The Baeyer−Villiger Reaction: New Developments toward Greener Procedures

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1. Introduction

In 1899, Adolf Baeyer and Victor Villiger reported the oxidation of menthone to the corresponding lactone (Figure 1) using a mixture of sodium persulfate and concentrated sulfuric acid (Caro's acid).[1] The persulfuric acid was subsequently replaced by an organic peracid, and the Baeyer−Villiger (BV) reaction became one of the most well-known and widely applied reactions in organic synthesis.[2,3] Its success is largely due to its versatility: (i) A variety of carbonyl compounds can be oxidized; that is, ketones are converted into esters, cyclic ketones into lactones, benzaldehydes into phenols, or carboxylic acids and α-diketones into anhydrides. (ii) A large number of functional groups are tolerated. (iii) The regiochemistry is highly predictable with the migratory aptitude being tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > CH_3.[4] (iv) The reaction is generally stereoselective; that is, the migrating group retains its configuration. (v) A wide range of oxidants may be used with their activity decreasing in the order: CF_3CO_3H > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > *m*-CPBA ∼ HCO_3H > $C_6H_5CO_3H$ > CH_3CO_3H ≫ H_2O_2 > *t*-BuOOH.

Although more than a century has gone by since its discovery, the BV reaction is far from being at the end of its development. The standard protocol for a BV oxidation suffers from several disadvantages. The use of an organic peracid results in the formation of one equivalent of the corresponding carboxylic acid salt as waste, which has to be recycled or disposed of (returning it to the manufacturer of the peracid is generally not an option). Moreover, organic peracids are expensive and/or hazardous (because of shock sensitivity), which limits their commercial application. For example, the transport and storage of peracetic acid have been severely curtailed, making its use prohibitive. Consequently, increasing attention has been focused on the in situ generation of organic peracids, via reaction of either the corresponding aldehyde with oxygen or the carboxylic acid with hydrogen peroxide. In an alternative approach, the use of an organic peracid is dispensed with altogether by employing hydrogen peroxide in the presence of a catalyst. A prerequisite for success is that the method should be amenable to the use of commercially available (30 or 60%) aqueous hydrogen peroxide and preferably avoid the use of environmentally unattractive solvents such as chlorinated hydrocarbons. If successful, such a method would circumvent both the environmental and the safety issues associated with the classical BV oxidation.

In short, there is a definite need for a green BV oxidation procotol, which utilizes aqueous hydrogen peroxide as the stoichiometric oxidant in an environmentally attractive solvent or (preferably) under solvent-free conditions. From the viewpoint of scope in organic synthesis, the method should also exhibit high degrees of chemo-, regio-, and enantioselectivity and broad substrate specificity.

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Isabel W. C. E. Arends (born 1966) studied chemistry at the University of Leiden (The Netherlands), where she received her Ph.D. in physical organic chemistry in 1993, under the supervision of Professor R. Louw and Dr. P. Mulder. Postdoctoral work followed with Professor K. U. Ingold at the National Research Council in Canada on liquid phase oxidations catalyzed by biomimetic iron complexes. She joined the group of R. A. Sheldon in 1995, where she was appointed Assistant Professor in 2001. Her research interests focus on enzyme- and metal-catalyzed redox reactions and green selective oxidations employing O_2 and H_2O_2 in particular.

Roger Sheldon (1942) received a Ph.D. in organic chemistry from the University of Leicester (United Kingdom) in 1967. This was followed by postdoctoral studies with Professor Jay Kochi in the United States. From 1969 to 1980, he was with Shell Research in Amsterdam, and from 1980 to 1990, he was R&D Director of DSM Andeno. In 1991, he moved to his present position as Professor of Organic Chemistry and Catalysis at the Delft University of Technology (The Netherlands). His primary research interests are in the application of catalytic methodologies—homogeneous, heterogeneous, and enzymatic—in organic synthesis, particularly in relation to fine chemicals production. He developed the concept of E factors for assessing the environmental impact of chemical processes.

Consequently, in this review, we will focus on green BV reactions using hydrogen peroxide. In the first part, some general features of reactions with hydrogen peroxide and dioxygen are delineated. In the second part, the mechanism of the BV reaction is analyzed to identify ways in which a catalyst might improve the reaction. In the third part, reactions catalyzed by homogeneous catalysts, biocatalysts, and heterogeneous catalysts are discussed.

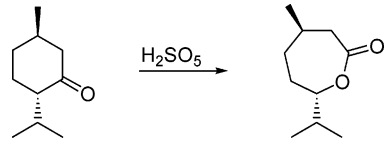


Figure 1. Oxidation of menthone with Caro's acid.

2. H_2O_2 and O_2 as Green Oxidants

2.1. Hydrogen Peroxide

The above-mentioned drawbacks of the classical BV reaction have stimulated considerable activity—especially in the past few years—in the development of catalysts that employ hydrogen peroxide as a clean oxidant.[3b,5] The use of hydrogen peroxide has many advantages: it is safe and cheap, the active oxygen content is high, it does not require a buffer, and it is clean, since the byproduct formed is water. These points make the use of hydrogen peroxide extremely interesting from an industrial (large-scale) point of view. However, there are some disadvantages concerning the use of hydrogen peroxide.[6]

(i) Because water is always present in solution, hydrolysis of the product esters may occur, and not all substrates are therefore compatible with water. (ii) Hydrogen peroxide is one of the weakest oxidants of a wide range of available peroxides and peracids (see above), and a catalyst is required to activate it. (iii) Some catalysts show a low selectivity on hydrogen peroxide. This may cause the formation of unselective hydroxy or hydroperoxy radicals. Furthermore, pure dioxygen may evolve from H_2O_2 decomposition, causing a build-up of pressure and creating a potentially unsafe combination with flammable organic solvents. (iv) High concentrations of hydrogen peroxide (>40% mol/mol) in organic solvents are unsafe.

To avoid dangerous situations as mentioned in points iii and iv above, Jones[6] recommends adhering to the following checklist: (i) Avoid any contamination in the reaction vessel (which may induce an uncontrolled reaction). (ii) Avoid build-up of oxygen pressure (by venting and flushing with N_2). (iii) Keep the concentration of the peroxo compound below 20% mol/mol (by presetting the reaction temperature, adding the peroxo compound last,[7] stirring the reaction mixture, making sure that the peroxo compound reacts completely before adding more, and providing cooling if required). (iv) Destroy excess peroxo compound before work-up. (v) Never use acetone or other low boiling ketones as the solvent for cleaning or extraction.

2.2. Dioxygen

Free radical autoxidation of an aldehyde is facile and affords the corresponding peracid. In the presence of a reactive substrate, e.g., an olefin or a ketone,

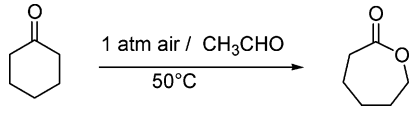


Figure 2. Mukaiyama oxidation of cyclohexanone to caprolactone.

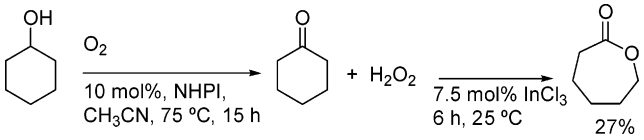


Figure 3. "Aerobic" BV reaction of KA oil.

the peracid can transfer an oxygen atom to the substrate, resulting in the formation of one equivalent of epoxide or ester and acid. Oxidations involving the in situ formation of a peracid from an aldehyde and dioxygen are generally referred to as the Mukaiyama method.[8] One industrial route to ϵ-caprolactone, for instance, involves the in situ formation of peracetic acid from acetaldehyde (Figure 2).[9] The use of metal catalysts is optional,[10] and the combination aldehyde/dioxygen is often not significantly different from peracids, although it should be noted that radical type chemistry may take place instead of the intended BV reactions. In alcoholic solvents, radical type side reactions are suppressed to a certain extent.[11]

Recently, Ishii[12] reported on the "aerobic" BV oxidation of a cyclohexanol/cyclohexanone mixture (KA oil) to yield lactones (Figure 3). However, in this reaction, cyclohexanol is first oxidized to give cyclohexanone and hydrogen peroxide and the latter is used as the true oxidant in the BV reaction.

The latter method—using O_2 for the in situ formation of hydrogen peroxide as the actual oxidant—has been receiving much attention over the past years because it is cheaper than hydrogen peroxide itself.[13]

3. Theoretical Considerations

3.1. Mechanism of the Reaction

For an in-depth discussion on the mechanism of the BV reaction, we refer to the excellent reviews of Krow[2] and Meunier.[3a] A few key issues are briefly mentioned here. The generally accepted mechanism for the BV oxidation is a simple two-step reaction that involves the so-called Criegee intermediate or adduct. In the first step, a peroxide attacks the polarized C=O bond. The second step follows a concerted pathway (Figure 4). Only with acylperoxo type oxidants can the hydroxyl proton in this intermediate migrate intramolecularly. Hence, these oxidants are more effective than alkylperoxo type oxidants, which generally require a catalyst.[14]

It should be noted that in many reactions the two steps have activation energies that are in the same order of magnitude. Hence, catalysts may need to facilitate both steps of the reaction. With some exceptions,[15] the rearrangement step is usually rate limiting.[16]

In the Criegee intermediate, a proper alignment is required for the rearrangement step: The migrating group R^M needs to be antiperiplanar[17] to the O–O

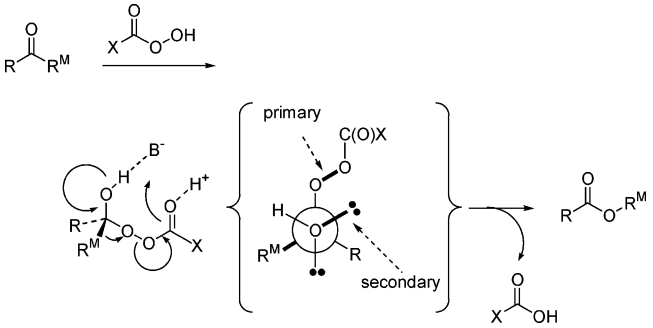


Figure 4. Mechanism for BV reaction as proposed by Criegee. R^M is the migrating group.

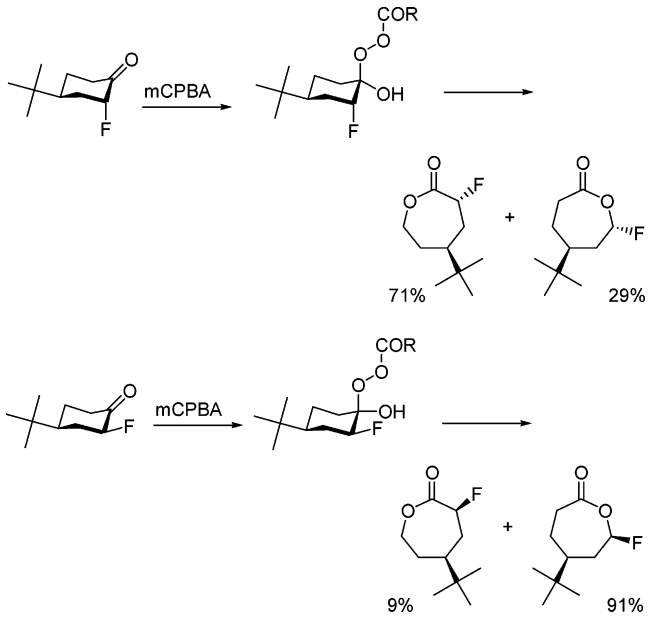


Figure 5. BV oxidation of *trans*- and *cis*-4-*tert*-butyl-2-fluorocyclohexanone.

bond of the leaving group (primary stereoelectronic effect) and antiperiplanar to a lone pair of the hydroxyl group (secondary stereoelectronic effect). In 1980, Noyori[18] provided evidence for the existence of the secondary effect, but compelling evidence for the primary effect was not yet available.[19] Criegee rearrangements in allyl hydroperoxides[20] already hinted at such an effect, but in 2000, Crudden et al. showed its existence in a true BV oxidation of *trans*- and *cis*-4-*tert*-butyl-2-fluorocyclohexanone (Figure 5).[21]

When the 2-fluoro substituent in 4-*tert*-butyl-2-fluorocyclohexanone is aligned in an axial position, differences in dipole effects in the various conformations are minimal and do not influence the migration of either the CH_2 or the CHF group. In this case, a normal product distribution[22] is observed and the electron-rich CH_2 group migrates preferentially. However, when the 2-fluoro substituent is placed in an equatorial position, the conformation with CH_2 antiperiplanar to the O–O bond creates an unfavorable dipole interaction of the perester with the CHF group. In this case, the electron-poor CHF group can achieve the required alignment more easily and is "forced" to migrate. Thus, at least in these cases, the primary stereoelectronic effect is more important than the migratory aptitude.[23]

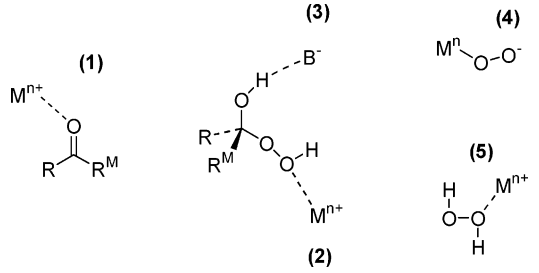


Figure 6. Electrophilic and nucleophilic activation of the BV reaction.

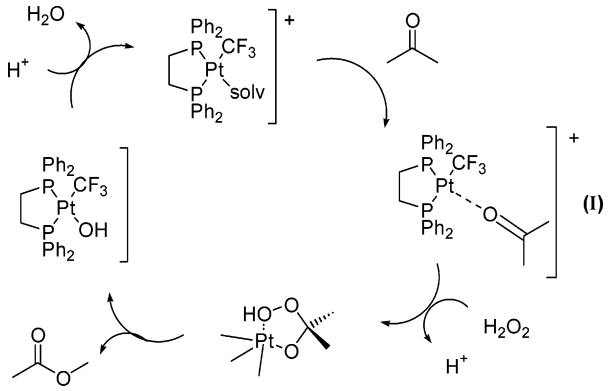


Figure 7. BV oxidation with $(dppe)Pt(CF_3)]^+$.

A more detailed mechanism (Figure 6) shows the possible mechanisms by which catalysts may improve BV reactions. Here, one can distinguish (1) electrophilic activation of the substrate, (2) electrophilic activation of the intermediate, (3) nucleophilic activation of the intermediate, (4) nucleophilic activation of (hydrogen) peroxide, and (5) electrophilic activation of (hydrogen) peroxide.

3.2. Electrophilic Activation of Substrate

The action of acids (H^+ or metal cations) is in part to activate the carbonyl functionality toward nucleophilic attack of peroxide or peracid via increasing the polarization of the C=O double bond (Figure 6, intermediate 1). Therefore, the combination CF_3CO_3H/CF_3CO_2H gives one of the most reactive peracids, even though $CF_3CO_3^-$ is a weak nucleophile, reluctant to attack the polarized carbonyl functionality. Indeed, in a buffered solution, the activity of CF_3CO_3H is strongly diminished indicating that an improved leaving group effect of CF_3COO^- may not be important. Other work, however, indicated that electron-withdrawing substituents on the leaving group did actually facilitate rearrangement, an effect observed in oxidation both with peracids[24] and with hydrogen peroxide.[3b]

One example of transition metal-catalyzed electrophilic activation of substrates is the platinum−CF_3 system, described below, which was developed in the group of Strukul (Figure 7).[25] Activation of the ketone via coordination to Lewis acids seems to be the most general way to activate substrates for BV oxidation.

In this case, the ketone coordinates to an electron-poor platinum center and becomes susceptible to attack of free hydrogen peroxide (intermediate **I**). This activation is somewhat reminiscent of activation of α,β-unsaturated ketones in Diels−Alder reactions.

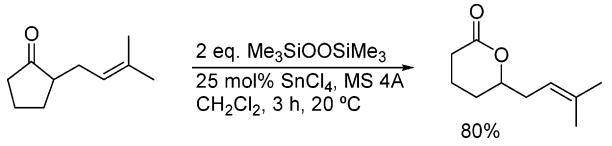


Figure 8. Lewis acid-catalyzed oxidation of 2-(3-methyl-2-butenyl)cyclopentanone.

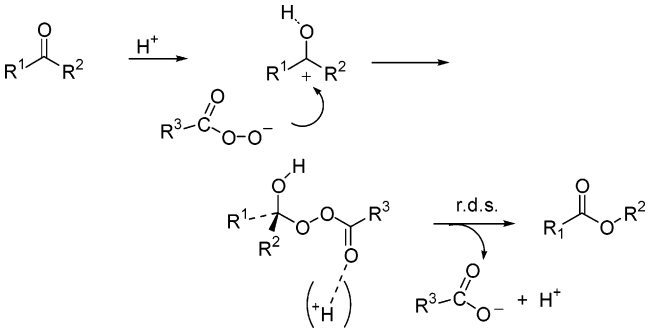


Figure 9. Acid-catalyzed BV oxidation with peracids as the oxidant.

Not surprisingly, cationic platinum complexes of (chiral) diphosphines proved to be active in this reaction as well.[26] To our knowledge, catalysts that are typically successful in Diels−Alder reactions, such as lanthanides, are rarely used to activate ketones for BV reactions with H_2O_2,[27] although these water stable Lewis acids seem to meet all of the requirements for a successful BV reaction. Other Lewis acids such as gallium(III) or tin(IV) chloride are too water sensitive and have mainly been successful under anhydrous conditions with, e.g., bis(trimethylsilyl)peroxide as the oxidant (Figure 8).[28,29]

Clearly, the method is far from green. Corma et al.[30] developed solid tin catalysts that are water stable and use hydrogen peroxide as the oxidant (see later under solid Lewis acids).

3.3. Electrophilic Activation of Intermediate

In BV reactions with peracids as oxidants, strong acids, such as CF_3CO_2H, may also catalyze the rearrangement step via protonation of the carbonyl functionality of the leaving group (Figure 9). As this rearrangement step is usually rate limiting, the catalyst has a large effect here.

Activation of the intermediate hydroperoxy adduct is similar to activation of the acylhydroperoxy intermediate. A Lewis acid may also facilitate the migration step, via coordination or protonation of the hydroxide (alkoxide), which is otherwise a very poor leaving group. This is again illustrated with the $(dppe)Pt(CF_3)]^+$ complex where the platinum center facilitates the rearrangement step via coordination to hydroxide (Figure 7, intermediate I). In most if not all cases, Lewis acid catalysts can facilitate both steps of the reaction.

It is not always trivial to make a distinction between Brønsted and Lewis acid catalysis, as the pH of a solution may decrease when Lewis acidic metals are added to the reaction mixture. Therefore, carrying out BV reactions in buffered solutions may sometimes lead to surprising results. One important difference in BV reactions with hydrogen peroxide is

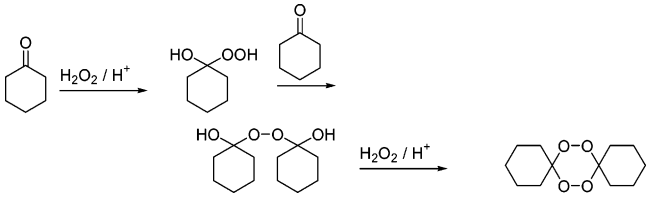


Figure 10. Formation of organic peroxides under acidic conditions.

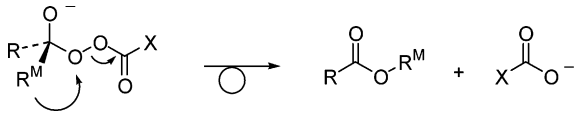


Figure 11. Rearrangement of anionic Criegee adduct.

that with Brønsted acid catalysts, dimeric, trimeric, or polymeric peroxides seem to be formed more easily—compounds that are potentially explosive (Figure 10). Indeed, a BV reaction can sometimes proceed via such a dimeric peroxide intermediate as recently shown by Berkessel and co-workers (see also later Figure 17).[31]

3.4. Nucleophilic Activation of Intermediate

On the basis of the mechanism depicted in Figure 9, it is difficult to imagine base catalysis to activate the intermediate. Base catalysis was observed when bicarbonate was added to a solution of *m*-CPBA and a bicyclic ketone in dichloromethane.[32] The reaction rate nearly doubled, which was ascribed to an accelerated rearrangement step of an anionic Criegee adduct as compared to the neutral adduct (Figure 11).

Renz and Meunier noted in their review[3] that in the reaction mentioned above, bicarbonate also removed the coproduct, *m*-CBA, from the reaction mixture via deprotonation and precipitation. In this way, the *m*-CBA could not compete with *m*-CPBA for the substrate, resulting in an increase in rate. Although BV reactions are sometimes carried out under neutral to basic conditions to avoid acid-catalyzed side reactions, base catalysis is not commonly observed in BV reactions with hydrogen peroxide.[33]

3.5. Nucleophilic Activation of Hydrogen Peroxide

Very few transition metals can catalyze BV reactions with hydrogen peroxide. The early transition metals (Ti, V, Mo, and W) may form peroxo complexes with hydrogen peroxide, but these are generally electrophilic in nature. Therefore, these complexes are active in, for example, epoxidation via electrophilic attack on preferably electron-rich olefins. A nucleophilic attack on the partially positively charged carbon of the C=O functionality is unlikely to occur with these complexes. Such a reaction seems to be the domain of the late transition metal peroxo complexes such as (ligand)$Pt(O)_2$ or (ligand)$Pd(O)_2$, which are partly nucleophilic in nature (see later).

Indeed, the first example of transition metal catalysis, which involved a (dipicolinato)Mo^{VI} peroxo complex (Figure 12) in the oxidation of cyclic ketones with 90% hydrogen peroxide, later turned out to be a simple acid-catalyzed reaction, rather than the first

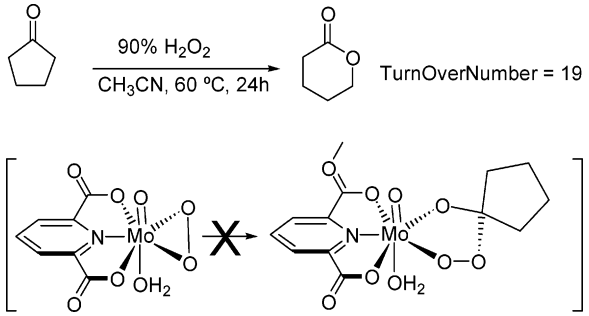


Figure 12. Molybdenum-catalyzed BV reaction of cyclopentanone.

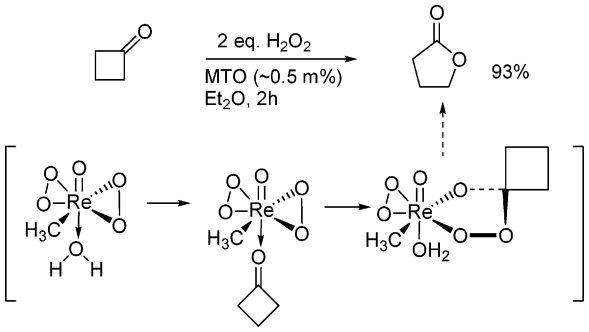


Figure 13. MTO-catalyzed oxidation of cyclobutanone.

example of nucleophilic reactivity of a group VI peroxo metal complex.[34]

With this in mind, the MTO-catalyzed BV oxidation of cyclobutanone with aqueous hydrogen peroxide becomes all the more suspicious.[35] MTO is an extremely active catalyst for the epoxidation of olefins with aqueous hydrogen peroxide.[36] The active bisperoxo intermediate gives an electrophilic attack on the double bond of the alkene. Therefore, a proposed nucleophilic attack of the same bisperoxo complex on the C=O double bond of, e.g., cyclobutanone (Figure 13), would seem unlikely. However, with the evidence available until now, it appears that MTO can exhibit electrophilic properties in epoxidation and nucleophilic properties in BV oxidation.[37]

The reason that MTO may change its nucleophilic/electrophilic behavior depending on the substrate is not entirely clear. If the ketone coordinates to rhenium, then the metal plays a role as a Lewis acid and induces electrophilic activation of the substrate. The coordination of basic ligands (ketone) also increases the electron density on the metal center, which in turn increases the nucleophilic character of the peroxo groups.[38] Reaction of the bisperoxo complex with thianthrene-5-oxide did reveal a partly nucleophilic character of the catalyst,[39] and in the oxidation of 1,3-diketones, MTO acts as both an electrophilic and a nucleophilic catalyst.[37]

A similar intermediate has been proposed for the rhenium-catalyzed reaction as for the molybdenum-catalyzed reaction, but in this case, ^{17}O NMR revealed polarization of the peroxo moiety, which might explain the nucleophilic character. Furthermore, contrary to the Mo^{VI} system, a stoichiometric reaction between the rhenium bisperoxo complex and cycloalkanones in the absence of hydrogen peroxide did lead to product formation, indicating that the rhenium bisperoxo complex is more than an expensive (Brøn-

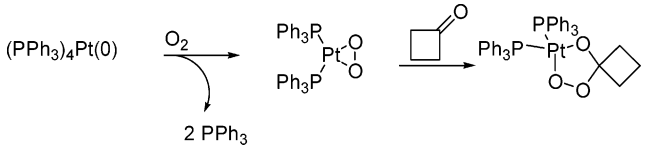


Figure 14. Nucleophilic reaction of platinum-η^2-peroxo complex on ketone.

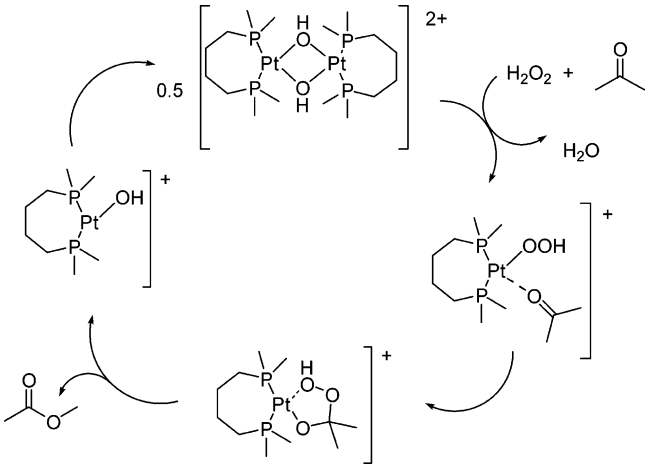


Figure 15. BV oxidation with $[(dppb)Pt(\mu\text{-}OH)]_2^{2+}$.

sted) acid. It should be noted, however, that the active rhenium complex contains one aqua ligand, which is highly acidic (similar to the molybdenum complex). This acidity may still account for part of the activity of MTO under catalytic conditions.

Examples of catalysis with late transition metal complexes are the Pt systems with bridging hydroxy ligands developed in the group of Strukul.[40] The work is based on the premise that platinum-η^2-peroxo complexes, which can be formed from (ligand)Pt(0) in a reaction with dioxygen, give a nucleophilic attack on ketones. However, such platinum-η^2-peroxo species only react in stoichiometric reactions (Figure 14). When platinum salts are used in combination with hydrogen peroxide, a platinumhydroperoxo complex may be active.

In the $[(dppb)Pt(\mu\text{-}OH)]_2^{2+}$-catalyzed oxidation of ketones (Figure 15), again, the platinum center gives an electrophilic activation of the ketone via coordination. In this case, hydrogen peroxide is also believed to coordinate to the platinum center and attack on the ketones proceeds intramolecularly. The difference with the previous platinum system (Figure 7) is that the platinum center may activate the hydrogen peroxide if $(dppb)PtOOH]^+$ is indeed more nucleophilic than HOOH.

It should be noted, however, that attack of coordinated hydrogen peroxide and attack of free hydrogen peroxide on the ketone are indistinguishable in kinetic investigations. Alternatively, coordination of platinum to hydrogen peroxide makes the latter more acidic, which might also promote BV oxidation. This would constitute an electrophilic activation of hydrogen peroxide. Again, platinum facilitates the rearrangement step by coordinating with the hydroxide leaving group (= electrophilic activation).[41] The platinum systems will be discussed further in asymmetric BV (see above and section 4.1.5).

3.6. Electrophilic Activation of Hydrogen Peroxide

Interestingly, in a recent study, Brinck et al.[42] showed that in the BF_3-catalyzed reaction of acetone and hydrogen peroxide the Lewis acid facilitated the reaction via coordination to hydrogen peroxide, making the latter more acidic and increasing hydrogen bonding to the carbonyl functionality (Figure 16). The coordination of BF_3 to acetone was calculated to lead to stabilization of the adduct, rendering it nearly unreactive! The same Lewis acid also facilitated the rearrangement step after migration to the outer peroxygen, creating a BF_2OH leaving group rather than a hydroxide leaving group.

As was pointed out above, many early transition metals can coordinate to hydrogen peroxide, making it more electrophilic and more eager to attack electron-rich substrates such as olefins. By the same token, such electrophilic activation would decrease the tendency to attack already electron-poor ketones in a BV reaction.

Neumann recently reported on the electrophilic activation of hydrogen peroxide by 1,1,1,3,3,3-hexafluoro-2-propanol in the oxidation of olefins and ketones.[43] This solvent may form hydrogen bonds with hydrogen peroxide, but it is not able to receive hydrogen bonds back, due to the decreased electron density on $CF_3CHOHCF_3$ itself. This particular solvent, therefore, makes hydrogen peroxide more electrophilic, which should indeed promote attack of the peroxygens on olefins but not on ketones. This apparent anomaly was subsequently explained by Berkessel and co-workers[31] who showed that Brønsted acid-catalyzed BV oxidations with hydrogen peroxide proceed by a nonclassical mechanism in $CF_3CHOHCF_3$ (Figure 17). The intermediacy of spiro bisperoxide (**1**) was established by following the course of the reaction in $(CF_3)CDOD$ with ^{13}C NMR.

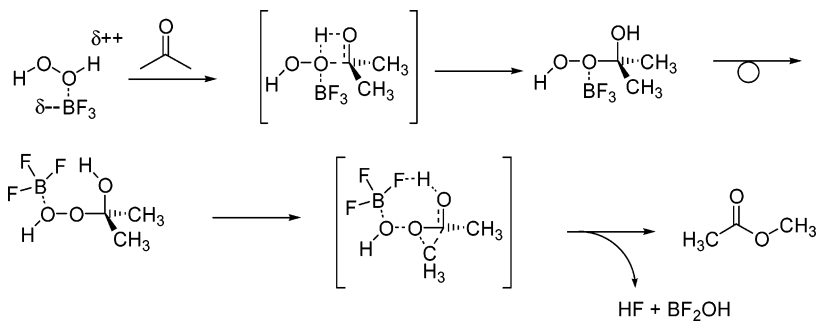


Figure 16. BF_3-catalyzed oxidation of acetone with hydrogen peroxide.

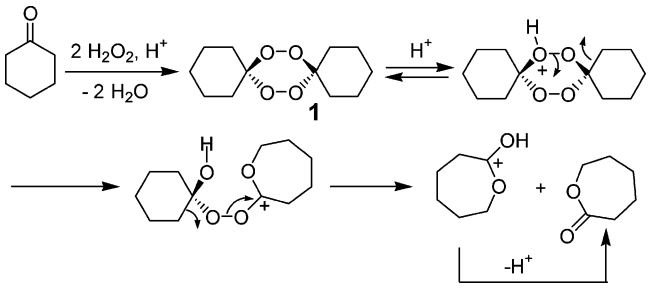


Figure 17. Nonclassical Brønsted acid-catalyzed BV oxidation in $(CF_3)_2CHOH$.

4. Catalytic Reactions

4.1. Homogeneous Catalysts

4.1.1. Oxidation of Aldehydes

One of the most underestimated oxidation reactions is undoubtedly the oxidation of (benz)aldehydes. A selective route to form benzoic acids is oxidation of the hydrate—formed from the aldehyde and water—with strong inorganic oxidants such as $KMnO_4$, CrO_3, fuming HNO_3, Jones reagent, etc. However, environmental considerations have shifted the attention to BV type reactions. In this case, the reaction can yield two products: the corresponding benzoic acid and the ester of the corresponding phenol and formic acid. Formation of the latter product from benzaldehydes is a useful alternative to direct hydroxylation of aromatics (Figure 18). With electron-donating hydroxy or amino substituents on the ortho or para position, the so-called Dakin reaction can be carried out without a catalyst under alkaline conditions.

Recenty, a number of articles have appeared on the oxidation of aldehydes with aqueous hydrogen peroxide. The reaction is catalyzed by, e.g., Brønsted acids,[44] MTO,[45] arylseleninic acids, and SeO_2.[46] Although the titles of some articles may imply that the catalysts involved are particularly effective to direct the reaction to either acid or phenol, the electron density on the phenyl ring largely determines this selectivity. Electron-donating substituents favor ring

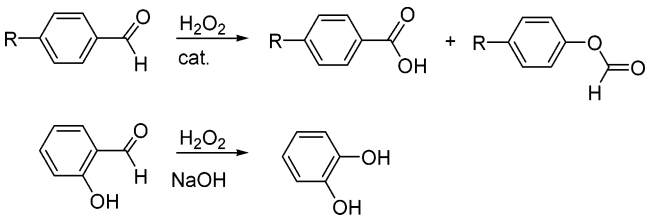


Figure 18. BV reaction of aldehydes.

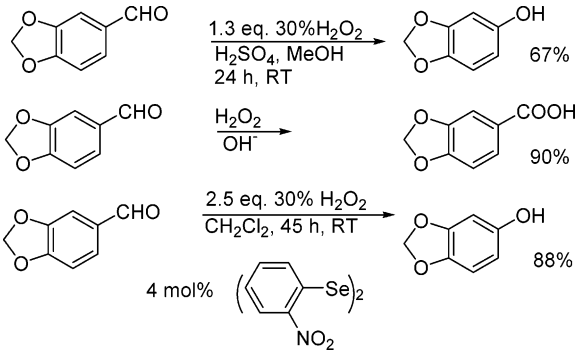


Figure 19. Oxidation of piperonal.

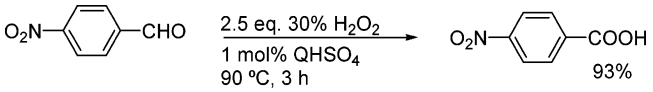


Figure 20. Oxidation of 4-nitrobenzaldehyde.

migration to yield phenols, whereas electron-withdrawing substituents favor hydrogen migration to yield acids.[47] However, some differences in selectivity can be found depending on solvent type and pH. For instance, the oxidation of piperonal (Figure 19) gives the phenol under acidic conditions,[48] whereas under alkaline conditions mainly the corresponding acid is formed.[49] Under more or less neutral conditions, the selectivity is directed to the phenol when bis(2-nitrophenyl) diselenide is used as the catalyst (precursor).[50]

Generally speaking, seleninic acid catalysts show a high tendency to form phenols if electron-donating substituents are present on the aromatic ring of the substrate.[51] With MTO,[45] selectivity to the (electron-rich) phenols is lower than with bis(2-nitrophenyl) diselenide.

Table 1 gives an overview of the selectivity of several catalysts active in the oxidation of aldehydes. Several catalysts based on selenium—notably SeO_2 and Ph_2Se_2 in THF[52]—showed a high selectivity for the carboxylic acid. Noyori et al.[44] used a simple lipophilic acid catalyst, $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$, to convert aldehydes to carboxylic acids under halide and metal-free conditions without the presence of any organic solvent (Figure 20). Although details were not given, it seems reasonable that substantial amounts of phenol were formed in those cases when only low yields of acid were reported. Possibly, the phenols are oxidized further. The system developed by Noyori is probably the easiest and greenest way to oxidize aldehydes to carboxylic acids to date, and the protocol is suitable to oxidize aldehydes on a mole-scale. The

Table 1. H_2O_2 Oxidation of Aldehydes to Acid/Phenol Mixtures

substrate[a]	SeO_2[b] (ref 46)	ArSe(O)OH[b,c] (ref 51)	WO_4^{2-}[d] (ref 53)	$[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$[d] (ref 44)	H^+/MeOH[b] (ref 48)
4-NO_2-φ	87/0	99/0	89	93	80/0
4-Cl-φ	83/0	50/50	86	76	87/0
4-CH_3-φ	88/0	45/55	57	41	51/28
4-H-φ	97/0	ND[e]	84	85	ND[e]
4-MeO-φ	46/41	0/95	6	9	0/90
octanal	91/0	95/1	87	82	ND[e]

[a] φ: $-C_6H_4CHO$. [b] Acid to phenol ratio. [c] ArSe(O)OH is 3,5-$(CF_3)_2C_6H_3Se(O)OH$. [d] Selectivity to acid; yield of phenol not given. [e] ND = not determined.

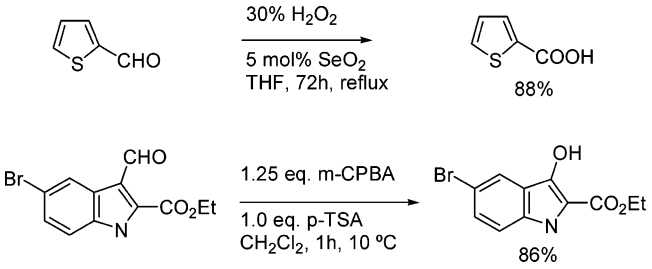


Figure 21. Oxidation of heteroaromatic aldehydes.

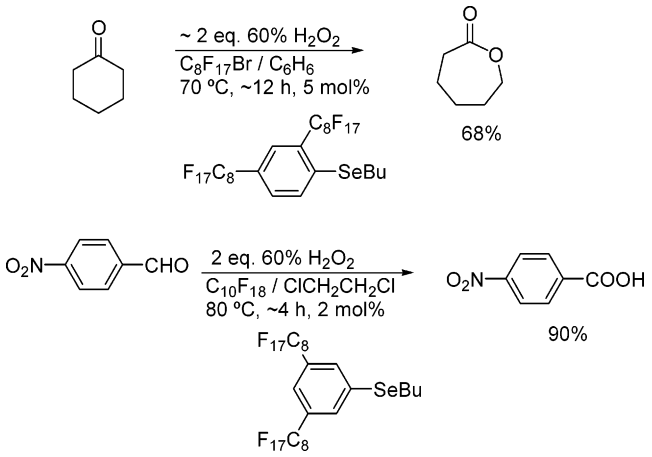


Figure 22. Fluorous phase BV oxidation immobilized selenium catalysts.

results were not greatly different from those obtained by Venturello with a tungstate catalyst.[53]

SeO_2 is especially good for the oxidation of linear aldehydes to acids but also for the oxidation of heteroaromatic aldehydes to acids.[46] Both electron-poor pyridine-3-carbaldehyde (86%) and electron rich thiophene-2-carbaldehyde (88%) and furan-2-carbaldehyde (73%) were oxidized to the respective acids (Figure 21).[54] The SeO_2/H_2O_2 combination was not useful in the oxidation of 2-indolecarbaldehyde, as these types of compounds are too sensitive. However, a combination of *m*-CPBA and *p*-toluenesulfonic acid proved to be successful for a series of substituted indole derivatives.[55] In this case, however, the 3-hydroxyindole derivative was formed, instead of the acid.

To avoid contamination of the products with selenium catalysts, Knochel[56] immobilized 2,4-bis(perfluorooctyl)phenyl butyl selenide in a fluorous phase.[57] The system was improved slightly by using the 3,5-bis(perfluorooctyl)phenyl butyl selenide isomer of the catalyst and by using the more polar dichloroethane as a cosolvent system instead of benzene (Figure 22).[58] The latter selenium isomer is slightly more difficult to synthesize, but both catalysts could be recycled without a serious loss of activity.

Alternatively, aldehyde oxidation can be carried out with dioxygen as the sole oxidant. In this case, a peracid is formed from the aldehyde that attacks a second equivalent of aldehyde to yield two equivalents of acid. The nickel bis(triacontafluoroheptadeca-8,10-dionate) catalyst[59] (Figure 23)—also developed in the group of Knochel—can be recycled with a minimal loss of activity when operating under fluorous biphasic conditions, but it should be noted that

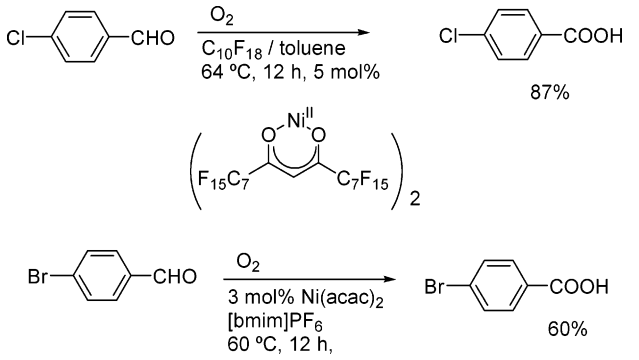


Figure 23. Nickel-catalyzed aerobic oxidation of substituted benzaldehydes.

solvent properties of perfluoroalkanes are not optimal for these (polar) oxidations reactions. Ionic liquids[60] allow more fine tuning of the solvent properties, but so far, only one example of aerobic aldehyde oxidation in $[bmim]PF_6$ has been reported and the results are suboptimal.[61]

4.1.2. Oxidation of Cycloalkanones

From an industrial point of view, oxidation of cyclohexanone to ϵ-caprolactone is one of the more interesting BV reactions. The product lactone is polymerized and used in foams, biodegradable plastics, etc. The reaction is often carried out with oxygen in combination with a sacrificial aldehyde such as acetaldehyde or benzaldehyde.[62] Alternatively, oxidation is carried out with a carboxylic acid, which is converted in situ to its corresponding peracid by the action of hydrogen peroxide plus an acid catalyst.[63]

A large number of catalysts have been shown to be active in the oxidation of cycloalkanones to lactones using only hydrogen peroxide as the oxidant. MTO is moderately active in the oxidation of linear ketones[37] or higher cycloalkanones,[64] but it is particularly active in the oxidation of cyclobutanone derivatives (Figure 24), which are oxidized faster with MTO than with other existing methods.[65]

Interestingly, with bicyclo[3.2.0]hept-2-en-6-one (Figure 24) competing, epoxidation of the olefin was negligible, even though MTO is an extremely good epoxidation catalyst. With <1 mol % MTO, cyclobutanones are fully converted within 1 h. Even α,α-dichlorocyclobutanones are oxidized, compounds that

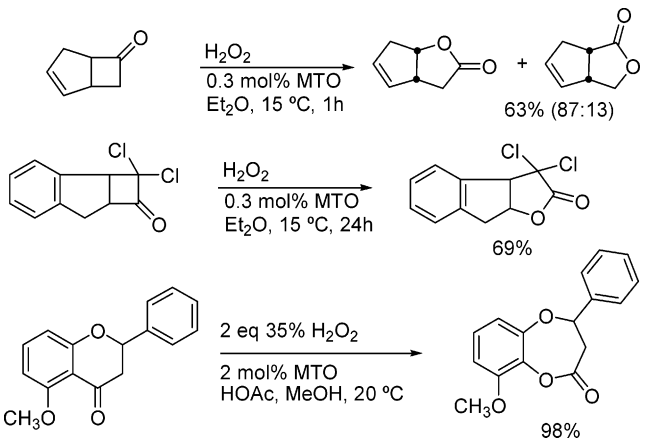


Figure 24. MTO-catalyzed oxidation of cycloalkanones.

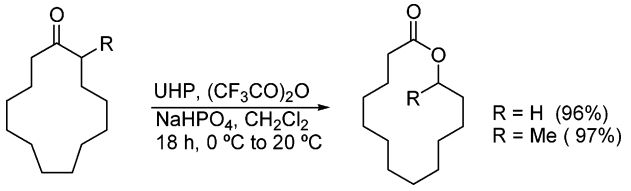


Figure 25. BV oxidation of cyclotridecanone.

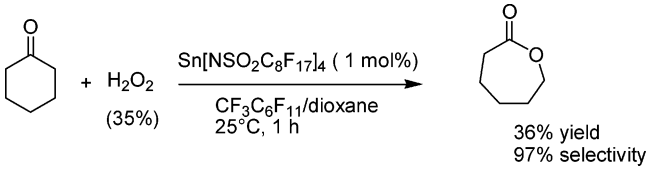


Figure 26. Use of a fluorous Sn catalyst for BV oxidations in a fluorous biphasic system.

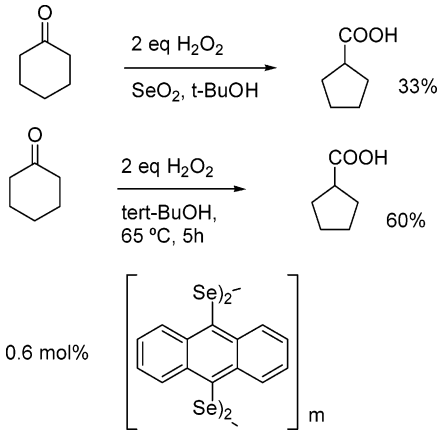


Figure 27. Oxidative ring contraction of cyclohexanone.

are otherwise almost inert.[65] Successful oxidation of a 4-chromanone derivative was achieved with a β-methoxy substituent present in the substrate.[64]

Other (higher) cycloalkanones react very slowly, and the use of strong acids in combination with (anhydrous) urea hydrogen peroxide (UHP; Figure 25) or preformed peracid catalysts is required[66] (see also linear ketones).

Another approach consists of the use of a fluorous Sn catalyst under biphasic conditions.[67] A perfluorinated tin(IV) compound, $Sn[NSO_2C_8F_{17}]_4$, was recently shown to be a highly effective catalyst for BV oxidations of cyclic ketones with 35% hydrogen peroxide in a fluorous biphasic system (Figure 26).

The catalyst, which resides in the fluorous phase, could be easily recycled without a loss of activity. Analogous compounds of Hf, Sc, and Yb were also shown to catalyze the BV oxidation, albeit less effectively than the Sn compound.

4.1.3. Oxidative Ring Contraction

The oxidation of cycloalkanones to lactones is probably the standard BV reaction. For some time, however, ring contraction of cycloalkanones with SeO_2/H_2O_2 has been known to be a synthetically useful side reaction.[68] Recently, Mlochowski reinvestigated the reaction and developed effective catalysts for the conversion of cycloalkanones to cycloalkanecarboxylic acids (Figure 27).[69] It has been proposed[6] that a Se(VI) species is responsible for oxidative ring contraction, whereas a Se(IV) species catalyzes conventional BV reactions. This is consistent with the observation that only electron-rich selenium species seem to catalyze this side reaction.

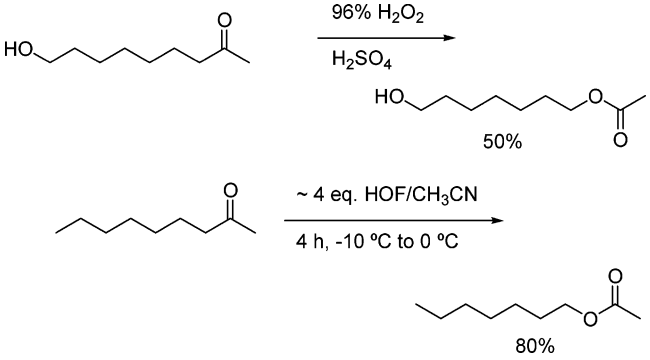


Figure 28. BV oxidation of 2-alkanones.

Products such as cyclopentanecarboxylic acid and cyclohexanecarboxylic acid are important in the synthesis of natural products and pharmaceuticals. They cannot always be obtained via the Favorski reaction. The present route is considerably more environmentally friendly than the use of stoichiometric amounts of thallium(III) salts.[70]

4.1.4. Oxidation of Linear Ketones

Partly because of the lack of ring strain, linear ketones are generally reluctant to undergo the BV reaction. For the reaction of linear ketones with H_2O_2, strong protic acids are required to activate the ketone, but this also facilitates hydrolysis of the ester and the formation of stable peroxides or polymers containing peroxy groups.[71] An alternative oxidant is HOF/CH_3CN formed in situ from elemental fluorine.[72] In this case, the reaction proceeds via an oxirane intermediate rather than the Criegee intermediate (Figure 28).

The use of Lewis acid catalysts can largely circumvent the problem of peroxide formation. Lewis acids such as BF_3 and SbF_5 have already been used in BV reactions to activate (linear) ketones. Also, the platinum catalysts developed by Strukul[26] and the tin zeolite β developed by Corma[30] facilitate the reaction in a similar fashion.

4.1.5. Enantioselective Oxidations

In 1994, Strukul et al. were the first to report an enantioselective BV reaction of a racemic mixture of 2-substituted cycloalkanones using hydrogen peroxide as an oxidant and chiral Pt complexes as catalysts.[73] Shortly after, Bolm et al. published their system, using chiral Cu complexes and aldehyde/O_2 as the oxidant for this reaction.[74] Since then, a number of chiral catalysts for such reactions of racemic ketone mixtures (Figure 29 and Table 2) and

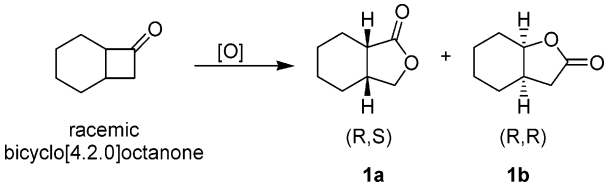
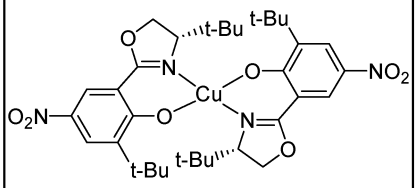
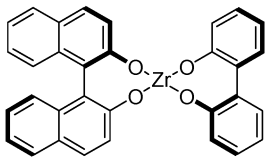
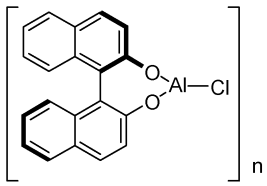
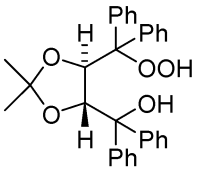


Figure 29. Asymmetric BV oxidation of bicyclo[4.2.0]-octanone.

Table 2. Comparison of Chiral Oxidation Catalysts in BV Oxidation of Bicyclo[4.2.0]octanone

entry	Catalyst/ reagent	Conditions	yield/e.e. versus **1a+b** (see *fig.* 29)	ref
1		O_2/t-BuCHO 1mol% (S,S) Cu-complex benzene, RT	92% e.e. (15 % yld) (R,S); 67% e.e. (46% yld) (R,R).	77
2		1.5 eq. TBHP 100% Zr-complex toluene	87% e.e. (R,S), 14% e.e. (R,R) (ratio 1a:1b = 1:6)	77
3		1 eq. TBHP, 25mol% Me_2AlCl + R-BINOL, conv <100%	90% e.e. (R,S) 25% e.e. (R,R)	77
4		0.7 eq. ROOH, -30°C, 60h, DBU /LiCl, conv. 70%	55% e.e.(R,R) (66% yld)	78
5	acinetobacter NCIMB 9871 (whole cells)		>95% e.e. (18% yld) (R,S); 61% e.e. (30% yld) (R,R)	79
6	acinetobacter TD 63 (whole cells)		>95% e.e. (12% yld) (R,S); 53% e.e. (24% yld) (R,R)	79

for the desymmetrization of prochiral ketones have been developed. Only a few catalysts are used in combination with hydrogen peroxide as the oxidant. The reactions often require low temperatures to obtain any appreciable ee; therefore, mainly cyclobutanones such as bicyclo[4.2.0]octanone (see Figure 29) are used as substrates.[75] In this case, enantiodivergent oxidation takes place.

The zirconium reagent modified with either (*S*)-BINOL[76] or (*R*)-BINOL[77] gives fairly good enantioselectivity for the (*R*,*S*) or (*S*,*R*) isomer of the **1a** product, respectively. The reagent, although relatively easy to prepare, exhibits a low activity and is used in stoichiometric amounts. When aluminum is used as the Lewis acid center with the same (*R*)-BINOL,[77] lower catalyst loadings (25 mol %) still prove successful. Better results were also obtained by using a substoichiometric amount of a chiral organic hydroperoxide (TADDOOH).[78] In this case, the normal product (*R*,*R*) is formed solely and 26% of the starting material is recovered with 98% ee (*S*,*S*). In this particular case, enzymatic reactions[79]

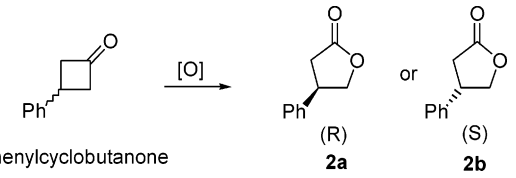


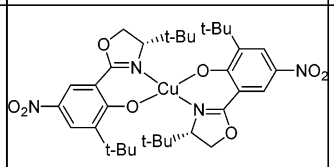
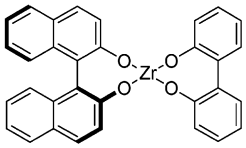
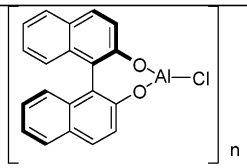
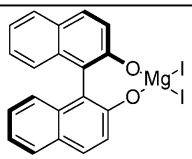
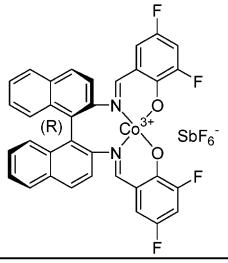
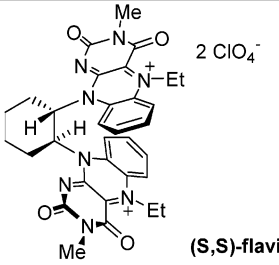
Figure 30. Asymmetric BV oxidation of prochiral 3-phenylcyclobutanone.

hardly provide an advantage over metal-catalyzed BV reactions.

Another often used substrate is the prochiral 3-phenylcyclobutanone (Figure 30 and Table 3), and with some exceptions,[80] better results are obtained.

The chiral BINOL complexes of zirconium,[76] aluminum,[77] and magnesium[81] are not only active in the asymmetric oxidation of racemic ketones, they also catalyze the asymmetric BV oxidation of prochiral substrates (see Table 3). The cobalt salen catalyst developed in the group of Katsuki is by far the most effective catalyst. Good results are obtained with only 1 mol % of cobalt catalyst in combination with the UHP adduct or with aqueous hydrogen peroxide.[82] Alternatively, the ketone can be modified with a C2-symmetric 2,4-pentanediol to form a ketal, which is

Table 3. BV Oxidation of 3-Phenylcyclobutanone

entry	reagent / catalyst	Conditions	yield/e.e. versus **2a+b**	Ref
1		1 mol% (S,S)-Cu-complex O_2/t-BuCHO	44% e.e. (S) 66-88% yld	87
2		1 eq. Zr- (S)-BINOL complex, 1.5 eq. TBHP, toluene, -25 °C to RT, 12 h	31% e.e. (R)	76
3		15 mol% Al-(R)-BINOL complex CHP	68% e.e. (R) 100% yld	77
4		50 mol% (R)- BINOL-MgI_2, 1.5 eq. CHP, CH_2Cl_2, -25 °C, 8 h	65% e.e. (R) 91% yld	81
5		5 mol% Co-complex, 1.3 eq. 30% H_2O_2, EtOH, 24 h, 0 °C	75% e.e. (S) 85% yld	82
6		10 mol% (SS) flavin-catalyst, 1.5 eq. H_2O_2 (30%), 25 mol% AcONa, CF_3CH_2OH/MeOH/H_2O (6:3:1), -30°C, 6 dys	63% ee (S) 67% yld (62% ee (R) when using RR flavin)	85
7	Cunninghamella echinulata (whole cells)	28°C, pH = 8, cell conc.: 5 g/l, 3.4 mM ketone.	>98% e.e. (R) 71% yld	86

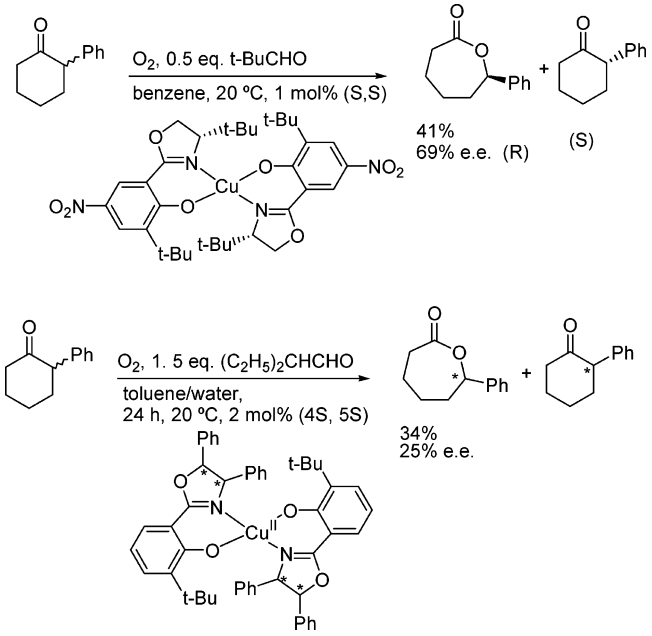


Figure 31. BV oxidation (resolution) of racemic 2-phenylcyclohexanone.

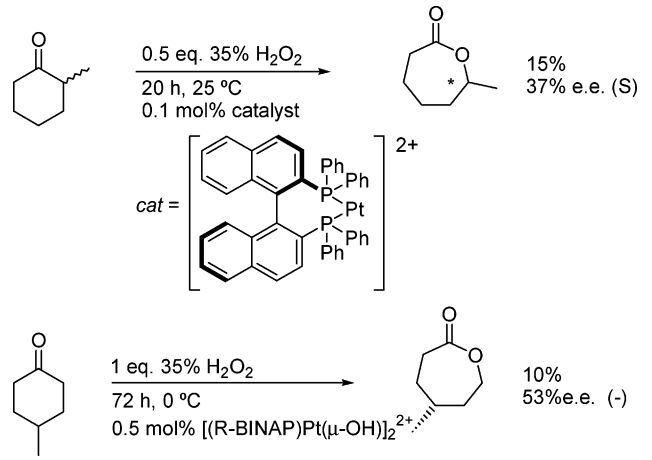


Figure 32. BV oxidation of 2- and 4-methylcyclohexanones with the platinum−BINAP system.

then converted to the protected lactone (at very low temperatures) followed by deprotection. Although the results are good, the waste stream in this reaction is considerable.[83] Noteworthy is the use of a biomimetic flavin-derived catalyst, which forms the corresponding peroxy compound as an oxidant with H_2O_2 (see later in section 4.2.2). Following the work of Furstoss et al.,[84] Murahashi et al. synthesized a planar chiral bisflavin, which was able to convert 3-arylcyclobutanones enantioselectively (67% ee) to the corresponding lactones.[85] It should be noted, however, that high amounts of catalyst (10 mol %) and additives (25 mol % AcONa) are still needed. With the fungus *Cunninghamella echinulata*, still better results have been obtained.[86]

Results for larger ring substrates are poor, and bulky substituents at the 2-position (e.g., 2-phenylcyclohexanone; Figure 31) are required to induce some chiral discrimination.

With a copper oxazoline complex, 2-phenylcyclohexanone derivatives can be converted.[87] Furthermore, 4-phenylcyclohexanone or 2-alkylcyclohexanones is not converted selectively, thus seriously limiting a broad applicability of the catalyst system. The chiral platinum systems developed by Strukul show significantly better results in the asymmetric oxidation of 2-alkylcyclohexanones[73] (Figure 32) and desymmetrization of *meso*-cyclohexanones.[88]

4.2. Biocatalysis

The enantioselectivities obtained with chiral organometallic catalysts in BV oxidations have generally been moderate (see preceding section). Better results have been obtained with monooxygenase enzymes (see later), which, generally speaking, have a clear advantage over homogeneous catalysts with regard to chemo-, regio-, and enantioselectivity.

4.2.1. Lipases

Lipases can indirectly catalyze BV oxidations by mediating the in situ formation of peroxycarboxylic acids from a carboxylic acid or ester and hydrogen peroxide. However, they often give poor selectivities to ester or lactone products as they are more active in the hydrolysis of the product than in its formation (Figure 33).

There are only a few examples in which a selective BV oxidation was observed.[89] Furthermore, because the enzyme is not involved in the oxidation of the ketone, these reactions are not enantioselective. On the other hand, the lipase can catalyze the enantioselective (per)hydrolysis of the lactone, forming the corresponding (per)carboxylic acid and leaving an enantiomerically enriched lactone behind.[90]

4.2.2. BVMOs

BVMOs are NAD(P)H-dependent flavoenzymes that catalyze the chemo-, regio-, and enantioselective oxidation of aliphatic ketones to esters or lactones, utilizing molecular oxygen as the primary oxidant (Figure 34). BVMOs are produced by a wide variety of bacteria, and in vivo, the BV oxidation constitutes one step in the microbial degradation of alicyclic hydrocarbons to innocuous products. The cyclohex-

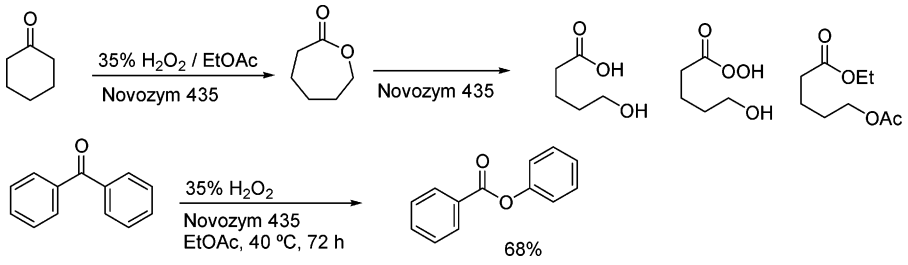


Figure 33. Lipase-catalyzed BV oxidation with hydrogen peroxide.

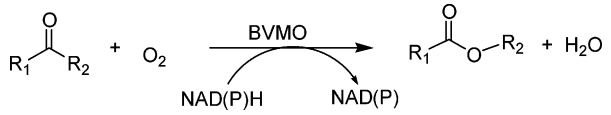


Figure 34. BV reactions catalyzed by BVMOs.

anone monooxygenase (CHMO) from *Acinetobacter calcoaceticus* NCIMB is the best characterized and most studied of these enzymes.[91]

BVMOs, in particular CHMO, are versatile biocatalysts that have been widely used in synthetic biotransformations.[91−99] They contain a flavin moiety as the prosthetic group and utilize NAD(P)H as a stoichiometric cofactor (see Figure 35). In view of the requirement for cofactor regeneration, these reactions are generally performed with whole microbial cells in a fermentation mode. Degradation of the lactone product can be circumvented by the addition of hydrolase inhibitors and/or heterologous expression. The latter also obviates the problem, in the case of CHMO, of handling the pathogenic *Acinetobacter* strain. To this end, two different *Escherichia coli* strains have been engineered to overexpress CHMO.[100] It has also been successfully overexpressed in baker's yeast.[101]

Several CHMOs are now commercially available, e.g., from Fluka, and they are easy to use, even for nonspecialists. A disadvantage of the methodology is the low volume yield (concentrations are typically 10 mM as compared to 1 M solutions in homogeneous catalysis). Furthermore, many organic substrates have limited solubility in water. This problem could possibly be solved by performing the reactions in organic media.[102]

The generally accepted mechanism[103] for BV oxidations catalyzed by BVMOs is shown in Figure 35. The active oxidant is a flavin hydroperoxide, formed by the reaction of the reduced flavin with dioxygen. Recently, Massey et al. suggested that instead of the flavin hydroperoxide the actual oxidant is the flavinperoxide anion, which is formed at high pH ($pK_a \sim 8.4$).[104]

The state-of-the-art with regard to scale-up of BVMO-catalyzed oxidations has been recently reviewed.[99,103] The reaction suffers from both substrate and product inhibition, and the optimum ketone concentration was shown to be 0.2−0.4 g L^{-1}; at product concentrations above 4.5−5 g L^{-1}, the activity of the whole cell biocatalyst fell to zero. This suggests that a fed-batch operation with continuous product removal, by adsorption on a solid resin, is necessary in order to obtain reasonable volumetric yields. In this way, volumetric yields up to 20 g L^{-1} could be obtained.

In principle, the use of the isolated enzyme should allow for the reaction to be performed at higher substrate concentrations, avoid side reactions, and facilitate downstream processing. However, this requires an ancillary enzymatic cofactor regeneration system. Encouraging results have been obtained by coupling CHMO-catalyzed BV oxidation to cofactor regeneration mediated by an NADPH-dependent formate dehydrogenase (Figure 36).[105,106] The overall reaction constitutes an enantioselective BV oxidation with stoichiometric consumption of O_2 and formate to give water and carbon dioxide as the coproducts. The reaction was carried to complete conversion with a 40 mM substrate concentration, and the enzymes were separated by ultrafiltration and reused.

4.2.3. Enantioselective Reactions

The enzyme-catalyzed hydrolysis of the lactone and subsequent oxidation are unwanted side reactions, obviously. Several yeasts[107] and *E. coli*[108] have been engineered to convert the ketone to the lactone exclusively. Thus, 2-substituted[107] and 4-substituted (or prochiral)[108,109] cyclohexanones can be converted with high selectivity (Figure 37).[110] The (racemic) 3-substituted[111] cyclohexanones are synthetically less interesting as they can yield two regioisomeric lactones, each in two enantiomers. For small substituents, there is little discrimination by the enzyme.

The first example of a dynamic kinetic resolution involving a CHMO-catalyzed BV oxidation was recently reported (Figure 38).[112] The reaction was performed with whole cells of CHMO-containing recombinant *E. coli* sp. at pH 9. Under these conditions, the ketone substrate underwent facile racemization, via keto−enol tautomerism, and the lactone product was obtained in 85% yield and 96% ee.

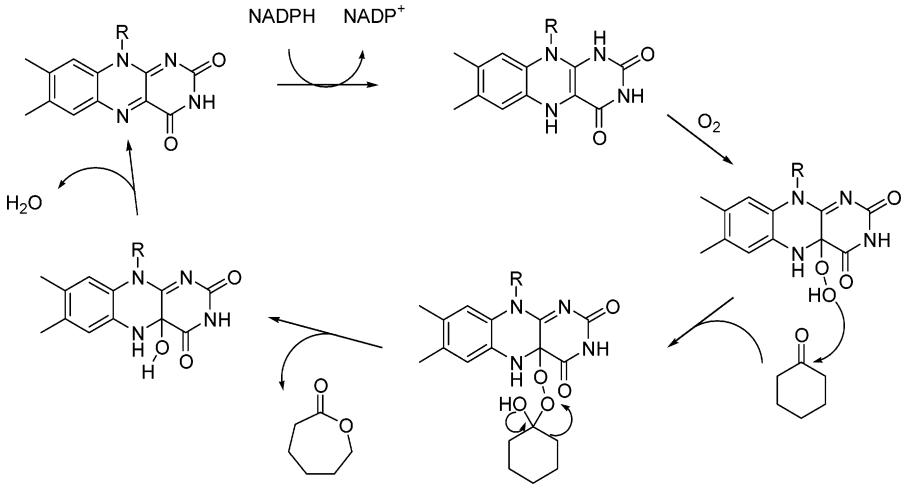


Figure 35. Mechanism of CHMO-catalyzed BV oxidation.

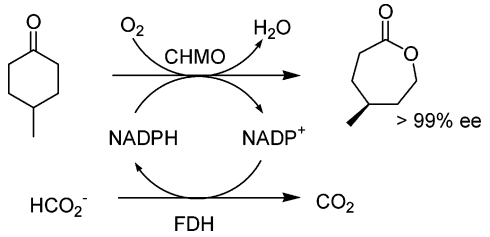


Figure 36. CHMO-catalyzed BV reaction coupled to cofactor regeneration by formate dehydrogenase.

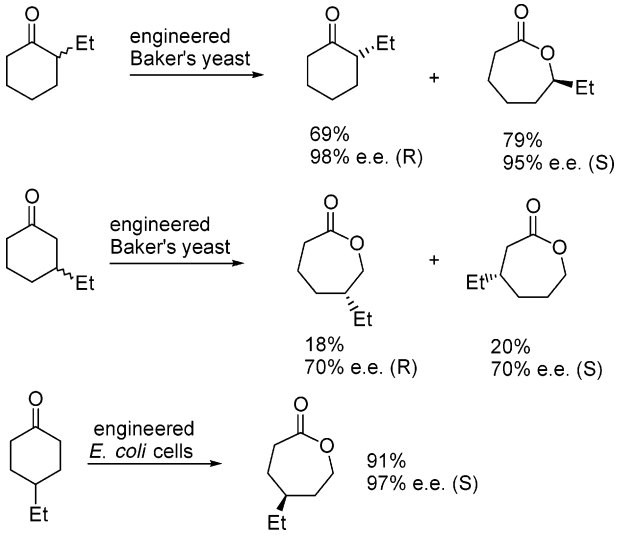


Figure 37. Enzyme-catalyzed asymmetric BV oxidation of 2-, 3-, and 4-ethylcyclohexanones.

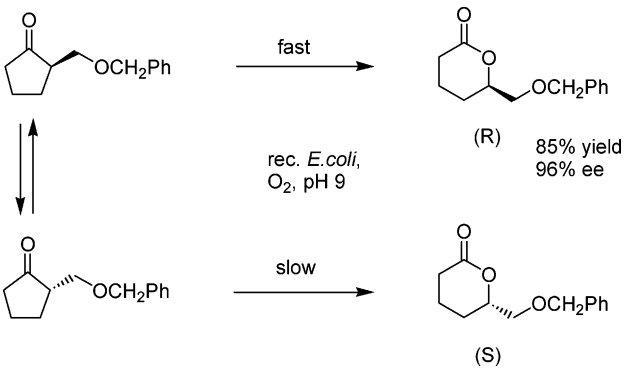


Figure 38. Dynamic kinetic resolution of ketones using CHMO-containing rec. *E. coli*.

4.2.4. Regioselective Reactions

In some cases, the enzyme has a "natural" preference for one ketone enantiomer but may still convert "nonnatural" ketone, leading to unexpected products. With conventional methods, the tertiary α-carbon in (+)-dihydrocarvone migrates with some preference over the secondary α-carbon. However, using whole cells of *A. calcoaceticus* NCIMB 9871, the hydroxyacid **3** is formed as the sole product (Figure 39).[90,113] In the oxidation of (−)-dihydrocarvone with the same biocatalyst, the tertiary carbon migrates selectively and hydroxyacid **4** is obtained. In a similar fashion, a relatively high yield of the "abnormal" lactone (42 vs 44% normal lactone) is obtained in the oxidation of racemic bicyclo[3.2.0]hept-2-en-6-one.[79,114] This bicyclic ketone has become the standard substrate for asymmetric BV reactions with bio- or metal catalysts. Alternatively, the biocatalyst may convert only one isomer of a racemic mixture to the lactone and reduce the other isomer to its corresponding alcohol.[86,115]

The regioselectivity can also be solvent-dependent as was shown in the oxidation of norbornanone by whole cells of *Pseudomonas putida* NCIMB 10007.[116] Although migration of the bridgehead carbon is favored normally, with chemical transformation (peracid), only 10% of the **5** lactone was formed. In *n*-octane, the enzyme was specific to lactone **5**. In mixtures of organic solvents with water, however, high amounts of the isomeric lactone **6** were formed (Figure 40).

4.2.5. Chemoselectivity

Although the hydroperoxyflavin reacts as a nucleophile with ketones, it is also able to oxidize heteroatoms, such as S, Se, N, and P, acting as an electrophile.[117] Nevertheless, engineered *E. coli* cells showed a high selectivity for BV oxidation over heteroatom oxidation (Figure 41),[118] which is otherwise preferred by peracid catalysts. Another interesting example, impossible to carry out with conventional methods, involves the oxidation of naphthaquinone derivatives (Figure 42).[119]

4.3. Heterogeneous Oxidation

4.3.1. Solid Peracids

A straightforward approach for heterogeneous oxidations with hydrogen peroxide is a two-step process, in which carboxylic acid groups are attached to an insoluble support.[120] In the first step, the acid groups on the resin are converted to percarboxylic acids with H_2O_2 and a stoichiometric amount of methanesulfonic acid. In the second step, the substrate is passed over the support (Figure 43).

This principle was shown previously for epoxidation[121] and, recently, in BV oxidation[120] (see figure above). The disadvantages of the method are clear as follows: it requires a two-step reaction and large amounts of a strong acid and hydrogen peroxide (both ∼10 equivalents with respect to substrate) to shift the equilibrium reaction for peracid formation, yielding a large amount of waste. It should be noted, however, that the catalyst is active in oxidation of both cyclic and linear ketones, and good results were obtained in *n*-alkane solvents. The disadvantage of the two-step process can be overcome by the use of resin-bound seleninic acids[122] or arsonic acids.[123] Both types of catalysts form highly active peracid derivatives without added strong acids and have proven to be successful in epoxidation and BV oxidation. Furthermore, simple solid acid catalysts such as Amberlyst 15 (sulfonated polystyrene cross-linked with divinylbenzene) show good activity in the BV reaction of cyclopentanone with aqueous hydrogen peroxide (Figure 44).[124] The main side products are glutaric acid and dicyclopentylidenediperoxide. The latter product is typical of Brønsted acid catalysis.

4.3.2. Solid Lewis Acid Catalysts

Many zeolitic materials are inferior to Amberlyst 15 due to their higher acidity ($H_0 < -5$ as compared

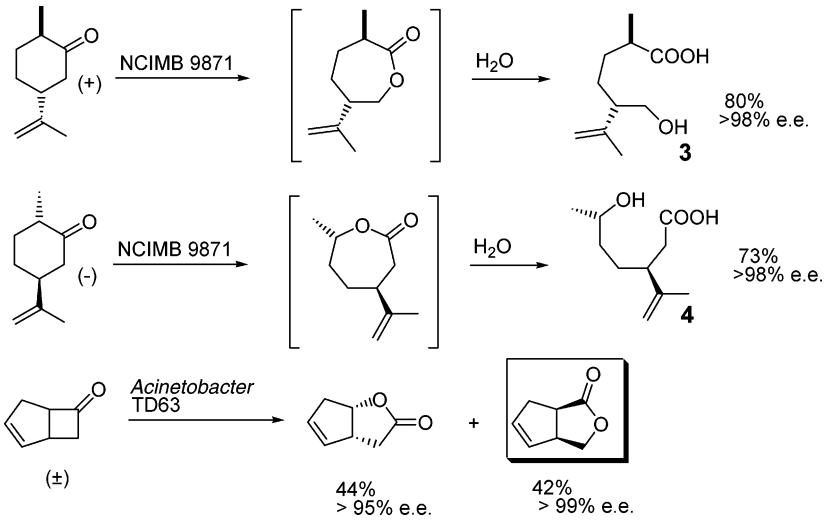


Figure 39. Enzyme-catalyzed BV oxidation of "nonnatural" ketones.

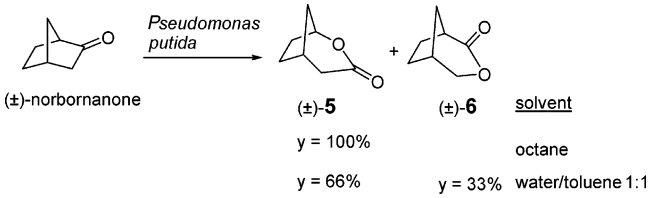


Figure 40. Solvent-dependent BV oxidation of norbornanone.

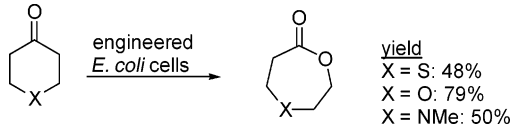


Figure 41. Enzymatic BV oxidation of heteroatom derivatives.

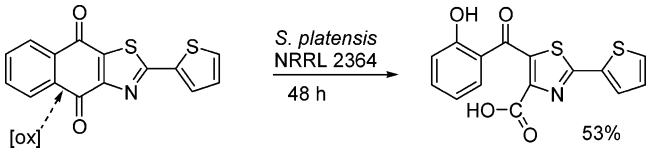


Figure 42. Enzymatic oxidation of naphthaquinone derivatives.

to −2 for Amberlyst 15) leading to more peroxidic materials and incompatible pore size. Clark et al. developed a hexagonal mesoporous silica-supported SbF_3 with a similar acidity as Amberlyst 15 ($H_0 \sim -2$).[125] This catalyst was used in the oxidation of cyclohexanone (TOF ~100 h^{-1}) under reduced pressure (70 mbar at 70 °C) with azeotropic removal of water.

A still better solid catalyst—based on 1.6 wt % tin in zeolite β—was developed in the group of Corma.[30,126] It provides a green method for BV oxidations in that it utilizes hydrogen peroxide as the oxidant, a recyclable catalyst, and avoids the use of chlorinated hydrocarbon solvents. It is believed that the Sn Lewis acid sites solely activate the ketone for BV reaction and leave hydrogen peroxide nonactivated. Corma proposed that in this way, side reactions, such as epoxidation, which require electrophilic activation of hydrogen peroxide, are largely avoided. Oxidation of bicyclo[3.2.0]hept-2-en-6-one with hydrogen peroxide in the presence of tin zeolite β gave selective oxidation of the ketone, leaving the olefin intact. With *m*-CPBA (using similar conditions with MTBE as the solvent at 30 °C), extensive epoxidation of the cyclopentene ring was observed (Figure 45). Okuda et al. showed that with *m*-CPBA, selective oxidation of the ketone is possible under seemingly similar conditions using dichloromethane as a solvent.[127] It should be noted that in general epoxidation of olefinic moieties in the substrate can be largely avoided by using alkaline hydrogen peroxide or alkylhydroperoxide solutions.[2] As noted before, MTO also selectively catalyzed formation of the lactone (Figures 24 and 45).[65] The tin catalyst may be particularly effective, because it can expand its coordination sphere to six, thereby providing room for coordination of both the ketone and the hydroxide leaving group.

Surprisingly, in the oxidation of both bicyclo[3.2.0]-hept-2-en-6-one and dihydrocarvone (not shown), isomeric lactones formed by migration of the secondary carbon, as is usual in BV reactions, were not observed. Other ketones (e.g., cyclohexanone; Figure 46) were oxidized with remarkable selectivity (>98%) considering the reaction conditions, and the catalyst was recycled several times without a loss of activity.

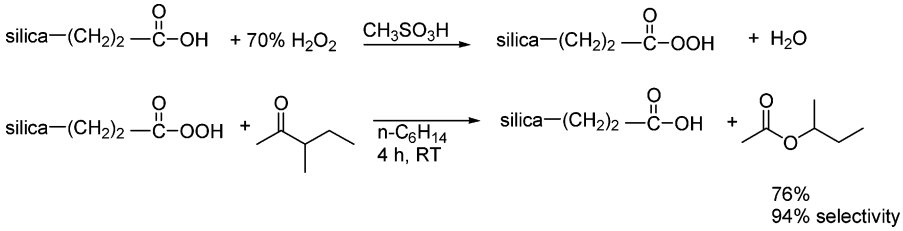


Figure 43. BV oxidation by silica-supported perpropionic acid.

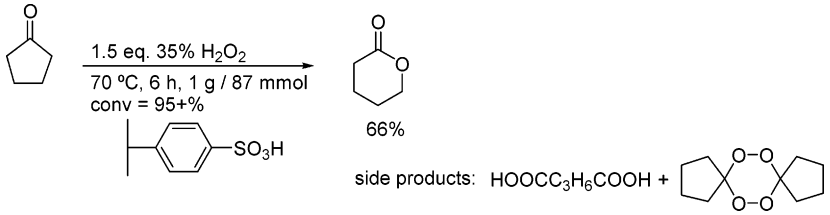
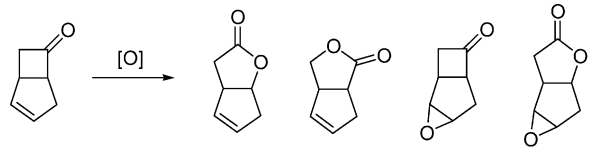


Figure 44. BV oxidation of cyclopentanone with hydrogen peroxide catalyzed by Amberlyst 15.



Catalyst[a]	Conv. (%)	sel. (%)	sel. (%)	sel. (%)	sel. (%)
Sn zeolite Beta[30]	>95	67	33	0	0
m-CPBA[30]	>95	29	0	34	37
m-CPBA[127]	>95	95	0	1.4	2.8
MTO[65]	100 [b]	87	13	0	0

(a) Conditions: Sn-beta and m-CPBA (ref. 30): 1.5 wt% Sn-beta + 1.5 eq 35% H_2O_2 or m-CPBA, 30°C, MTBE, 2h. m-CPBA (ref. 127): 1 eq m-CPBA in dichloromethane. (b) 63% isolated yield of indicated products.

Figure 45. Sn-β-catalyzed BV oxidation of bicyclo[3.2.0]-hept-2-en-6-one.

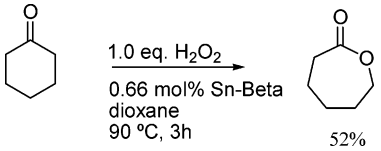


Figure 46. BV oxidation of cyclohexanone catalyzed by Sn-β.

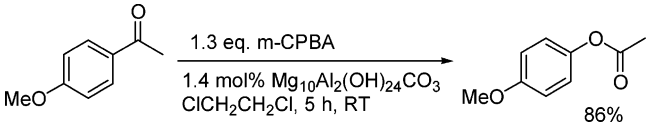


Figure 47. Hydrotalcite-catalyzed BV oxidation.

Dioxane or the more attractive, MTBE, were used as solvents in these transformations.

More recently, the Sn-β catalyst was applied to the BV oxidation of aromatic aldehydes to the corresponding formate esters, affording a one-pot synthesis of phenols from aromatic aldehydes.[128] The pore size of zeolite β (~6.5 Å × 7.5 Å) may pose some restrictions on the substrate size. For (much) bulkier substrates, a new tin-MCM-41 (pore size around 20 Å) has been developed in the same group.[129] Results with this material, however, do not match those obtained with tin-substituted zeolite β.

Over the past few years, (basic) hydrotalcites have received tremendous attention as catalysts for a variety of reactions. These materials consist of Brucite layers containing Lewis acidic metal cations and anionic interlayers. Kaneda et al. developed several materials that are active in BV oxidations with *m*-CPBA and O_2/aldehyde (Figure 47).[130] The Lewis metals may improve the reaction via coordination to

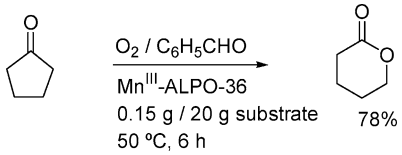


Figure 48. Oxidation of cyclopentanone with peracids catalyzed by Mn-ALPO-36.

peracid and intermediate. Additionally, the basic interlayers may remove the coproduct *m*-CBA from the reaction mixture to avoid competition (see also section 3.4).

More recently, the BV oxidation of a range of cyclic ketones with 30% H_2O_2 in acetonitrile catalyzed by a Sn-doped hydrotalcite was reported.[131] The reaction was successful only in acetonitrile as solvent, strongly suggesting that the actual oxidant is the Payne reagent,[132] $CH_3(C{=}NH)OOH$, formed by reaction of the hydrogen peroxide. The latter reaction is base-catalyzed and is, presumably, catalyzed by the basic hydrotalcite. This would imply that one equivalent of acetamide is formed as a coproduct.

4.3.3. Solid Catalysts for in Situ Formation of Peracids

The main group metal cations in hydrotalcites can also be exchanged for transition metal cations [Fe(III), Cu(II), and Ni(II)] that promote the in situ formation of peracids from benzaldehyde and oxygen.[130] Other sophisticated solid catalysts—Mn^{III}-ALPO-36 and Co^{III}-ALPO-36—were developed by Thomas et al. In these cases, the transition metals play a similar role and the active oxidant is formed from benzaldehyde and oxygen in the micropores.[133] The catalysts are highly active and selective in the oxidation of cyclic ketones (such as cyclopentanone; Figure 48; TOF = 250 h^{-1}, selectivity >98%; results for cyclohexanone, 2-methylcyclohexanone, and adamantanone were similar) at low temperatures, and the catalyst could be reused without a significant loss of activity. A surprising result was the observation that in the oxidation of 2-methylcyclopentanone the "wrong" lactone, 2-methylvalerolactone, is formed selectively,[134] which makes the occurrence of a peracid mechanism doubtful.

A more simple approach to immobilize transition metal salts (Cr, Cu, Co, Mn, and Ni) that catalyze the formation of peracids is via an anionic spacer (Figure 49).[135] However, in this case, the results—more equivalents of oxidant needed, benzene as solvent, TOF ~50 h^{-1}—were less promising.

The catalysts presented here are already significantly better in the BV reaction than the TS-1 catalyst developed by researchers at Enichem.[136] This

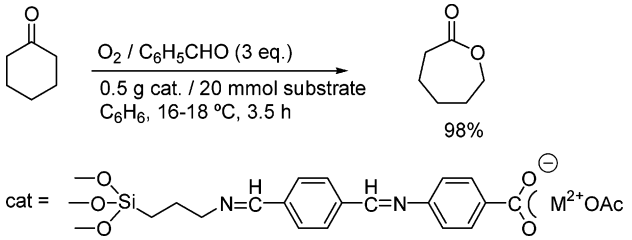


Figure 49. Transition metal catalysts for BV reaction immobilized on a spacer.

titanium silicalite catalyst is used in combination with aqueous hydrogen peroxide. To obtain appreciable reaction rates, extra acid must be added, and selectivity is generally poor.[137]

5. Outlook

In this review, we have given examples that illustrate in which direction the BV reaction is developing. There is certainly a need for cleaner reactions that preferably use hydrogen peroxide as the terminal oxidant. New (nonchlorinated) solvents are required because the use of dichloromethane is becoming prohibitive. Still better catalysts are needed for the activation of hydrogen peroxide. For reactions on a large-scale, solid Lewis acid catalysts such as the Sn-MCM-41 developed by Corma[30] are highly interesting, but one can also think of other materials such as hydrotalcites.[131] We also note that another class of robust oxidation catalysts that has not yet been explored are the heteropolyanions.

The area of metal-catalyzed enantioselective BV reactions is only about 10 years old. Therefore, significant progress is still to be expected. However, biocatalytic methods would seem to have the edge with regard to enantioselectivity, regiochemistry, and functional group selectivity. Standard protocols have already been developed so that any organic chemist without a background in biocatalysis or biochemistry may use these commercially available biocatalysts. Furthermore, in the pharmaceutical industry, product contamination is less likely to be a problem with biocatalytic methods than with metal-catalyzed reactions. It will be interesting to follow the competition between bio- and chemocatalytic methodologies for BV oxidations in the future. In any event, it has led to the development of greener procedures for this classical reaction in organic synthesis.

6. Abbrevations

ALPO	aluminophosphates molecular sieves
BVMO	Baeyer–Villiger monooxygenase
m-CPBA	*meta*-chloroperbenzoic acid
m-CBA	*meta*-chlorobenzoic acid
CHP	cumene hydroperoxide
MCM-41	denotion of specific type of mesoporous molecular sieves
MTBE	methyl-*tert*-butyl ether
MTO	methyl trioxorhenium
NHPI	N-hydroxy-phthalimide
TOF	turn over frequency
TS-1	titano-silicalite 1 (a titanium containing molecular sieve with a MFI structure)

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(7) Exception: When acid anhydrides are used, these are added last to avoid the formation of diacyl peroxides.
(8) Carbonyl compounds can be oxidized with dioxygen in combination with a sacrificial aldehyde (Mukaiyama system). However, this system is not significantly different from systems using stoichiometric amounts of peracids. Therefore, we largely ignore this system. See, for an example: Kaneda, K.; Ueno, S.; Imanaka, T.; Shimotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 2915.
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