photocatalysis is depicted in Scheme 23. The catalyst is promoted to an excited state by a photon and oxidizes a substrate by removing an electron, creating a radical cation. In most cases O_2 is involved in the reoxidation of the photocatalyst, but depending on the specific mechanism other oxidants can also be used.¹³² In the reoxidation with O_2 , the superoxide formed can either react directly with the substrate radical or be further reduced to H_2O_2 and ultimately to H_2O . The substrate derived radical cation typically does not react directly but loses either a hydrogen atom by HAA or a proton. In the first case a cation is formed which can be quenched by a nucleophile, like water, to create a C-O bond.¹³³ In the latter case a carbon centered radical is formed which can react with a second molecule of O_2 or with superoxide, obtained in the catalyst reoxidation, to generate oxygenated products. While some photocatalysts can directly oxidize a substrate by an electron transfer, sometimes secondary catalytic mediators such as NHPI are used which will, after activation, abstract a hydrogen atom from the substrate and can subsequently be reoxidized by the

photocatalyst. This type of reactions is known as cooperative photoredox.¹⁰⁰ Most photochemical reactions are performed at room temperature, which is a big advantage towards safety aspects when working in air or O_2 , though flash points of most common organic solvents are even below this temperature (Table 1). Reactions making use of light are not easily scaled up as the reactor size is limited by the permeability of light; typically only a few centimeters in organic solvents. Performing these reactions in flow provides an elegant solution as flow reactors feature a high surface-to-volume ratio, allowing for efficient irradiation of the reaction mixture.¹³⁴



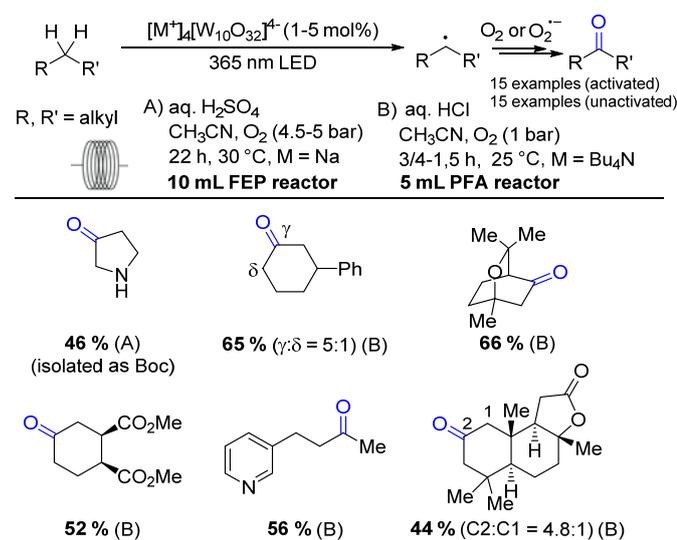
Scheme 23. Generalized mechanism of photocatalytic oxidation (left) and cooperative photoredox oxidation using a mediator (right)

An example of a cooperative photoredox oxidation is a benzylic oxidation using a dicyanopyrazine (DPZ)-derived photocatalyst in combination with *N*-hydroxysuccinimide (NHS) as the mediator (Scheme 24).^{100a} For the oxygenation reaction ($\text{X} = \text{H}$), Fe^{II} oxalate dihydrate is used as a Lewis acid to activate the NHS, while for alcohol oxidation ($\text{X} = \text{OH}$) the use of the Brønsted acid dibenzylphosphoric acid (DPA) proved more efficient.



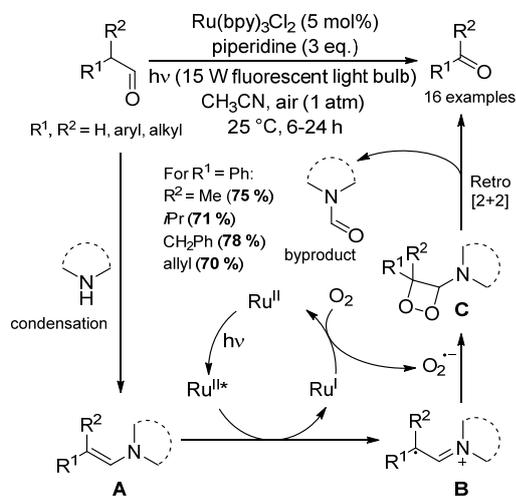
Scheme 24. Selected scope of benzylic $\text{C}(\text{sp}^3)\text{-H}$ oxidation using cooperative photoredox catalysis

Decatungstate has been used for photocatalytic oxidation of both activated and unactivated C(sp³)-H bonds with O₂ using 365 nm UV LED (Scheme 25). While for aliphatic amines acid avoids alpha oxidation via protonation, its addition is generally beneficial in other substrates. Flow reactors are crucial to obtain full conversions.¹³⁵ The species generating the radical can alter the possible products formed as exemplified for sclareloide with organocatalysis (C2:C3) (Scheme 19) versus photoredox (C2:C1) (Scheme 25).



Scheme 25. Selected scope of unactivated C(sp³)-H oxidation using photocatalytic oxidation

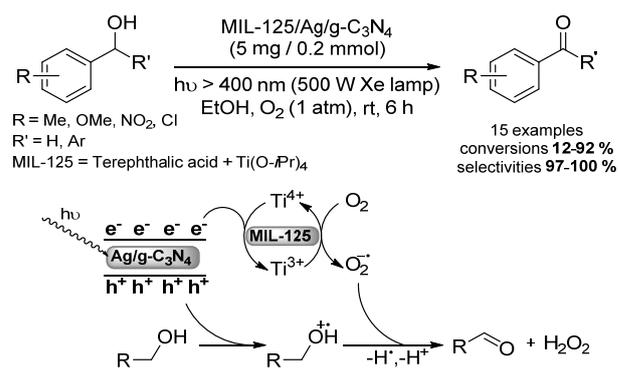
Oxidation can also involve C-C bond cleavage. A very mild oxidative deformylation of aliphatic aldehydes was reported by Xia (Scheme 26).¹³⁶ The mechanism of this transformation is thought to occur via the enamine **A**, formed *in situ* through condensation of the aldehyde with a secondary amine. Enamine **A** is then oxidized to the radical cation **B** through a reductive quenching process with photoactivated Ru(II)*. Reoxidation of the Ru catalyst by O₂, generates O₂^{•-}, which reacts with **B** to form 1,2-dioxetane **C**. A retro [2+2] cycloaddition in **C** produces the desired ketone/aldehyde and a formamide byproduct.



Scheme 26. Oxidative deformylation of aliphatic aldehydes via photoredox catalysis

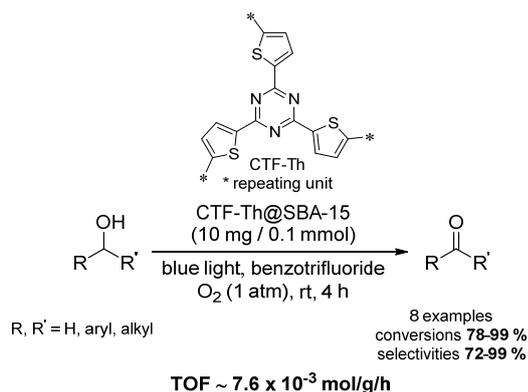
Heterogeneous catalysts with semiconducting properties are also frequently employed in combination with light.¹³⁷ The promotion of an electron from the valence band to the conduction band by an incoming photon generates an electron-hole pair where the positively charged hole can generate a substrate radical by taking up an electron. Alternatively, mediator radicals such as chlorine or hydroxyl radical can be generated in a similar way and be used to abstract a hydrogen atom from the substrate. Both methods generate a substrate radical which can be trapped by O₂/O₂^{•-} resulting in the formation of oxygenated products. The electron of the semiconductor gets captured by O₂, generating O₂^{•-}, reverting the catalyst back to its original state. Graphitic carbon nitride (g-C₃N₄), obtained by calcination of urea, was recently shown to be a suitable and recyclable photocatalyst in the oxidation of C(sp³)-H bonds.^{137f} Pure g-C₃N₄ is however a poor photocatalyst due to the fast recombination of charge-separated states, therefore carbon-nanodot doped g-C₃N₄ (CD-C₃N₄) was used to enhance the catalytic activity. Carbon nanodots are nanoparticles that possess fluorescent properties that make them suitable photocatalysts. Benzylic-, allylic-, and even unactivated cyclic C(sp³)-H bonds could be oxidized with this protocol under mild conditions in a two phase system of substrate and water.^{137f}

Charge-separation efficiency of g-C₃N₄ can also be increased when combined with Ag nanoparticles. Yang and Lei developed a heterostructured MIL-125(Ti)/Ag/g-C₃N₄ nanocomposite as photocatalyst for the oxidation of benzylic alcohols (Scheme 27).¹³⁸ Ag nanoparticles were used to increase the visible light absorption, and to create an electron-conduction bridge between MIL-125(Ti) and g-C₃N₄ to retard the recombination of charge-separated states. Both Ag nanoparticles and g-C₃N₄ absorb visible light and generate electrons and positive holes. The photoinduced electrons migrate to MIL-125(Ti) and allow the reduction of Ti⁴⁺ to Ti³⁺. O₂^{•-} is formed via electron transfer from Ti³⁺ to O₂. Alcohol substrates are converted into their corresponding cationic radicals by action of the photogenerated holes of g-C₃N₄ and Ag nanoparticles, and react further with O₂^{•-} to obtain the carbonyl product.



Scheme 27. Benzylic alcohol oxidation via photoredox catalysis with MIL-125(Ti)/Ag/g-C₃N₄ and simplified mechanism

Zhang developed a metal-free visible light promoted aerobic oxidation of primary and secondary alcohols using CTF-Th (thiophene-triazine framework) as organophotocatalyst (Scheme 28).¹³⁹ This catalyst has a low-energy HOMO, which increases its oxidation nature. Mesoporous silica was used as support as it dramatically increased conversions. The authors attribute this to the increase in surface area for the supported variant.



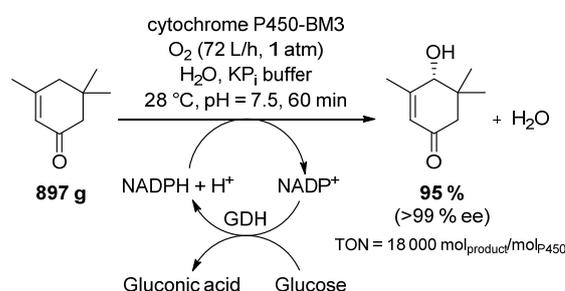
Scheme 28. Alcohol oxidation via photoredox catalysis with CTF-Th@SBA-15

3.5 Biocatalysis

The use of cell cultures to promote chemical transformations is a concept that is as old as civilization itself. The brewing of beer is believed to have already been practiced in ancient Mesopotamia as far back as 7000 BC. Up until the late 1970s only whole cells or cell extracts could be used to perform reactions since isolated enzymes could not be obtained in sufficient quantities.¹⁴⁰ Recombinant DNA technology now makes enzymes available in quantities that were previously unattainable, although several problems, such as insufficient stability under operating conditions, remain. While enzymes usually provide unrivaled chemo-, regio- and enantioselectivity compared to transition metal- and organocatalysis, their substrate scope is unfortunately usually very narrow and they often require the use of (stoichiometric) cofactors and/or coreductants. With the emergence of directed evolution these problems can now be mostly overcome. Directed evolution comprises cycles of gene mutagenesis, expression and selection of mutant enzyme for a desired parameter. Parameters such as organic solvent tolerance, stereoselectivity and substrate scope can thus be improved. As the majority of life is aerobic, a large pool of enzymes employing molecular oxygen as a reagent/reactant is available. Of special interest are the cytochrome P450 oxygenases (CYPs),¹⁴¹ present in all kingdoms of life. Mammalian CYPs can metabolize exo- and endogenous substrates into more polar, oxygenated, compounds and are important for both detoxification, as well as for controlling the level of hormones, cholesterol synthesis and vitamin D metabolism.

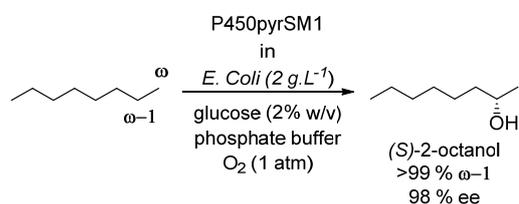
Upscaling of biocatalytic reactions hinges on the reusability of the enzyme.¹⁴² This has caused the area of heterogeneous biocatalysis (immobilized in or on solid carriers), to dominate the field, as these can be easily recovered by filtration.¹⁴³ It should be noted however that while the enzymes may be recoverable, the cofactors are often not so, meaning they need to be added in each batch. A large scale synthesis of (*R*)-4-hydroxyisophorone using a whole cell paste containing wild type (non-engineered) CYPs enzymes from *Bacillus megaterium* was reported by Kaluzna (Scheme 29).¹⁴⁴ To avoid superstoichiometric addition of NADPH cofactor in this oxidation reaction, heterologous coexpression of a glucose dehydrogenase (GDH) was used to allow cofactor regeneration with glucose. This process was limited by O₂ mass transfer and self-deactivation of the catalyst. Catalyst recovery and reuse were not attempted. Bühler

presented an elegant solution to the problem of O₂ mass transfer limitation.¹⁴⁵ By engineering the phototrophic cyanobacterium *Synechocystis* sp. PCC6803 to synthesize alkane monooxygenase AlkBGT from *Pseudomonas putida* Gpo1, light can be used to generate O₂ *in situ* through oxygenic photosynthesis. The O₂ produced is trapped within the cell and is thus readily available to bind with the monooxygenase for oxygenation. The authors used this cellular machinery to convert methyl nonanoate to methyl ω-hydroxynonanoate in a regioselective manner. While the results are a proof-of-concept for coupling between photosynthetic O₂ evolution and oxidation reactions, further optimization is still required. Indeed, the increase in reaction rate compared to a “dark” reaction where O₂ was not generated *in situ*, but provided from the atmosphere, is rather small (1.5 ± 0.2 Vs. 1.3 ± 0.0 μmol·min⁻¹·g⁻¹). Alternatively, O₂ supersaturation can be achieved by combining an oxidation reaction with *in situ* biocatalytic decomposition of H₂O₂ in a flow reactor. This greatly increased the space-time yields in the enzymatic oxidation of benzylic alcohols.¹⁴⁶



Scheme 29. Monooxygenase-catalyzed allylic hydroxylation of α-isophorone

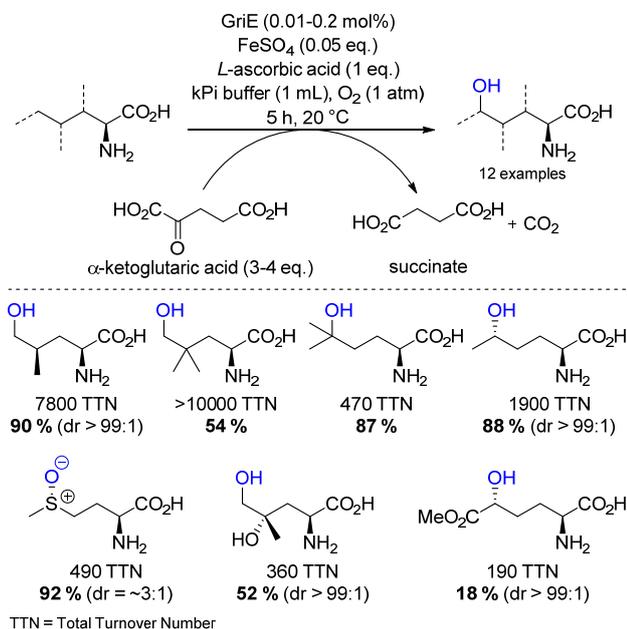
An example of directed engineering was reported by Li where terminal-selective (ω) cytochrome P450pyr was engineered for the subterminal (ω-1) hydroxylation of octane with excellent regio- and enantioselectivity in 6 mutation cycles (Scheme 30).¹⁴⁷ A calorimetric high throughput screening assay was developed to measure the respective selectivities of the screened mutants. Additionally, the authors provided structural information of the binding pocket of both the wild-type and mutant enzyme to elucidate the mode of binding and the change in selectivity. Glucose is added for co-factor regeneration.



Scheme 30. Monooxygenase-catalyzed C2 hydroxylation of octane

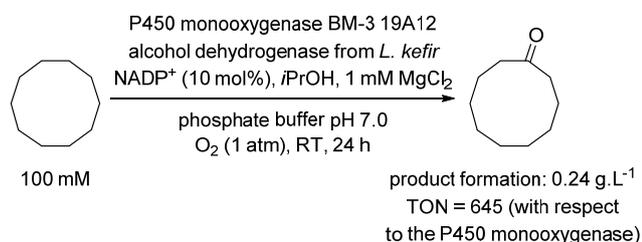
In contrast to monooxygenases, which incorporate one O-atom in the substrate and convert the other to H₂O, dioxygenases incorporate both O-atoms into an organic substrate, albeit not necessarily the same one. Such an enzyme was recently used in the selective δ-C-H hydroxylation of aliphatic amino acids by Renata (Scheme 31).¹⁴⁸ For this reaction an α-ketoglutarate-dependent (αKG) dioxygenase was used in combination with ferrous salts and ascorbic acid. αKG acts as an acceptor for the

second O-atom and is oxidized to succinate and CO₂. The enzyme (GriE) was added pure and not as a cell extract; however during its purification from the cell extract mostly apoenzyme was obtained, explaining the need to add FeSO₄ separately. Ascorbic acid is added to reduce Fe^{III} salts, resulting from oxidation of Fe^{II} by O₂ back to catalytically active Fe^{II}.



Scheme 31. Selected scope of dioxygenase-catalyzed amino acid hydroxylation

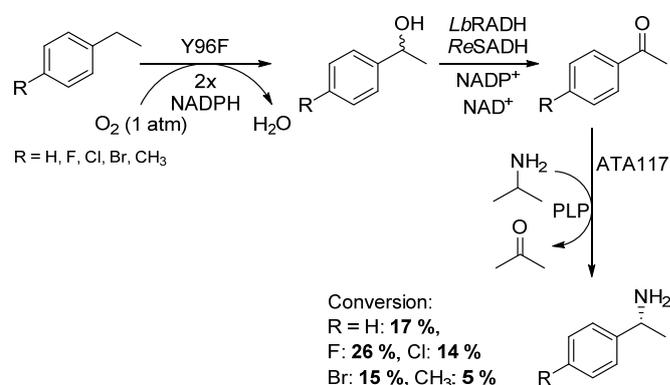
While oxidation by an oxygenase type enzyme results in the formation of alcohols, further oxidation to ketones requires the addition of an alcohol dehydrogenase.¹⁴⁹ This can be achieved in *one-pot* as exemplified by the double oxidation of cycloalkanes reported by Gröger (Scheme 32).¹⁵⁰ First, cycloalkane is hydroxylated with concomitant oxidation of the cofactor NAD(P)H to NAD(P)⁺. Then the alcohol dehydrogenase converts the cycloalkanol to the desired cycloalkanone and hereby recovers the NAD(P)H. This is more interesting than relying on a sacrificial dehydrogenase such as glucose dehydrogenase (GDH, Scheme 28). Besides cyclodecane also cyclohexane and cyclooctane proved suitable substrates. Both enzymes were added as a lyophilized crude extract.



Scheme 32. Cascade monoxygenase and dehydrogenase oxidation of cyclodecane

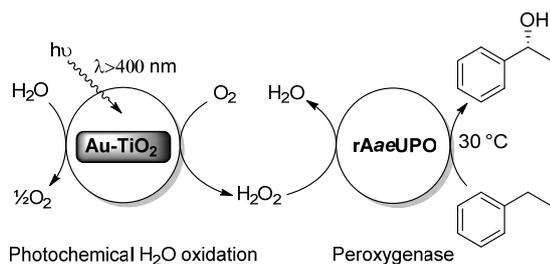
These multienzyme cascades can also be performed inside a single cell organism as exemplified by the stereoselective C-H amination of ethylbenzenes reported by Flitsch (Scheme 33).¹⁵¹

This cascade uses four heterologously expressed recombinant enzymes with cofactors provided by the host cell and isopropyl amine as the amine donor. The initial C-H activation is performed by a CYP monoxygenase (Y96F) and results in the non-stereoselective hydroxylation of the benzylic position. This step is also thought to be the rate determining step in the entire sequence, as starting from benzylalcohol results in a much faster reaction. In the second step two alcohol dehydrogenases with complementary stereoselectivity are employed. *Lb*RADH from *lactobacillus brevis* oxidizes *R*-alcohols using NADP⁺, while *Re*SADH from *rhodococcus erythropolis* oxidizes *S*-alcohols using NAD⁺ as the cofactor. Finally, an ω -transaminase (ATA117) converts the acetophenones products into the corresponding amines in an enantioselective fashion using pyridoxal 5'-phosphate (PLP) coenzyme and *i*PrNH₂ (IPA) as an amine donor. IPA was found to inhibit the first step of the cascade and had to be added after 24 h.



Scheme 33. Reaction cascade inside *E. coli* harboring a monoxygenase, *R*- and *S*-selective alcohol dehydrogenase and an ω -transaminase

The requirement of (super)stoichiometric reducing agents such as NAD(P)H or FADH₂ for activation of O₂ at the enzyme's active site is a common feature of all monoxygenases. These reductants can also get consumed in several side reactions via O₂ reduction, known as *uncoupling*, which additionally causes the formation of reactive oxygen species (ROS) giving rise to more side reactions and reductant waste.¹⁵² In contrast, peroxygenases do not require reducing agents, as H₂O₂ is an already reduced form of O₂, and are able to perform similar oxidations as monoxygenases. These enzymes are however unstable if large concentrations of H₂O₂ are present, making *in situ* generation a necessity.¹⁵³ The synthetic viability was recently shown by Hollmann, combining photocatalytic H₂O₂ generation from H₂O with an anatase-Au-TiO₂ photocatalyst with *rAae*UPO peroxygenase-catalyzed stereoselective hydroxylation of ethylbenzene (Scheme 34).¹⁵⁴ Due to low concentrations of the substrate the system still suffers from low space-time yields making it unlikely to be economically feasible. The catalytic turnover of the enzyme is however excellent and exceeds that of established CYP monoxygenases.



Scheme 34. Photochemical H₂O oxidation generating H₂O₂ from O₂ to promote peroxygenase-catalyzed hydroxylation of ethylbenzene

In contrast to protein engineering techniques the use of decoy molecules can be applied to broaden the substrate scope of wild-type CYPs. CYPs recognize their specific substrates by intermolecular interactions in the binding pocket. The binding of a substrate activates the enzyme to perform the oxidation reaction, which in itself can be quite aselective. By adding an inert decoy molecule that binds and thereby activates the enzyme, catalytic turnover for a non-native non-binding substrate might be achieved. This method was applied by Watanabe in the hydroxylation of small gaseous alkanes, ethane and propane, using wild-type P450BM3 as catalyst and *N*-perfluoroacyl amino acids (PFCs) as decoys.¹⁵⁵ Hydroxylation rates of respectively 45.min⁻¹.P450⁻¹ and 256.min⁻¹.P450⁻¹ could be achieved with *N*-perfluorononanoyl-*L*-leucine.

4. Summary and outlook

In the last 5 years major advances have been made in catalytic aerobic oxidation of C(sp³)-H bonds. Both with homo- and heterogeneous catalysts interesting transformations and mechanistic insights have been disclosed. While transition metal catalysis still dominates the field, areas such as photoredox, organocatalysis and biocatalysis have received much attention. These also often occur in combination with a TM co-catalyst. Achieving aerobic regio-/chemoselective oxidation of a specific unactivated C(sp³)-H bond remains a challenge, though a few excellent examples have appeared which will surely stimulate more research in this fascinating area. Selectivity is still mostly substrate controlled, but innovative solutions to switch innate oxygenase reactivity in a molecule will be the next horizon of research. For example, (reactive) directing groups offer the inherent potential to achieve this challenging goal with organocatalysis. Like with every auxiliary tool, an efficient removal/recovery strategy is crucial for successful application in synthesis. Directed evolution of enzymes is another way to obtain selectivity but suffers from drawbacks such as narrow substrate scope when high conversions and yields are required. Furthermore, it is a specialized technique not yet commonly present in the toolbox of an organic chemist.

The heterogenization of homogeneous catalysts has been illustrated by some interesting examples providing an easy way to allow catalyst recovery. The macroscopic nature of the catalyst or carrier however provides other still mostly unexplored opportunities. It holds potential to generate a confined reaction center that can induce high regio-/chemoselectivity which can at present only be achieved in biocatalysis. Moreover, when chirality is introduced near the active site, stereoselective

oxidation should also be feasible. To achieve this level of control major developments in the precise synthesis of catalysts and nanostructured materials are needed. This would allow the synthesis of catalysts systems that are able to promote multiple reactions in sequence, akin to synthetic biology, ideally without influencing each other. It can be achieved either by having the different active sites in one heterogeneous catalyst or by addition of several with each performing a specific chemical transformation.

For reactions on simple unfunctionalized building blocks for commodity chemicals TOF values are typically reported, but such data is generally missing for more complex substrates making it difficult to judge whether the catalyst is suited for implementation in the industrial production of active ingredients (AIs). While commodity chemicals typically require TOF values >10 000 h⁻¹, >100 h⁻¹ is usually sufficient for AIs.¹⁵⁶ Asymmetric aerobic oxidation of a specific unactivated C(sp³)-H bond using chemocatalysis is still virgin territory, though several interesting studies with activated C(sp³)-H bonds have been published. In biocatalysis this is more common and multiple enantioselective examples have been disclosed. Considering the interest of the pharmaceutical and agrochemical industry to go beyond the typical 2D environment of molecules and fully exploit 3D space (the so-called “escape from flatland”), this is a priority area.

In comparison to oxygenase, oxidase type reactions transforming alcohols into ketones/aldehydes is a more mature field. When multiple alcohols are present a good distinction can usually be made between them by careful selection of the catalyst. Organocatalysis is a preferred technique though stability of the catalyst can hamper industrial application. Tandem catalysis for further transformation of the carbonyl products increases the synthetic potential as illustrated by amide synthesis from primary alcohols. The chiral environment of a biocatalyst offers a limited value in these reactions, as chirality is lost upon oxidation, however in multi-enzyme cascades it can still be useful.

The abundance and low price of O₂ and production of water as byproduct make it an ideal oxidant. However, considering it can form combustible mixtures with organic vapors, its use does not seem self-evident and safety is a special point of concern when scaling-up. Given the know-how from commodity chemicals (where aerobic oxidations are common practice) and the introduction of flow chemistry in the fine chemicals industry, this is not an unsurmountable obstacle and O₂ is therefore expected to become the first choice oxidant of the future.

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Keywords: aerobic • oxidation • oxygen • catalysis • C(sp³)-H bonds

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