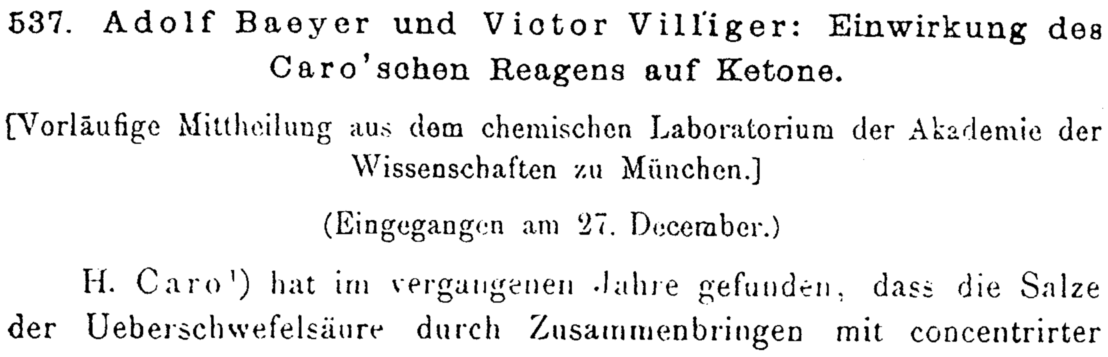
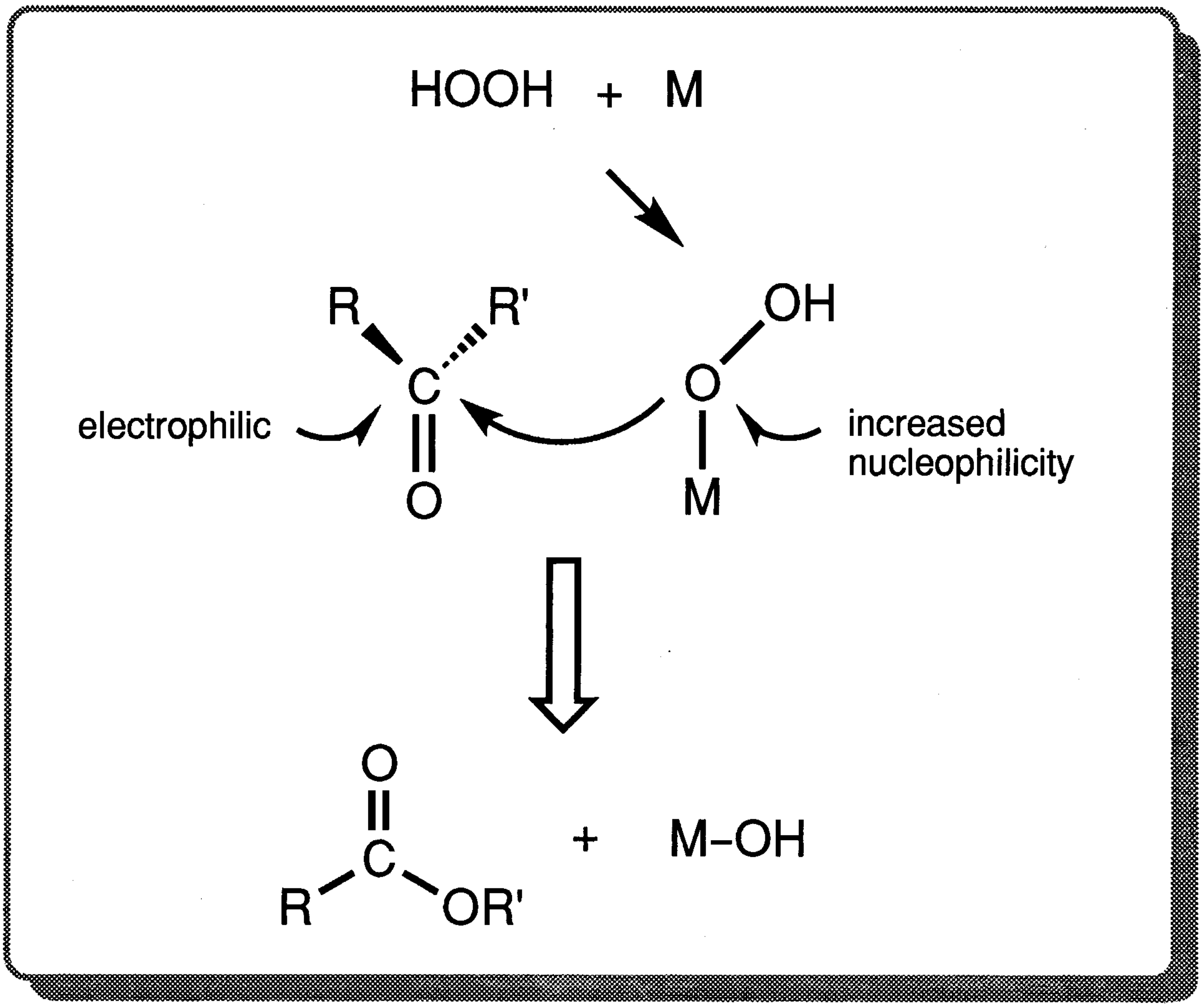


537. Adolf Baeyer und Victor Villiger: Einwirkung des Caro'schen Reagens auf Ketone.

[Vorläufige Mittheilung aus dem chemischen Laboratorium der Akademie der Wissenschaften zu München.]

(Eingegangen am 27. December.)

H. Caro¹) hat im vergangenen Jahre gefunden, dass die Salze der Ueberschwefelsäure durch Zusammenbringen mit concentrirter



Almost 100 years lie between the first publication on the Baeyer–Villiger oxidation (1899) and the modern variants of this reaction that are catalyzed by transition metal compounds.

Transition Metal Catalysis in the Baeyer – Villiger Oxidation of Ketones

Giorgio Strukul*

In memory of Fulvio Di Furia (1944 – 1997)

Increased ecological awareness and increasing restrictions are forcing the chemical industry worldwide to redesign some production lines in order to comply with the protection of the environment. In particular, industrial organic chemistry often makes use of multistep synthetic methods in which the amount of useful product is largely outweighed by the amount of by-products that need disposal. In this context catalytic methods capable of simplifying the synthetic procedures or the use of cleaner reagents is in principle more environmentally friendly than stepwise stoichiometric transformations. This review deals with an organic reaction (the Baeyer – Villiger oxidation) that is widely used in a variety of synthetic applications and the attempts that have been made over the years to make the reaction catalytic, particularly in association with a typically "green" oxidant such as hydrogen peroxide. The initial section summarizes briefly the general features of the Baeyer – Villiger oxidation with peracids that have made it so successful in organic synthesis. The next section emphasizes the use of hydrogen peroxide as oxidant and the number of transition metal systems based on Pt, Re, and Ti that so far have proved successful for the catalytic reaction. The mechanistic principles (in particular the need for a nucleophilic peroxygen) are compared with those of the stoichiometric reaction with peracids. The use of dioxygen as oxidant in the presence of sacrificial aldehydes and transition metal catalysts is reviewed. Finally, the systems capable of performing the transformation in both an enantiospecific and an enantioselective fashion are discussed. This analysis provides some useful strategies for the future development of new catalytic systems in this reaction.

Keywords: Baeyer – Villiger oxidation · homogeneous catalysis · ketones · oxidations · transition metals

1. Introduction

The Baeyer – Villiger oxidation of ketones is a reaction of major synthetic interest in organic chemistry with a large range of possible applications spanning such diverse areas as the synthesis of antibiotics and steroids, the synthesis of pheromones for agrochemistry, the synthesis of monomers for polymerization, etc. Over the years, the whole subject has been reviewed several times,[1] either in specific reviews[1a,f] or in the more general context of organic oxidations.[1b–e] The versatility of this reaction in synthetic organic chemistry is witnessed by the observation that the most recent of these reviews published by Krow[1f] includes more than 1000 references.

In contrast to this wealth of purely organic chemistry, the attempts to apply transition metal catalysis to this important organic transformation have met with only moderate success and have never been reviewed. Indeed, catalytic methods may have a number of advantages over their stoichiometric counterparts, ranging from the simplification of the operational conditions, to the use of cheaper reactants and the minimization of waste products. These benefits make them more attractive for practical applications both economically and also ecologically in the context of developing more environmentally friendly methods of production.

In this review, the use of transition metal catalysts for the Baeyer – Villiger oxidation will be analyzed critically in an attempt to understand the basic requirements for successful catalysis and set some possible guidelines for future developments in this field.

2. Historical Background

The Baeyer – Villiger reaction owes its name to the pioneering work of Adolf Baeyer and Victor Villiger who reported, almost a century ago, the possibility of converting cyclic ketones into lactones with a peroxy acid as oxidant.[2] The reactions studied by Baeyer and Villiger in 1899 were the oxidations of menthone and tetrahydrocarvone to the corresponding lactones [Eqs. (1) and (2)]. For this purpose these

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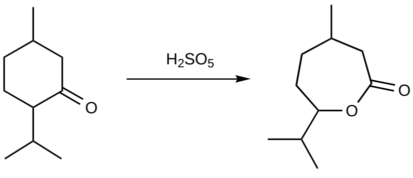

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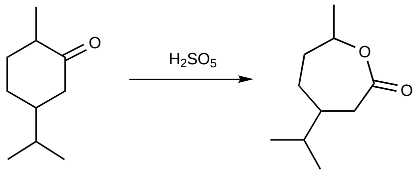


(2)

authors used the most powerful oxidant known at that time, monopersulfuric acid, the synthesis of which had been accomplished the year before by Caro[3] by mixing together equivalent amounts of potassium persulfate, concentrated sulfuric acid, and water [Eq. (3)].

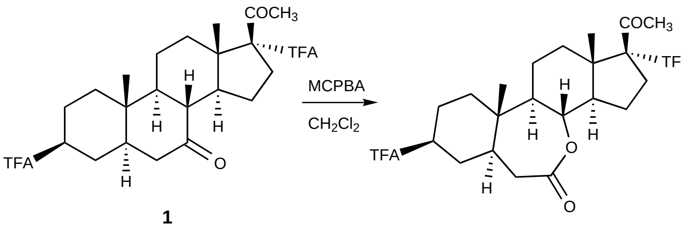
$$K_2S_2O_8 + H_2SO_4 + H_2O \longrightarrow 2\,KHSO_4 + H_2SO_5 \qquad (3)$$

2.1. Properties of the Baeyer–Villiger Oxidation

The Baeyer–Villiger oxidation of ketones, as it is practised nowadays, has a number of intrinsic advantages that have made it so successful in synthetic organic chemistry:

- It tolerates the presence of many functional groups in the molecule. For example, even in unsaturated ketones the oxidation with peracids occurs generally at the carbonyl group, provided the carbon–carbon double bond is not conjugated.
- The regiochemistry of the reaction can be normally controlled by reference to the scale of migratory aptitude for different groups, although there are cases (for example the bicyclic systems) in which various stereoelectronic aspects can influence the regioselectivity of the oxygen insertion.
- It is generally stereoselective, which implies that migrating chiral carbon atoms retain their absolute configuration also in the product ester.
- A wide variety of peroxy acids can be used as oxidants for the reaction.

Two examples that summarize the above points are shown in Equations (4) and (5). Pregnan-7,20-dione (**1**), a precursor of 7-oxyprogesterone, reacts only at the C-7 carbonyl,[4] and the acyl-substituted β-lactam **2**, an intermediate in the synthesis of carbapenem antibiotics, is converted exclusively into the corresponding acetate.[5] Both reactions proceed almost exclusively at the indicated carbonyl group despite the presence of other potentially oxidizable functional groups and with retention of configuration at the migrating carbon atom.



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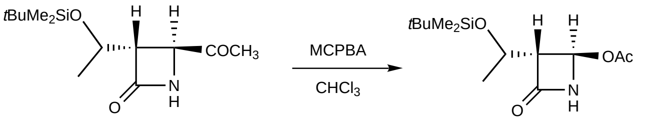

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2

2.2. Mechanism

The mechanism of the Baeyer–Villiger oxidation was first studied by Criegee[6] about 50 years ago and, in its general features, has remained essentially the same. As shown in Scheme 1, the stepwise process consists of an initial nucleophilic attack of the peroxy acid at the carbonyl carbon (step a) to form an intermediate species (**3**) known as the Criegee adduct. This step is followed by the migration of one of the alkyl groups onto the peroxygen and the concomitant release of the carboxylate anion (step b). Of these, step b is the more important in determining the properties of the overall reaction.

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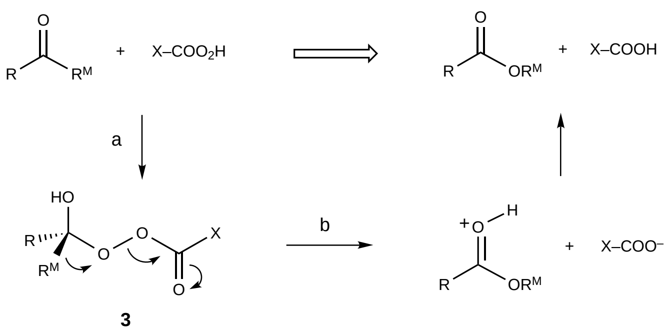
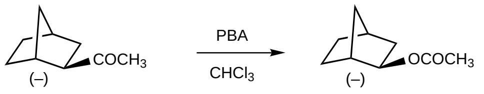


Scheme 1. Mechanism of the Baeyer–Villiger oxidation of ketones. R^M denotes the migrating group.

The migration step is, in fact, concerted, as was suggested for the first time by Berson and Suzuki in 1959[6] [Eq. (6); PBA = perbenzoic acid], which accounts for the selectivity of the reaction, and also rate-determining in the vast majority of cases. The latter point is consistent with the general observation that the reaction rate is increased by the presence of electron-withdrawing substituents on the peroxy acid, which make its conjugate base a better leaving group. For example, peroxotrifluoroacetic acid (PTFAA) is known to be a better oxidant than peracetic acid (PAA), and *m*-chloroperbenzoic acid (MCPBA) is better than perbenzoic acid. Also consistent with a rate-determining step b is the ability of electron-donating substituents in the migrating group to facilitate the rearrangement.



(6)

These observations are consistent with the well-known scales of migratory aptitude (*t*-alkyl > cyclohexyl > *s*-alkyl > benzyl > phenyl > *n*-alkyl > cyclopentyl > methyl) and reactivity of the oxidant (TFPAA > monopermaleic acid > mono-*o*-perphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > MCPBA ≈ performic acid > PBA > PAA ≫ H_2O_2 > *t*BuOOH). The reactivity scale is related to the strength of the conjugate acid of the leaving group.

3. Hydrogen Peroxide as Oxidant

Some of the above peracids are commercially available. In general, they are prepared from the corresponding acids and concentrated hydrogen peroxide under acid catalysis. In the past the use of 90% H_2O_2 as reagent for the synthesis of peracids was rather common. More recently, the withdrawal of 90% H_2O_2 from the market because of its highly explosive properties has forced the use of the commercially available 70% H_2O_2; however, only lower grade peracids can be prepared.

The most powerful oxidants that are also strong acids require the use of a buffer in the Baeyer–Villiger oxidation to avoid transesterification. In addition, at the end of the Baeyer–Villiger reaction the spent carboxylic acid is separated and discarded. This procedure, while normally viable in common laboratory practice, especially with peracids that are commercially available, is hardly acceptable for large-scale industrial operations. The alternative could be the use of the spent carboxylic acid to regenerate the peracid, but again this additional operation would imply additional costs.

While the use of peracids results in the ultimate consumption of hydrogen peroxide as primary oxidant, its direct use in the Baeyer–Villiger oxidation may have a number of advantages:

- It simplifies greatly the workup to allow the use of simpler reaction conditions and avoid the separation of the carboxylic acid.
- It has a higher active oxygen content (defined as the % active oxygen with respect to the molecular weight), which is economically advantageous as chemicals are sold by weight. For example, the active oxygen content of H_2O_2 is 47%, of PAA 21%, and of TFPAA 9.2%.
- As a consequence, it produces a lower amount of by-product (water) and is the most environmentally friendly among peroxidic oxidants.

All the above points have important economic implications that make hydrogen peroxide very attractive for industrial applications. Indeed, chemical industries are facing increasing costs to clean their off-streams, and it can be easily predicted that some productions will have to be redesigned to comply with regulations for the protection of the environment.

On the other hand, hydrogen peroxide has also disadvantages with respect to organic peracids:

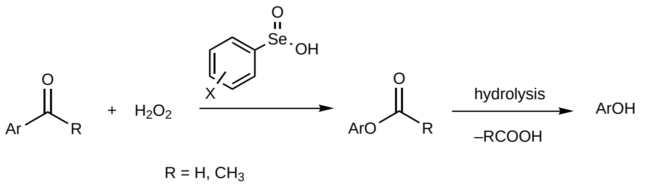
- Water is always present either as a co-solvent or in any case as a reaction product. Hydrolysis of the ester products may result, and incompatibility with the solvent/substrate system may hamper the substrate/oxidant interaction.
- It has a lower stability towards radical decomposition.
- It is kinetically more inert and requires the use of a suitable catalyst.

3.1. Early Catalytic Work

The use of acid or base catalysis with H_2O_2 as oxidant in the Baeyer–Villiger oxidation has been known for a long time.[1a] However, it is limited to strained cyclic ketones such as cyclobutanones or bicyclo[2,2,1]hepten-2-ones,[8] so the success of the reaction is more due to the reactivity of the substrate rather than that of the oxidant. Other early attempts to create catalytic systems tried generating peracids in situ.

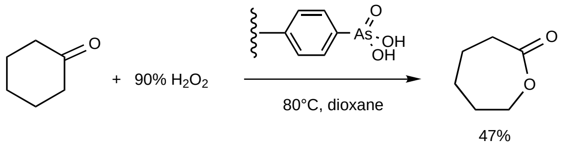
The easy reaction between substituted benzeneselenic acids and 30–90% hydrogen peroxide has been exploited to produce the corresponding peracids, which were successfully employed for the conversion of aromatic aldehydes and ketones into phenols by hydrolysis of the corresponding formates or acetates [Eq. (7)].[9] The major drawback of this system is that 30% H_2O_2 can be used only with the easily oxidizable aldehydes, while ketones require the no longer commercially available 90% H_2O_2.

Similarly, arsenated polystyrene resins catalyze biphasic and triphasic Baeyer–Villiger oxidations of ketones in



(7)

methanol, dioxane, or chloroform with 30 % or 90 % H_2O_2 at 80°C.[10] The use of water-miscible solvents could not avoid extensive hydrolysis of the product ester, particularly when 30 % H_2O_2 was employed as oxidant. The problem was partly circumvented either by using 90 % H_2O_2 [Eq. (8)] or in a triphasic system with chloroform as solvent. Under these conditions, water-immiscible cyclic ketones can yield the corresponding lactones with good selectivities.



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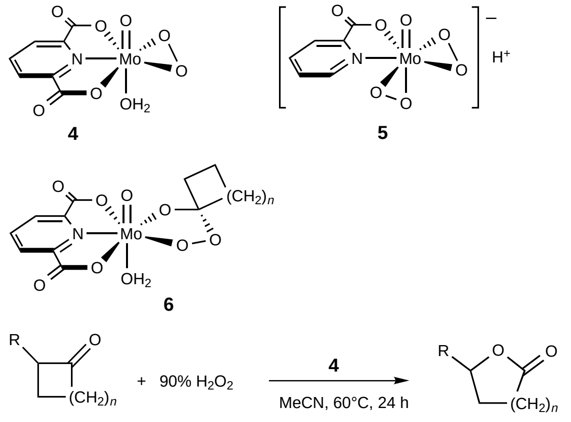
The first report of transition metal catalysis in the Baeyer–Villiger oxidation of cyclic ketones is due to Mares and coworkers, who reported in 1978 the use of picolinato and dipicolinato Mo^{VI} peroxo complexes (**4** and **5**) as catalysts and 90 % H_2O_2 as oxidant (Scheme 2).[11] Complexes **4** and **5** can be easily prepared from the corresponding oxo compounds by reaction with hydrogen peroxide.[12] Molar turnovers ranged from poor to moderate, thereby reflecting the difficulty to bring together two electrophiles such as the carbonyl carbon and the peroxygen in the peroxometallacyclic species **6** proposed by the authors to be the crucial intermediate.



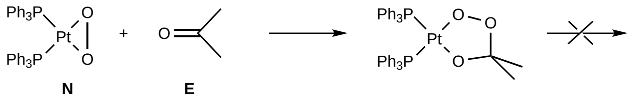
R	n	turnover
H	2	19
Me	2	25
H	3	3
Me	3	3

Scheme 2. Oxidation of cyclic ketones catalyzed by Mo^{VI} complexes.

This system has been recently reinvestigated by Campestrini and Di Furia,[13] who failed to observe the stoichiometric reaction between the peroxomolybdenum complex **4** and cyclopentanone, as one would expect if **4** was the actual oxidant. To explain the occurrence of the catalytic reaction when H_2O_2 was present, these authors suggested the likely involvement of acid catalysis as a consequence of the strong acidic character of peroxomolybdenum(VI) complexes such as **4**.[14] Interestingly, an equivalent amount of sulfuric acid instead of **4** resulted in the same catalytic activity.[13]

3.2. The Platinum System

The above results on the molybdenum system seem to suggest that, as the point of attack for oxygen transfer (the carbonyl carbon) is electrophilic in nature, the search for an efficient catalyst for the Baeyer–Villiger oxidation will have to be directed towards complexes capable of increasing the nucleophilicity of hydrogen peroxide. Indeed, the platinum dioxygen complex $[(PPh_3)_2Pt(O_2)]$ has long been known to interact easily with ketones to give stable peroxometallacyclic insertion products.[15] The driving force for the reaction has been recognized to be the nucleophilic attack of the peroxy moiety on the electrophilic carbonyl carbon (Scheme 3).



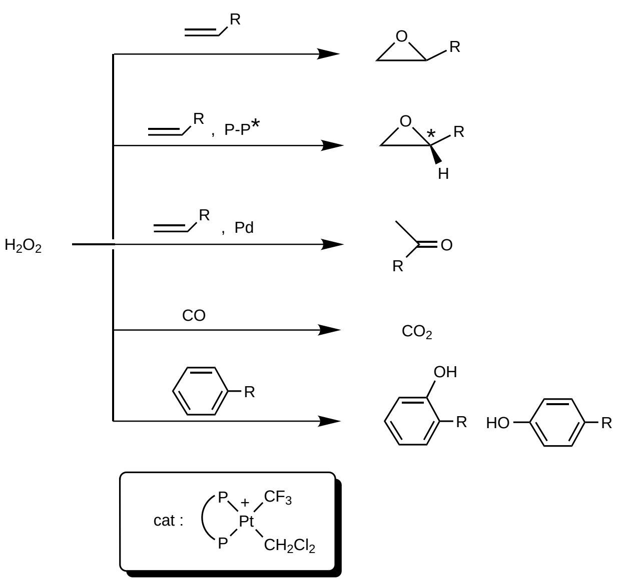
Scheme 3. Basic principle of the oxygen transfer to ketones by a peroxy complex of Pt^{II}. N = nucleophile, E = electrophile.

Unfortunately, the insertion complex is very stable, and no oxidation products evolve.

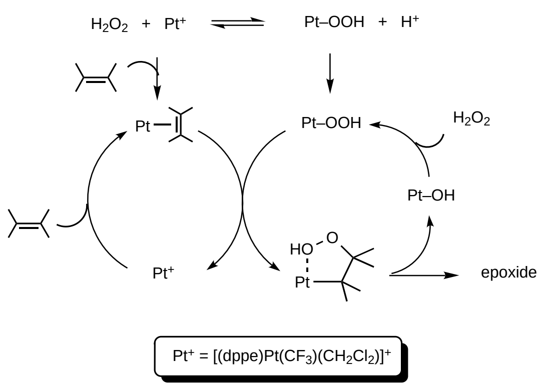
Since 1979 we have been studying the interaction of a variety of square-planar, *cis* complexes of the type $[(P-P)Pt(CF_3)X]$ (P–P = various diphosphanes; X = CH_2Cl_2, OH) with H_2O_2 and *t*BuOOH to yield stable peroxy compounds with the aim of increasing the nucleophilicity of the peroxygen through coordination.[16] Evidence on the extent of polarization of the Pt–O bond,[16c, 17] and hence on the nucleophilic nature of the coordinated peroxygen, was found through NMR spectroscopy by analyzing the $^1J_{P,Pt}$ coupling constant between Pt and the P donor *trans* to the peroxy oxygen and from the whole body of reactivity displayed by these complexes.

Over the years, this class of compounds proved very profitable as catalysts for a variety of oxidation reactions with hydrogen peroxide as oxidant (Scheme 4): these include the epoxidation of terminal olefins,[18] including the enantioselective version,[19] the ketonization of terminal olefins with a Pd cocatalyst,[20] the oxidation of carbon monoxide,[21] and the direct hydroxylation of aromatics.[22]

The mechanistic principle by which these catalysts operate[23] is shown in Scheme 5 for the epoxidation of olefins. The two catalytic cycles operate simultaneously and evidence the bifunctional role played by Pt, which increases the electro-



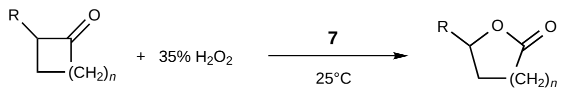
Scheme 4. Summary of Pt^{II}-catalyzed oxidation reactions with hydrogen peroxide.

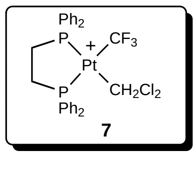


Scheme 5. Mechanism of the Pt^{II}-catalyzed epoxidation of olefins with hydrogen peroxide. dppe = ethane-1,2-diylbis(diphenylphosphane).

philic character of the substrate (olefin) on one hand and the nucleophilic character of hydrogen peroxide on the other.

The use of $[(dppe)Pt(CF_3)(CH_2Cl_2)]BF_4$ (**7**-BF_4) for the Baeyer–Villiger oxidation was successfully tested at room temperature for a variety of simple cyclic ketones[24] with 35% H_2O_2. As is shown in Scheme 6, this system, which represents the first unambiguous example of transition metal catalysis applied to the Baeyer–Villiger oxidation, is more efficient than the molybdenum-based one and allows operation under considerably milder conditions.



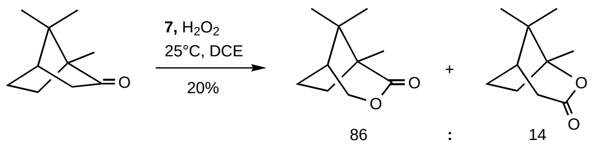


7

R	*n*	turnover	time [min]
H	1	333	8
H	2	68	108
Me	2	17	51
H	3	43	35
Me	3	60	49

Scheme 6. Catalytic activity of complex **7** in the oxidation of cyclic ketones.

Catalyst **7** was found to be inactive in the oxidation of acyclic ketones, even highly substituted ones such as methyl-*tert*-butylketone, while it behaves similarly to peracids in promoting the oxidations of substituted cyclic ketones such as menthone or camphor [Eq. (9); DCE = 1,2-dichloroethane].[25] Other than with peracids, unsaturated ketones first undergo epoxidation and then Baeyer–Villiger oxidation [Eq. (10)]. The chemoselectivity can be quite high, and this class of catalyst proved successful for the (even asymmetric) epoxidation of α,β-unsaturated ketones.[26]



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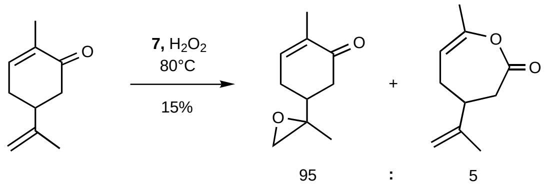
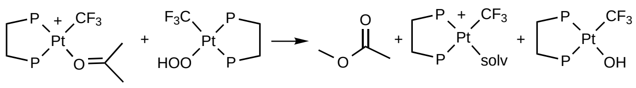


(10)

Catalyst **7** tends to deactivate as the oxidation proceeds, thereby limiting the maximum achievable turnover. This deactivation was associated to the presence of small amounts of hydroxycarboxylic acid arising from lactone hydrolysis, which can easily react with **7** to produce a no longer catalytically active carboxylate derivative [Eq. (11)].[25]

$$[(dppe)Pt(CF_3)(solv)]^+ + HO(CH_2)_5COOH \longrightarrow [(dppe)Pt(CF_3)(OOCC_5H_{10}OH)] \quad (11)$$

The mechanism of the reaction[25] is shown in Scheme 7 and differs from the epoxidation reaction (Scheme 5) as far as the nature of the oxidant is concerned. Although $[(dppe)Pt(CF_3)(OOH)]$ can be a possible oxidant, as was demonstrated by successfully performing the stoichiometric reaction shown in Equation (12), the actual oxidant of the catalytic reaction was found to be free H_2O_2 (Scheme 7). The catalyst behaves essentially as a Lewis acid, capable of increasing the electrophilic character of the carbonyl carbon, and indeed the quasi peroxometallacyclic intermediate bears strong similarities with the Criegee intermediate, with Pt^+ instead of H^+. However, the peculiar role of Pt seems to be rather to provide an easy pathway for the exit of the poor HO^- leaving group through coordination, thereby giving the system the driving force necessary to break down the quasi peroxo-



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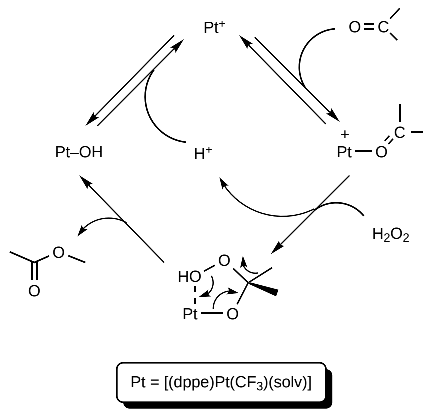
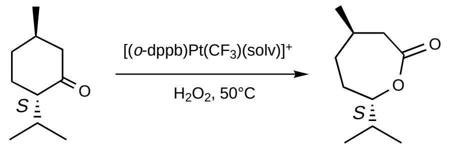


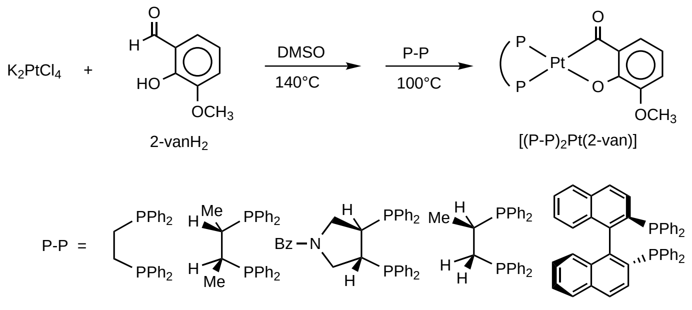
Scheme 7. Mechanism of the oxidation of ketones catalyzed by **7**.

metallacyclic intermediate and yield products. Again, the analogy with step b of the Baeyer–Villiger oxidation with peracids (Scheme 1) in determining the overall reactivity of the process is remarkable. Even more so, it was found in the case of menthone that the reaction proceeds with retention of configuration at the migrating carbon atom [Eq. (13), *o*-dppb = *o*-bis(diphenylphosphanyl)benzene].



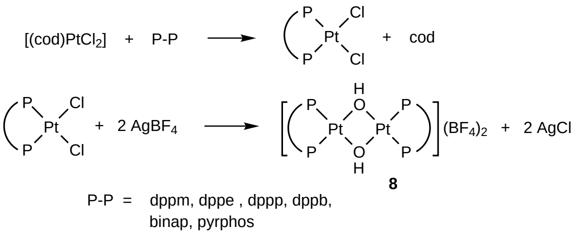
(13)

Other Pt species containing electron-withdrawing ligands capable of mimicking the effect of the CF_3 ligand were studied. Complexes of the type [(P–P)Pt(2-van)] (P–P = various diphosphanes; 2-van = 2-vanillin dianion) were synthesized following the general method outlined by Pregosin and co-workers (Scheme 8).[27] These complexes that, per se, are catalytically inactive can be promoted with the addition of one equivalent of a strong non-coordinating acid and can perform the catalytic oxidation of a series of simple cyclic ketones.[28] Studies on the evolution of these platinum(II) compounds under acidic conditions has led to the identification of a class of known bridging hydroxy complexes that proved interesting catalysts for the Baeyer–Villiger oxidation of ketones.[29]

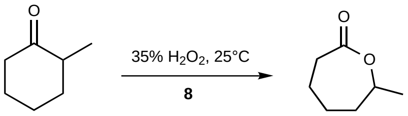


Scheme 8. Synthesis of [(P–P)Pt(2-van)] complexes. Bz = benzyl.

The synthesis of this class of complexes (Scheme 9) was reported for the first time in 1972 by Bushnell et al.;[30] however, in about 25 years they have been scarcely studied because they are hardly reactive. The synthetic route outlined in Scheme 9 that was originally reported only for PPh_3 derivatives has been employed by several authors for the preparation of homologous compounds containing a variety of diphosphanes. Interestingly, the ability of **8** to promote the Baeyer–Villiger oxidation with hydrogen peroxide is dependent on the size of the diphosphane–platinum ring,[31] as was demonstrated for a series of homologous complexes on the substrate methylcyclohexanone (Scheme 10). The most active catalyst $[(dppb)Pt(\mu\text{-}OH)]_2^{2+}$ was also reactive towards a series of acyclic ketones,[31] thus representing the first example of transition metal catalysis (Scheme 11). The reactivity observed indicates the scale of migratory aptitude *tert*-alkyl > vinyl > *s*-alkyl > phenyl > *n*-alkyl and parallels the reactivity known with peracids as oxidants (see above).

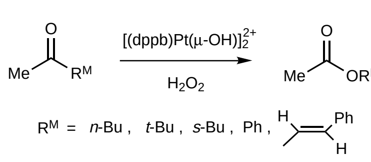


Scheme 9. Synthesis of $[(P-P)Pt(\mu\text{-}OH)]_2^{2+}$ complexes. dppm = methanediylbis(diphenylphosphane); dppp = propane-1,3-diylbis(diphenylphosphane); dppb = butane-1,4-diylbis(diphenylphosphane); binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; pyrphos = 3,4-bis(diphenylphosphanyl)pyrollidine.



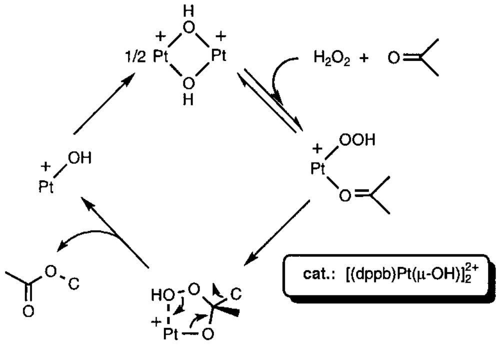
P-P	turnover
dppm	8
dppe	56
dppp	53
dppb	110

Scheme 10. Effect of the diphosphane P–P in the oxidation of methylcyclohexanone catalyzed by **7**.



Scheme 11. Catalytic oxidation of acyclic ketones.

The oxidation of methylcyclohexanone was also studied kinetically and suggested the mechanism of reaction shown in Scheme 12.[31] The dimeric complex first opens by the action

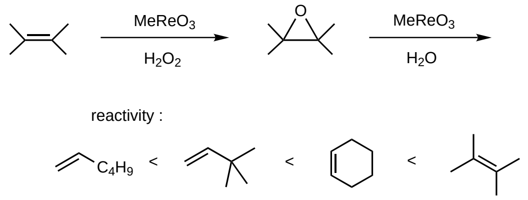


Scheme 12. Mechanism of the oxidation of ketones catalyzed by $[(dppb)Pt(\mu\text{-}OH)]_2^{2+}$.

of hydrogen peroxide and the ketone, followed by the apparently crucial step of an intramolecular nucleophilic attack of the hydroperoxy ligand on the coordinated ketone. The high activity of $[(dppb)Pt(\mu\text{-}OH)]_2(BF_4)_2$ relative to the homologous diphosphane derivatives could be due to a better ability to promote the initial dissociation equilibrium because of a larger P-Pt-P bite angle.

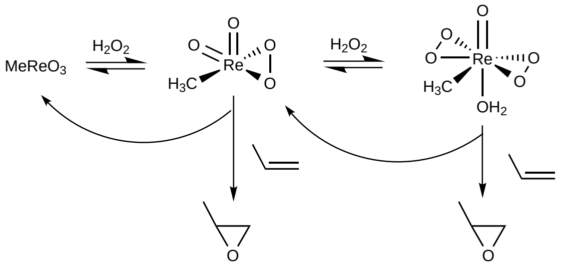
3.3. The Methyltrioxorhenium (MTO) Catalyst

MTO is a simple and easily accessible organometallic oxide, the synthesis of which was reported by Herrmann and coworkers.[32] MTO is a useful catalyst for oxidation reactions with hydrogen peroxide as oxidant including the oxidation of Baeyer–Villiger. Again, the discovery that cyclic ketones could be easily converted into lactones stemmed from previous work on the epoxidation of olefins.[33] It was observed that a variety of simple internal and cyclic olefins could be easily epoxidized at temperatures ranging from −10 to 70°C, although in some cases the reaction proceeds further, yielding the diol as the major oxidation product (Scheme 13).

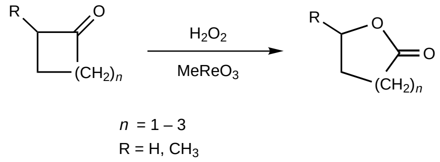


Scheme 13. Epoxidation of olefins catalyzed by $[MeReO_3]$.

Hydrogen peroxide is activated through the formation of mono- and bisperoxides,[34] which are the actual oxidants capable of transferring oxygen to olefins (Scheme 14). The reactivity observed[35] and a careful kinetic study of the reaction[36] have demonstrated that oxygen transfer occurs by nucleophilic attack of the olefin on an electrophilic peroxy oxygen via an intermediate "butterfly" transition state, as seems to be the general case for d^0 transition metal systems.[37]

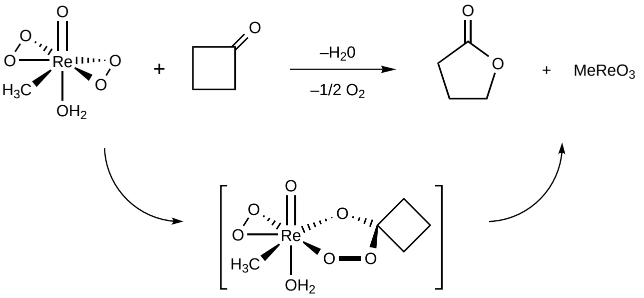


Scheme 14. Mechanistic pathway for the epoxidation of olefins catalyzed by $[MeReO_3]$.



Scheme 15. Oxidation of cyclic ketones catalyzed by $[MeReO_3]$.

So it was surprising that MTO is also involved as catalyst in the Baeyer–Villiger oxidation of cyclic ketones with hydrogen peroxide (Scheme 15) via the same reactive peroxy intermediates.[38] The reaction was suggested to proceed through the formation of an intermediate peroxometallacyclic species (Scheme 16), and to account for the reactivity observed the authors suggested that the peroxygen atoms are nucleophilic on the basis of the following observations:[38]



Scheme 16. Mechanistic pathway for the oxidation of cyclobutanone catalyzed by $[MeReO_3]$.

- ^{17}O NMR spectroscopy indicated the existence of inequivalent peroxy oxygens as should be expected by their relative position with respect to the equatorial methyl ligand. The observation of an uncommonly intense IR stretching at 877 cm^{-1} led to the conclusion that the O–O bond was substantially polarized;
- a solvent-dependent nucleophilic character was observed by reaction with thianthrene-5-oxide.

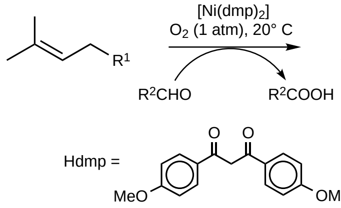
3.4. Titanium Silicalite (TS-1)

In the last decade, titanium silicalites have emerged as the major breakthrough in the use of H_2O_2 as oxidant in industrial organic chemistry.[39] The catalyst TS-1, in particular, is presently in use in the large-scale industrial production of diphenols, cyclohexanone oxime, and propylene oxide. Other reactions accomplished on a laboratory scale are the selective epoxidation of olefins and diolefins, the selective oxidation of primary alcohols to aldehydes and secondary alcohols to ketones, and the hydroxylation of aromatic and aliphatic compounds.[40] However, only very recently has the first example of Baeyer–Villiger oxidation been reported.[41]

The oxidation of cyclohexanone and acetophenone can be accomplished at 80°C with modest turnovers that increase moderately upon addition of a free acid. The selectivity to ester is generally below 50%, and the hydroxycarboxylic acid (or phenol and acetic acid) are the major by-products. Other products are the hydroxyketone, the diketone, and products arising from further hydroxylation of the aromatic ring, where present.[41] The modest activity observed seems in agreement with the nature of the actual oxidant, which is believed to be a surface Ti^{IV} (electrophilic) peroxy species;[40] in this respect TS-1 is similar to the old Mo^{VI} catalyst.[11]

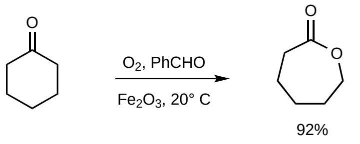
4. Dioxygen as Oxidant: the Mukaiyama System

In 1991 Mukaiyama and co-workers described the use of sacrificial aldehydes for the aerobic epoxidation of olefins in the presence of Ni complexes as catalysts (Scheme 17).[42] This report followed some earlier patents by, among others, Union Carbide, and Mitsubishi Kasei,[43] and exploits the easy autoxidation of aldehydes to promote the in situ formation of peroxy acids. This system has been highly successful in the promotion of the aerobic oxidation of a variety of substrates including olefins,[44] aldehydes,[45] silyl enolethers,[46] lactams,[47] and alkanes,[48] and has proved useful for the Baeyer–Villiger oxidation of ketones as well.

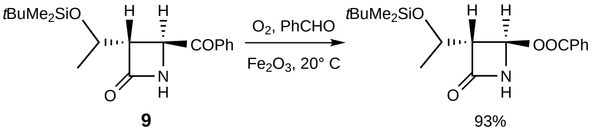


Scheme 17. Principle of the Mukaiyama system.

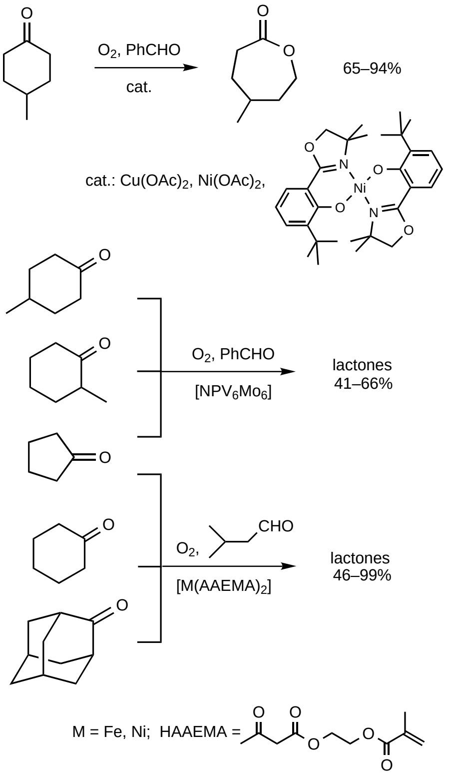
So Fe_2O_3 catalyzes the oxidation of cyclohexanone and other cyclic ketones to the corresponding lactones in high yields [Eq. (14)], but also the conversion of the benzoyl-β-lactam **9** into the corresponding benzoate ester with complete retention of configuration [Eq. (15)].[49] Similar results have been obtained for substituted cyclohexanones and cyclopentanone on use of β-diketonato complexes,[50] a Schiff-base derivative of Ni^{II},[50] or even polyoxometalates[51] (Scheme 18). Polymerizable β-diketonato complexes of nickel, iron, and cobalt have been also used for the oxidation of adamantanone, cyclohexanone, and cyclopentanone (Scheme 18).[52] Attempts to oxidize open-chain ketones such as benzophenone or *tert*-butylmethylketone were unsuccessful.[52]



(14)

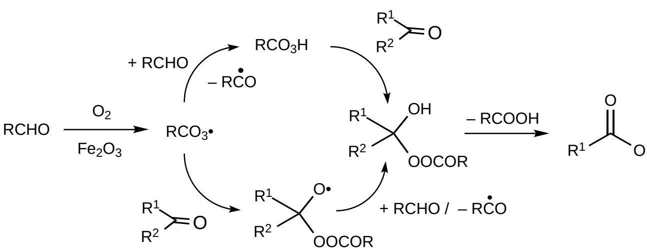


(15)



Scheme 18. Examples of oxidation of cyclic ketones with the Mukaiyama system.

A mechanistic interpretation of the Fe_2O_3-catalyzed oxidation has been proposed by Murahashi (Scheme 19).[49] The catalyst is suggested to be involved merely in the promotion of the easy autoxidation of benzaldehyde to produce perbenzoic acid in situ, in a way that is identical to the well-known industrial synthesis of acetic acid.[53] Once formed, perbenzoic acid (or its peroxy radical) performs the Baeyer–Villiger oxidation with no intervention of the catalyst. This view,



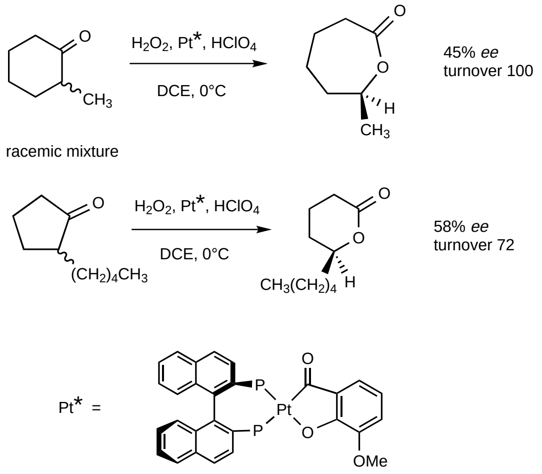
Scheme 19. Mechanistic pathway for the oxidation of ketones with the Mukaiyama system.

which appears the most obvious one, seems in agreement with the observation that, with Fe_2O_3 as catalyst, open-chain ketones can be oxidized [Eq. (15)][49] and with the fact that with benzaldehyde the reaction can proceed even in the absence of catalyst.[54] However, in all other systems reported above and based on more elaborate catalyst formulation, only cyclic ketones are reported to be oxidized in contrast with the known reactivity for an in situ produced peroxy acid. This observation and the fact that the system has been modified successfully to accomplish the Baeyer–Villiger enantioselective transformation (see Section 5) seem to suggest that the metal may also be actively involved in the oxygen transfer step, although how is still unclear.

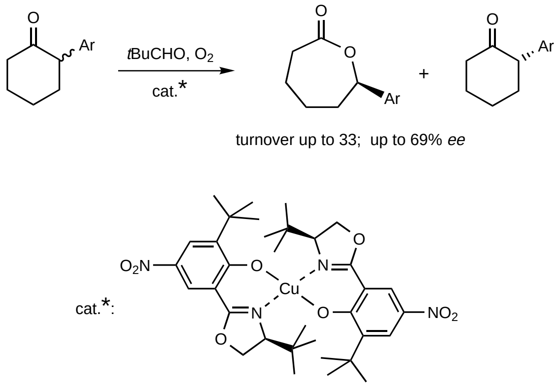
5. Asymmetric Oxidation

The use of microorganisms in the asymmetric Baeyer–Villiger oxidation of ketones has been known for several years and has been recently reviewed.[55] Whole cell cultures[56] or purified enzymes[57] extracted from the Acinetobacter bacteria family have allowed the preparation chiral lactones with optical purity higher than 98%.

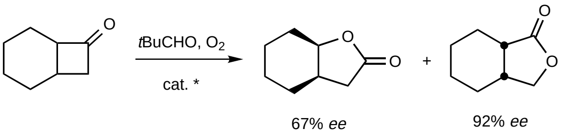
Recently, the first two examples of transition metal catalysis for the Baeyer–Villiger oxidation were published independently and almost simultaneously by Gusso et al.[28] and by Bolm et al.[58] In both cases the reaction was the kinetic resolution of racemic ketones through enantiospecific conversion into chiral lactones. The former studies were based on the use of Pt complexes modified with chiral diphosphanes and hydrogen peroxide as oxidant. Optimization of the catalyst structure[28, 29] led to the conversion of a series of racemic cyclohexanones and cyclopentanones into chiral lactones related to pheromones and fragrances with an *ee* of up to 58% (Scheme 20). The latter studies[58] were based on a modified Mukaiyama system consisting of a chiral copper complex (Scheme 21), pivalaldehyde, and oxygen as the primary oxidant. Racemic aryl-substituted cyclohexanones could be oxidized to the corresponding enantiomerically enriched lactones with an *ee* of up to 69%. No enantiospecificity was observed with homologous Ni complexes, while the use of other sacrificial aldehydes resulted in lower *ee*'s. The steric and electronic properties of the ligand influence the activity and enantiospecificity of the catalysts. Better yields and *ee*'s were obtained with the *p*-nitro-substituted complexes rather than their unsubstituted counterparts. Substituents less bulky than *t*Bu in the arene resulted in much poorer chemical yields (<10%).[58] The same catalyst system was extended to the oxidation of a variety of racemic substituted cyclobutanones, which again led to a kinetic resolution yielding chiral lactones with better *ee*'s [Eqs. (16) and (17)].[59]



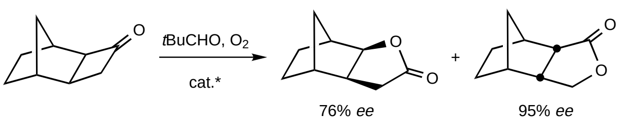
Scheme 20. Enantiospecific oxidation of ketones catalyzed by chiral platinum complexes. DCE = 1,2-dichloroethane.



Scheme 21. Enantiospecific oxidation of ketones catalyzed by chiral copper complexes.

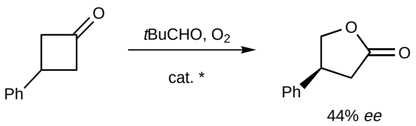


(16)

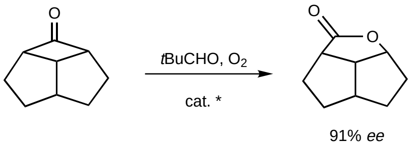


(17)

The first example of enantioselective Baeyer–Villiger oxidation has been very recently reported by Bolm with the same catalyst system in the oxidation of prochiral ketones.[60] Substituted cyclobutanones afforded the corresponding butyrolactones [Eqs. (18) and (19)] with an asymmetric induction up to 91% *ee*. Unfortunately, the system seems unable to oxidize ketones other than cyclobutanones.[60]

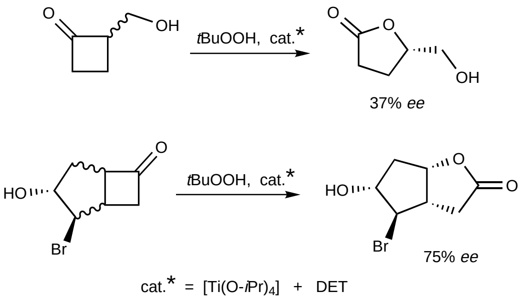


(18)



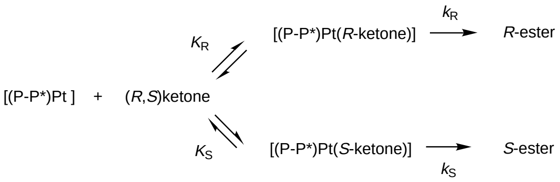
(19)

Similar results have been recently reported also by Lopp et al. (Scheme 22) with the Sharpless catalyst ($[Ti(O\text{-}i Pr)_4]$ + diethyltartrate) and *t*BuOOH as oxidant.[61] Yields are moderate, but the reaction cannot be considered catalytic in a true sense, as more catalyst than substrate was present in the reaction mixture. Again, only substituted cyclobutanones could be oxidized, probably reflecting the inadequacy of Ti^{IV} (a d^0 transition metal center) to bring about the reaction.



Scheme 22. Enantiospecific oxidation of cyclobutanones catalyzed by Sharpless reagent. (DET = diethyltartrate).

A possible mechanistic interpretation for the asymmetric induction in these systems seems relatively easy in the case of the Pt system for which the general mechanism of reaction has been studied (Schemes 7 and 12). Clearly, the asymmetric transformation occurs by formation of diastereomeric Pt(ketone) intermediates (formed by the chiral Pt complex in the presence of a racemic ketone), followed by a stereoselective oxygen transfer step. A schematic view of this kinetic resolution process is indicated in Scheme 23. A similar interpretation could well apply to the Ti case, assuming for the Baeyer–Villiger oxidation a reaction mechanism similar to that known for the epoxidation of allylic alcohols.[62] Unfortunately, no interpretation can be proposed for the most interesting case reported by Bolm,[60] the only one in which a real asymmetric induction is observed, and the only mechanistic interpretation for the overall reaction suggested by Murahashi (Scheme 19) is clearly inadequate.



Scheme 23. Basic principle of kinetic racemate resolution with chiral Pt complexes.

6. Summary and Outlook

Transition metal catalysis in the Baeyer–Villiger oxidation of ketones is still a challenging issue, as the reaction mechanism is to some extent elusive, and the number of transition metal systems capable of efficient catalysis is very limited. In this respect, it seems significant that versatile catalyst families, such as metalloporphyrins, that in the last two decades have been extensively studied and have proved successful in a wide variety of oxidation reactions, have been so far unable to catalyze the Baeyer–Villiger oxidation.

As this review has tried to demonstrate, the possible successful catalysts will have to be able to increase the nucleophilic character of the peroxy oxygens of the oxidant and, at the same time, assist the leaving group to depart from the "reactive intermediate" involved in the catalysis, as in the Criegee intermediate suggested for the organic transformation.

From a synthetic point of view, the use of chiral transition metal catalysts appears to be the only promising alternative to catalysis by microorganisms for the synthesis of esters with (medium) high optical purity in the enantioselective transformation. In order to compete with organic synthesis, the scope and applications of the transition metal catalyzed Baeyer–Villiger oxidation will have to be improved. In this respect a major breakthrough will be the finding of really efficient catalysts capable of promoting the oxidation of acyclic ketones to the corresponding esters.

I wish to thank the National Research Council and the Ministry of Education and Scientific Research of Italy for financial support of this work. I am deeply indebted to my colleagues and co-workers whose names are cited in the references for their invaluable intellectual and experimental contribution. Finally I would like to acknowledge the late Professor Fulvio di Furia, an eminent organic chemist and unforgettable friend, to whom I have dedicated this review.

Received: April 11, 1997 [A224IE]
German version: *Angew. Chem.* **1998**, *110*, 1256–1267

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