Chapter 23

Sustainability Trends in Homogeneous Catalytic Oxidations

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Green chemistry is strongly influencing all aspects of chemical research and oxidation reactions in particular are witnessing a shift from the use of toxic and less atom efficient oxidants to the preferred employment of hydrogen peroxide and molecular oxygen. Recent developments in the field span from the discovery of more efficient metal catalysts characterized by higher turnovers or selectivities (especially enantioselectivity), to the advent of more economic and less toxic metal catalysts, to the replacement of organic solvents with water as reaction medium and to the implementation of efficient techniques to ensure simple catalyst recycling. The present contribution adequately covers all the above subjects, enriching the discussion with recent examples of timely and cutting edge catalytic systems characterized by high degree of novelty and possible future developments.

23.1. Introduction

The field of catalytic oxidation involving soluble transition metal complexes has experienced a boom in research over the past three decades. In this period a huge variety of new catalysts have been discovered and tested in reactions such as alkene epoxidation, sulfoxidation, alkane oxidation, the Baeyer–Villiger oxidation of ketones, N-oxidation, etc. The synthesis and mechanistic operating principles of prominent categories of catalysts, such as biomimetic systems based on synthetic metalloporphyrins or polyoxometalates, have been established and a variety of mono-oxygen donors from alkyl hydroperoxides, to dioxygen, to bleach, etc. have been successfully tested, contributing to an impressive wealth of results. However, because of the complexity of oxygen transfer with respect to other catalytic processes, the field has not witnessed the discovery of “the” catalyst, similar to the situation found in e.g. the hydrogenation or hydroformylation with Rh-based systems or in C-C forming reactions with Pd-based systems. Still, quite distinct from these examples is the degree of efficiency in terms of activity and selectivity observed in oxidation reactions.

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Table 23.1. Papers focused on oxidation presented at different ISHC symposia.

Symposium	Year	Total contributions	Total on oxidation	Invited lectures (on oxidation)	Oral presentations (on oxidation)
ISHC 8, Amsterdam	1992	252	46	6	3
ISHC 12, Stockholm	2000	295	45	4	2
ISHC 17, Poznan	2010	312	24	—	2

In more recent times, the interest in the fundamental aspects of homogeneous catalytic oxidations has been declining as witnessed by e.g. the number of contributions presented at the International Symposium on Homogeneous Catalysis (ISHC). A comparison between the Amsterdam (1992), Stockholm (2000) and the recent Poznan (2010) meetings is reported in Table 23.1 and shows that of approximately 250–300 contributions presented at each symposium, over roughly 20 years, the number of those devoted to oxidations has decreased from 46 in Amsterdam, including 6 invited lectures and 3 oral presentations, to 24 in Poznan with just 2 oral communications and no invited lectures.

At the same time an analysis of the recent literature shows that the focus is shifting towards aspects related to making homogeneous oxidation catalytic systems more sustainable and/or more compatible with practical applications, looking for higher turnovers or selectivities (especially enantioselectivity), trying to get rid of organic solvents and eventually attempting to overcome the major problem with homogeneous systems, i.e. the separation of the catalyst from the reaction mixture and possible recycling. In other words, even this area is being strongly influenced by the implementation of the now binding twelve principles of green chemistry.

In this respect, in order to give an overview of the area, we have envisaged some trends towards the sustainability of homogeneous oxidation processes, namely:

- the use of environmentally acceptable oxidants such as O_2 and H_2O_2;
- enantioselective oxidations with O_2 and H_2O_2;
- the use of water as reaction medium;
- the use of less toxic metals as catalysts;
- the heterogenization of the most successful homogeneous systems.

These will be the subject of the sections to come. Because of the limitations of space, subjects such as enzymatic oxidation, the use of polyoxometalates in oxidation reactions, oxidations mediated by metal nanoparticles, oxidation of bioavailable feedstocks, oxidation of water to dioxygen, organocatalytic asymmetric oxidations and asymmetric phase transfer oxidations are not covered in this chapter.

23.2. Use of Oxygen and Hydrogen Peroxide

In accordance with the twelve principles of green chemistry,[1] oxidation reactions should evolve toward the exclusive employment of more benign oxidants for the benefit of both the environment and living organisms. Oxidants are also characterized by different kinetic stability which means very different handling conditions, also implying the need for correct storage and the limited lifetime for the most active ones, while the most stable require activation via catalysis in order to express their oxidizing power. After reaction, the reduced form of the oxidant is a by-product which needs to be removed and properly treated. In this respect, low molecular weight oxidants are preferred because the remaining mass of the by-product is the lowest possible. Atom efficiency[2] is a common criterion in green chemistry and is usually also applied to oxidants. In this case the value is calculated by dividing the atomic weight of one oxygen atom transferred to the product by the molecular weight of the oxidant. The meaning is determined by establishing how much of the mass of the oxidant is wasted in order to transfer one oxygen atom to the substrate. Table 23.2 shows the reported values for a series of common oxidants. In this respect it is evident that O_2 and H_2O_2 are characterized by the highest possible atom efficiency (50% and 48%, respectively) that is extremely important when considering large-scale industrial oxidation processes. More importantly, the common by-product formed by these oxidants is water, which is absolutely compatible with release into the environment. Just as a comparison, other common and widely employed oxidizing species such as hypochlorite, alkyl hydroperoxides and percarboxylic acids are characterized by much lower atom efficiencies (21, 22–12 and 27–29%, respectively) and the related by-products are usually difficult to remove from the crude product and require extraction or distillation steps. General reviews on the use of dioxygen[3] and hydrogen peroxide[4] have been published.

This is why in the following sections oxidations employing dioxygen and hydrogen peroxide will be considered whenever possible.

23.3. Enantioselective Oxidations

The importance of enantiomerically pure drugs is now common knowledge, but it is a relatively recent discovery. In fact, it was only in 1992 that it became mandatory for the chemical industry to meet the new criteria from the American Food and Drug Administration (FDA) that established a policy towards single enantiomer drugs.[5]

In this section landmark examples of homogeneous asymmetric catalytic oxidations using chiral organometallic complexes will be considered; the discussion will be limited to systems based on the use of O_2 and H_2O_2 as terminal oxidants because of the improvement in their environmental impact. However, when the catalytic system

Table 23.2. Comparison between different terminal oxidants in terms of green character.

Oxidant	By-product	Atom efficiency (%)[a]	Catalysis required	Cost (€/Kg) or (€/l)[b]	Title, appearance, packaging [b]
O_2	H_2O	50	✓	3.5	99.6%, gas, cylinder
H_2O_2	H_2O	47	✓	90	<30%, solution, bottle
Urea · H_2O_2	Urea + H_2O	17	✓	400	97%, solid, bottle
O_3	O_2	33	✓	c	c
CH_3COOOH	CH_3COOH	27	—	380	40%, solution, bottle
t-BuOOH	t-BuOH	22	✓	45	70%, solution, bottle
NaClO	NaCl	21	—	13	10%, solution, bottle
Pyridine-N-oxide	Pyridine	17	✓	440	95%, solid, bottle
N-methylmorpholine N-oxide	N-methylmorpholine	14	✓	1500	97%, solid, bottle
CumOOH	CumOH	12	✓	106	80%, solution, bottle
$KMnO_4$	$MnO_2 + H_2O$	10	—	85	>98%, solid, bottle
Caro's acid or Oxone® $2KHSO_5 + KHSO_4 + K_2SO_4$	$3\ KHSO_4 + K_2SO_4$	10[d]	—	53	≥47% $KHSO_5$, solid, bottle
4-Ph-pyridine-N-oxide	4-Ph-pyridine	9	✓	8500	98%, solid, bottle
m-CPBA	m-CBA	9	—	450	<77%, solid, bottle
$NaIO_4$	$NaI + H_2O$	8	—	350	>99%, solid, bottle
PhIO	PhI	7	✓	c	c
OsO_4	$OsO_2(OH)_2$	6	—	300000	<98%, solid, bottle
$PhI(OAc)_2$	PhI + 2HOAc	5	—	1500	>98%, solid, bottle

[a] Calculated considering transfer of only one O atom to the product.
[b] Data from www.sigmaaldrich.com, June 2011.
[c] Not sold.
[d] Two O atoms are transferred to products.

is highly enantioselective (enantioselectivity is measured by the enantiomeric excess or ee), examples of oxidations with urea · H_2O_2 will also be discussed. The most recent contributions are divided by reaction category and the most efficient and stereoselective catalysts are reported. Special emphasis is placed on those catalysts that show potential applications to large-scale production, synthesis of natural products or drugs and those that are suitable for catalyst recycling under homogeneous conditions.

23.3.1. *Asymmetric epoxidation*

This is the most studied reaction. For simplicity of presentation the different catalytic systems are divided by metal center.

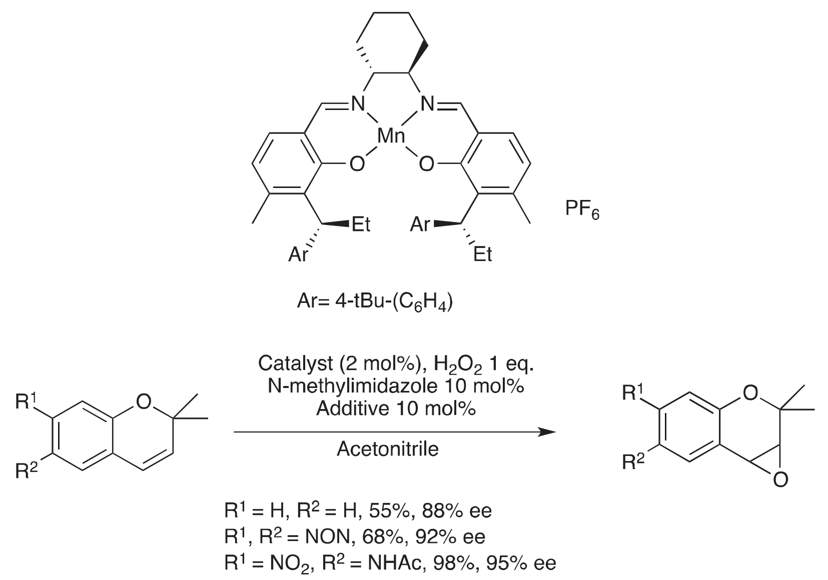
23.3.1.1. *Manganese*

Given its well-known role in redox processes such as peroxidases, catalases and photosystem II, manganese is a well-established metal center for oxidation reactions. Since the landmark discovery of Jacobsen and Katsuki in the 1990s concerning asymmetric epoxidation with salen Mn(III) species using iodosylbenzene as the oxidant, more than 40 papers have appeared in the literature concerning asymmetric epoxidation with hydrogen peroxide as the terminal oxidant, and many more if we consider other related oxidants such as urea · H_2O_2 adduct or peracetic acid. While for a detailed and exhaustive description of all systems we refer the reader to a recent publication,[6] we here describe selected contributions characterized by high asymmetric induction and original ligand design.

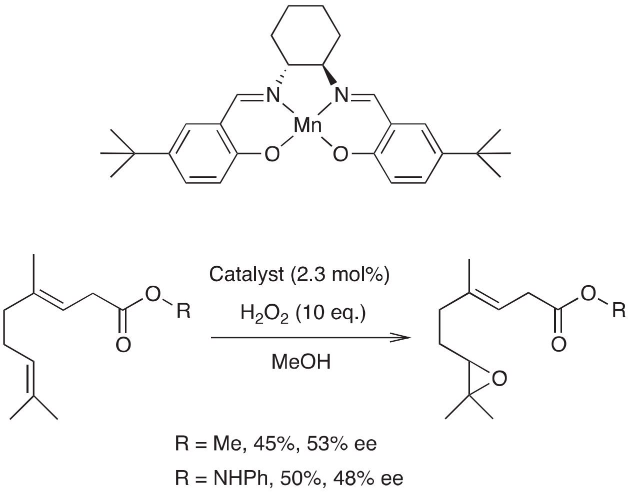
Salen-type ligands have been extensively investigated for Mn(III)-based epoxidation catalysts, the first example concerning the use of hydrogen peroxide coming from the group of Katsuki.[7] The catalytic system was based on chiral salen ligands with stereogenic centers, both on the diimine backbone as well as in the ortho position of the phenolic groups. After a careful optimization of the experimental conditions involving optimization of the solvent and of the concentrations of the species in solution, good yields (55−98%) and good enantioselectivities (up to 95%) were obtained for a series of chromene-based substrates (Scheme 23.1).

Allyl alcohol derivatives proved to be suitable substrates for the asymmetric epoxidation with classical chiral salen Mn(III) complexes, showing both good regioselectivity in the case of geraniol derivatives where only the allylic double bond was converted into the epoxide,[8] as well as moderate enantioselectivities and yields, the latter being obtained with a large excess of oxidant because of the concomitant decomposition of H_2O_2 induced by the chiral catalysts itself, as commonly observed with catalase (Scheme 23.2).

A step forward in the reaction was made when Katsuki disclosed the asymmetric epoxidation reaction with achiral salen Mn(III) complexes in the presence of chiral additives, whose role was to coordinate as fifth ligand to the metal center, steering the existing equilibrium between two enantiomeric conformations of the salen ligand preferentially towards only one. Subsequently, this led to the direct covalent connection of a nitrogen-based ligand to the salen scaffold leading to pentadentate

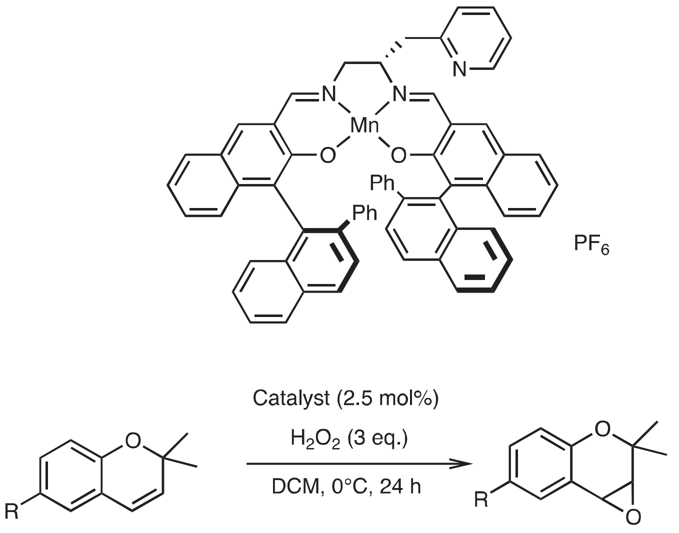


Scheme 23.1. Asymmetric epoxidation of chromene derivatives mediated by a Mn(salen) complex with H_2O_2 as the terminal oxidant.



Scheme 23.2. Epoxidation of geraniol derivatives with a Mn(salen) complex and H_2O_2 as the oxidant.

ligands bearing atropoisomeric binaphthyl moieties (Scheme 23.3).[9] In particular, the complex containing a methylimidazole residue as a fifth coordinating moiety turned out to be the best catalyst towards electron-rich alkene substrates belonging to the chromene or styrene families, with excellent yields and extremely high enantiomeric excesses.



R = CN, 95%, 99% ee

R = Br, 98%, 98% ee

R = NO_2, 85%, 99% ee

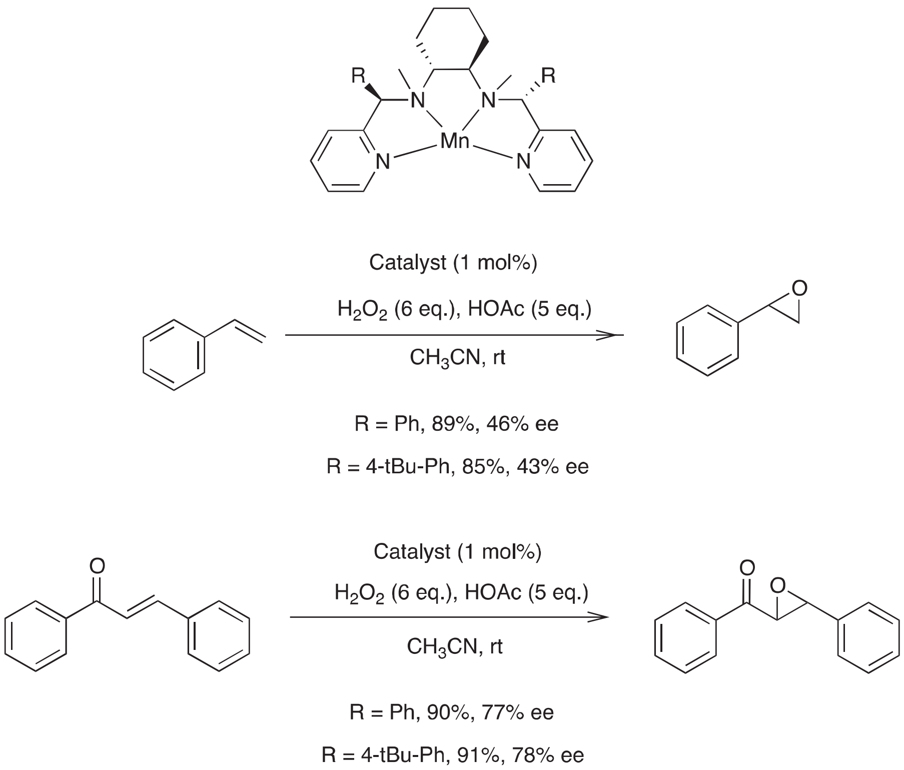
R = Me, 80%, 97% ee

Scheme 23.3. Asymmetric epoxidation of chromene derivatives with H_2O_2 mediated by a Mn(salen) complex bearing a pentadentate ligand.

More recently, other nitrogen-based chiral ligands started to be employed for the development of Mn(II) epoxidation catalysts. In particular, pyridine and bipyridine-based ligands obtained more encouraging results. In most cases the oxidant employed was peracetic acid or combinations of H_2O_2 and acetic acid that provide the percarboxylic oxidant *in situ*. One representative system is reported in Scheme 23.4 based on tetradentate nitrogen ligands bearing two pyridines and two tri-substituted amines.[10] The catalytic system was active towards styrenes as well as chalcone derivatives with good catalytic activities and moderate enantioselectivities.

23.3.1.2. *Titanium*

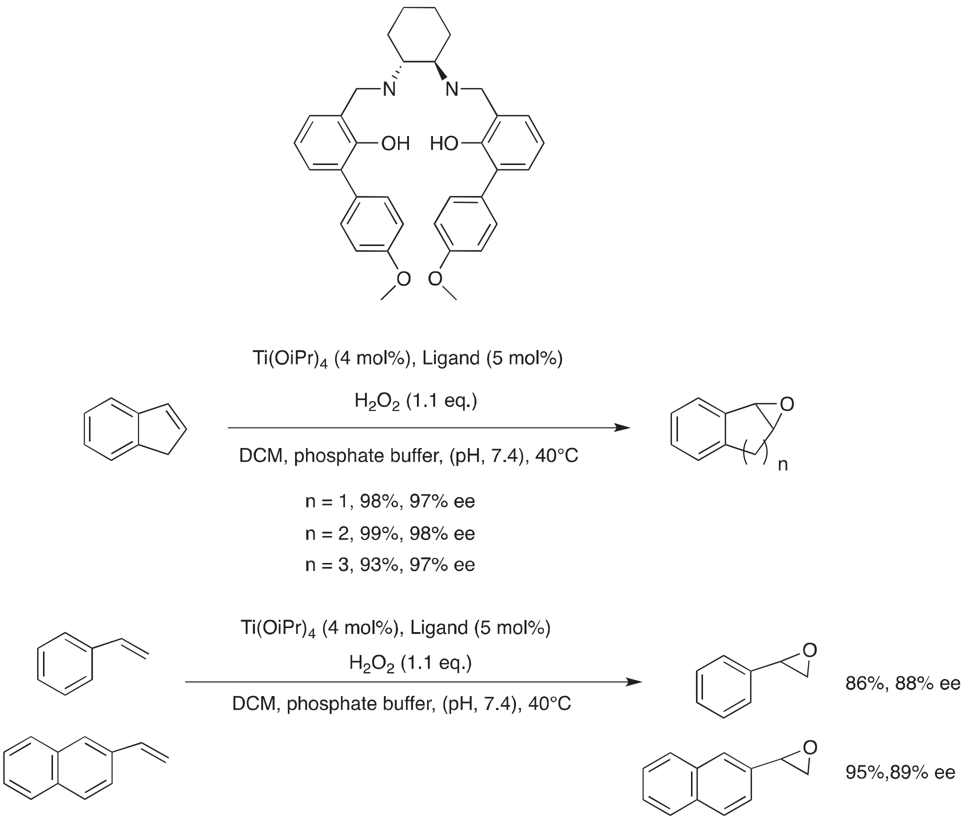
Chiral Ti complexes with tetradentate NOON ligands of the salan family were intensively investigated, in particular by the group of Katsuki. As far as non-atropoisomeric ligands are concerned, the effects of the substituents on the aromatic rings of the phenol residues were investigated in detail, and it was observed that the presence in the ortho position of an aromatic residue,[11] ranging from phenyl to 9-anthracenyl, ensured high ees in the range 78–89%, with the best value with an *o*-OMe-phenyl group, indicating that the enantioselectivity was only slightly affected by the steric hindrance present on the ligand (Scheme 23.5).



Scheme 23.4. Asymmetric epoxidation of styrene and chalcone with H_2O_2 mediated by a Mn catalysts bearing tetradentate pyridine ligands.

Berkessel further extended the study tailoring the substituents in the *ortho* and *para* positions of the phenol group position for half-reduced Salalen ligands. The results observed were in agreement with the findings of Katsuki, once again stressing the importance of aromatic substituents in the three position and confirming that even electronic effects are not very important in determining the enantioselectivity of the reaction (Scheme 23.6).[12]

Atropoisomeric salalen ligands showed even better results forming robust dimeric μ-oxo species that ensured high catalytic activity and enantioselectivity with catalyst loading as low as 0.02%, keeping the amount of oxidant stoichiometric with respect to the substrate.[13] This catalytic system proved to be very general in terms of the structure of the substrate. In fact, not only rigid cis aromatic alkenes such as indene, tetrahydronaphthane or styrene derivatives were efficiently and selectively oxidized with ee in the range of 93–99%, but also poorly reactive terminal (72–95% ee) and internal (71–97% ee) aliphatic alkenes provided the enantioenriched corresponding epoxide, with good enantioselectivity and moderate to good activity.

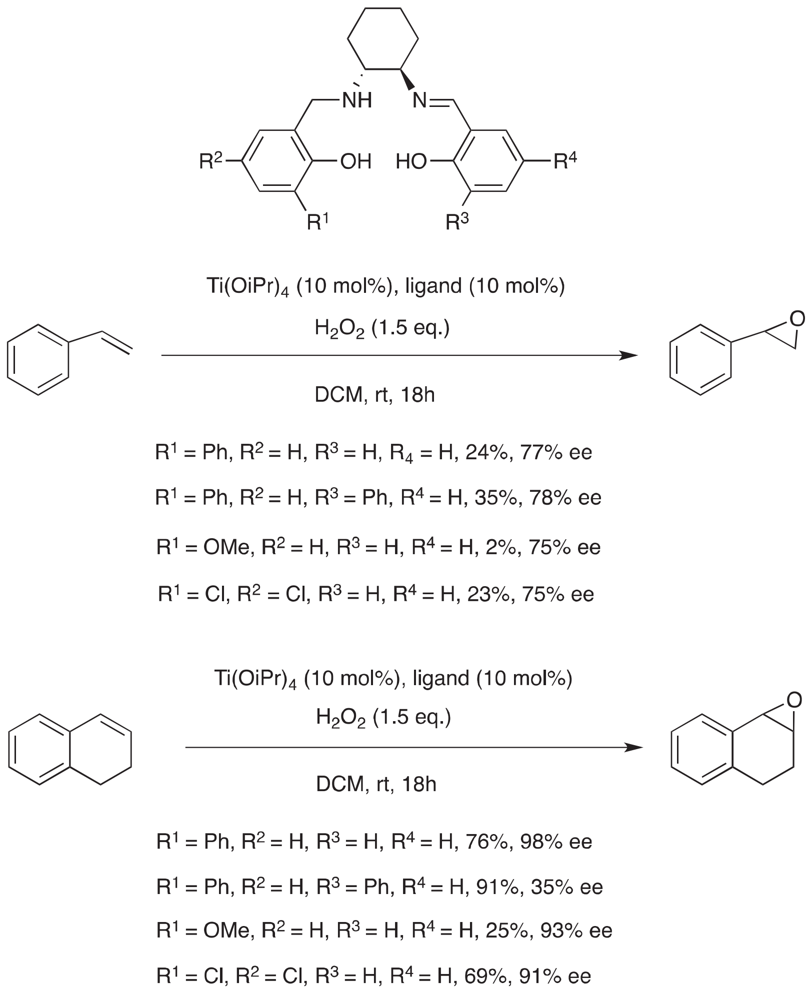


Scheme 23.5. Asymmetric epoxidation of vinyl arenes with H_2O_2 mediated by Ti(IV) complex bearing salan ligand.

The preference for unsubstituted C=C double bonds enabled the development of highly region- and stereoselective epoxidation of dienes bearing both an electron-rich substituted and an electron-poor terminal double bond (Scheme 23.7),[14] which is an uncommon behavior observed for the first time in the asymmetric epoxidation with chiral Pt(II) complexes[15] and described in the following paragraphs. Though the intrinsic mechanism remains to be solved, Ti salalen catalysts bearing atropoisomeric ligands represent one of the most versatile, efficient and selective catalysts for asymmetric epoxidation with hydrogen peroxide.

23.3.1.3. *Niobium*

While Ti(salan) complexes showed good activity and enantioselectivity towards unfunctionalized olefins, the corresponding Nb(salan) allowed asymmetric epoxidation of allyl alcohols via coordination of the heteroatom to the metal center, which is

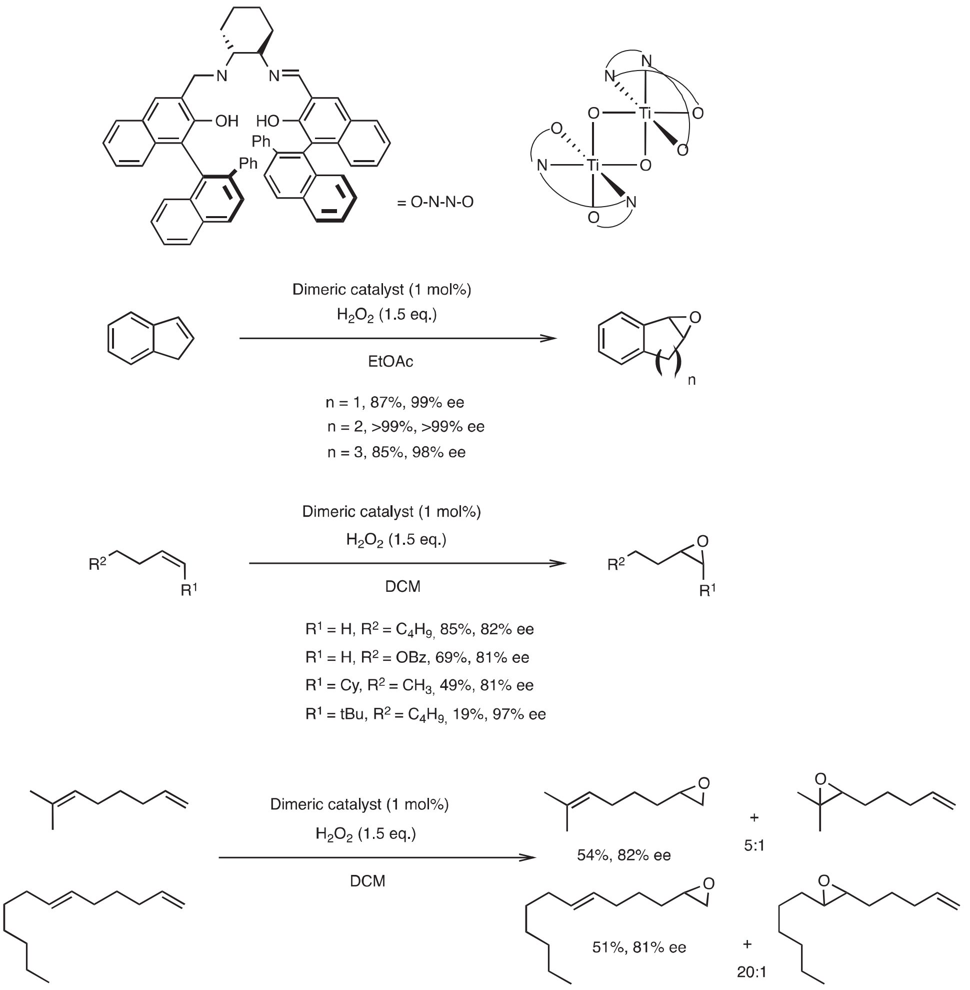


R^1 = Ph, R^2 = H, R^3 = H, R_4 = H, 24%, 77% ee
R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = H, 35%, 78% ee
R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, 2%, 75% ee
R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = H, 23%, 75% ee

R^1 = Ph, R^2 = H, R^3 = H, R^4 = H, 76%, 98% ee
R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = H, 91%, 35% ee
R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, 25%, 93% ee
R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = H, 69%, 91% ee

Scheme 23.6. Asymmetric epoxidation of viny arenes with H_2O_2 mediated by Ti(IV) complex bearing salalen ligands.

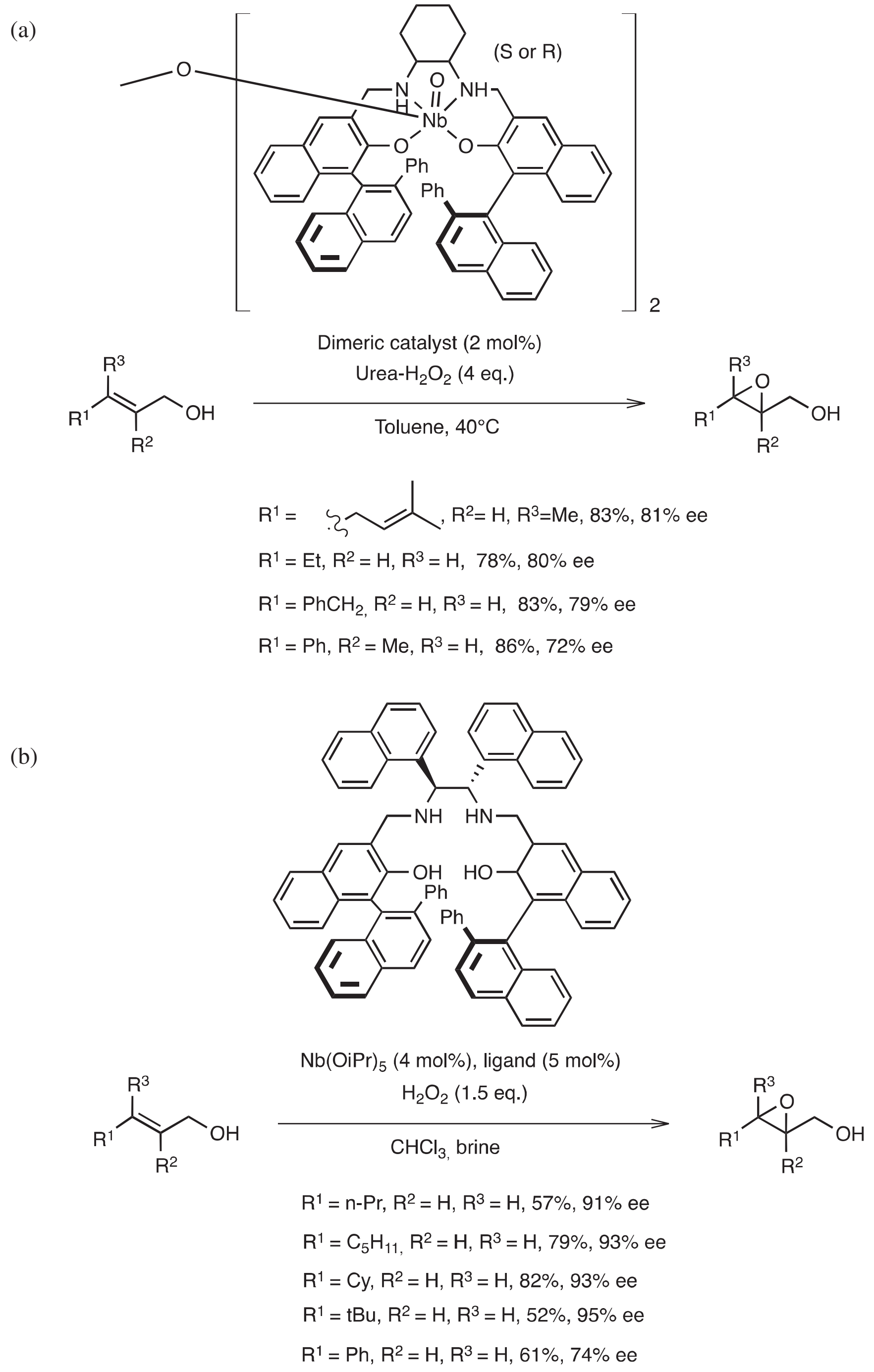
a stringent requirement for this oxidation reaction (Scheme 23.8a).[16,17] The catalytic system employs urea-H_2O_2 as the terminal oxidant under mild conditions, which is atypical for asymmetric epoxidation of allylic alcohols that are usually obtained with alkyl hydroperoxides. Second generation salen ligands turned out to be better performing, and the correct combination of chirality of the binaphthalene residues and diamine backbone was investigated, observing that the complex reported in Scheme 23.8b enabled high catalytic activity and high enantioselectivity towards allyl alcohols, with higher selectivity for three substituted substrates and lower for geminal substituted substrates.



Scheme 23.7. Preferential asymmetric epoxidation of terminal over internal alkenes with H_2O_2 mediated by a dimeric Ti(IV) catalyst bearing atropoisomeric salalen ligand.

23.3.1.4. *Iron*

The widespread presence in nature of Fe containing enzymes for oxidative degradation of xenobiotics, together with the recent attention paid to the development of iron-based homogeneous catalysis because of the much lower cost of this metal compared to other transition metals, prompted the development of several iron-based asymmetric epoxidation systems. Moreover, the stringent requirements concerning trace metals in marketed pharmaceutical products represent an important push for the use of iron in homogeneous catalysis. Most of the known catalytic systems rely on oxidants which do not include O_2 or H_2O_2. It was only



R^1 = , R^2= H, R^3=Me, 83%, 81% ee

R^1 = Et, R^2 = H, R^3 = H, 78%, 80% ee

R^1 = $PhCH_2$, R^2 = H, R^3 = H, 83%, 79% ee

R^1 = Ph, R^2 = Me, R^3 = H, 86%, 72% ee

R^1 = n-Pr, R^2 = H, R^3 = H, 57%, 91% ee

R^1 = C_5H_{11}, R^2 = H, R^3 = H, 79%, 93% ee

R^1 = Cy, R^2 = H, R^3 = H, 82%, 93% ee

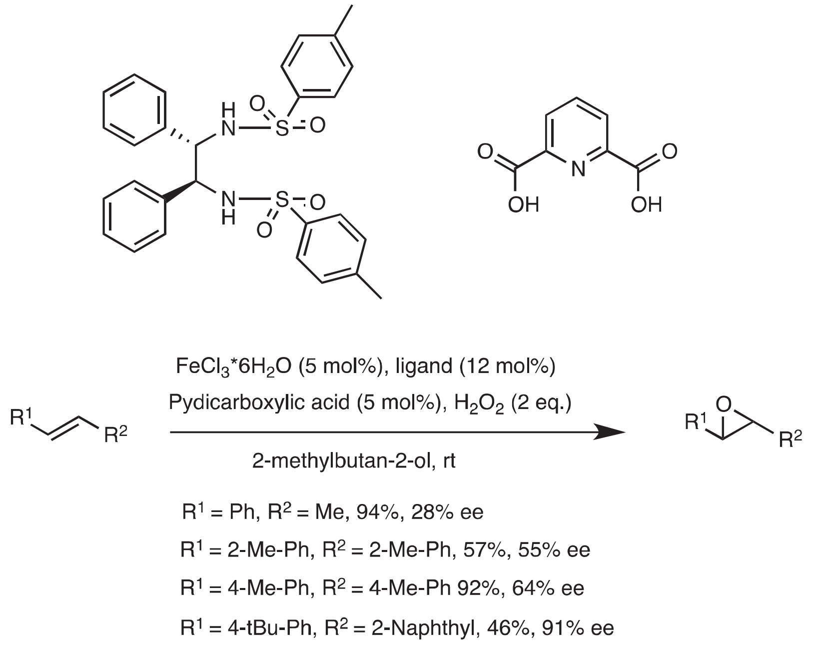
R^1 = tBu, R^2 = H, R^3 = H, 52%, 95% ee

R^1 = Ph, R^2 = H, R^3 = H, 61%, 74% ee

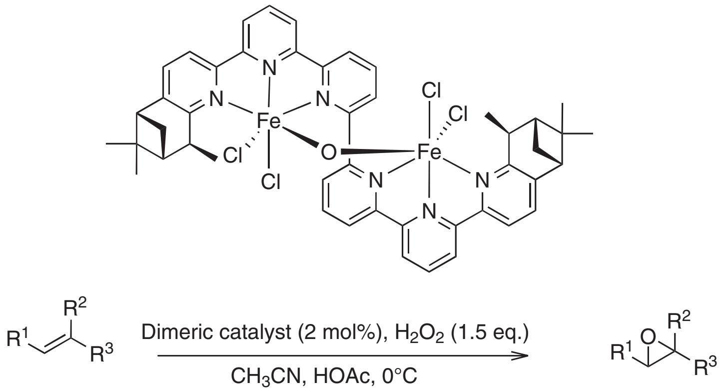
Scheme 23.8. Examples of asymmetric epoxidation of allyl alcohols with urea · H_2O_2 and H_2O_2 mediated by Nb(V) salan complexes.

after the year 2000 that the first asymmetric epoxidation methods based on iron catalysts with non-heme ligands came on the scene. Beller introduced the use of chiral N-arenesulfonyl-N′-benzyl-substituted ethylene diamine ligands in combination with tridentate pyridine-2,6-dicarboxylic acid and $FeCl_3$, observing that with 12 mol% catalyst loading under mild experimental conditions, it was possible to obtain good conversions and moderate to good yields in epoxides, together with enantioselectivity that was very sensitive to the steric hindrance of the substrate. Best results in terms of asymmetric induction were observed with *p*-disubstituted trans-stilbenes as reported in Scheme 23.9.[18,19] Detailed mechanistic investigations on the reaction and solution speciation with different techniques established that the oxidation proceeds via radical intermediates, the relative concentrations and reactivities of which determine the observed ee value. This is confirmed by the observation of a positive nonlinear effect (NLE)[20] on enantioselectivity, suggesting the participation of more than one iron center in the rate-determining step of the reaction.

A recent example of an Fe asymmetric epoxidation catalyst is based on the employment of a polypyridine ligand bearing two rigid chiral bicyclic structures at



Scheme 23.9. Asymmetric epoxidation of stilbenes with H_2O_2 catalyzed by Fe(III) complexes bearing the chiral bidentate sulfonamide ligand and pyridine dicarboxylate as the achiral tridentate ligand.

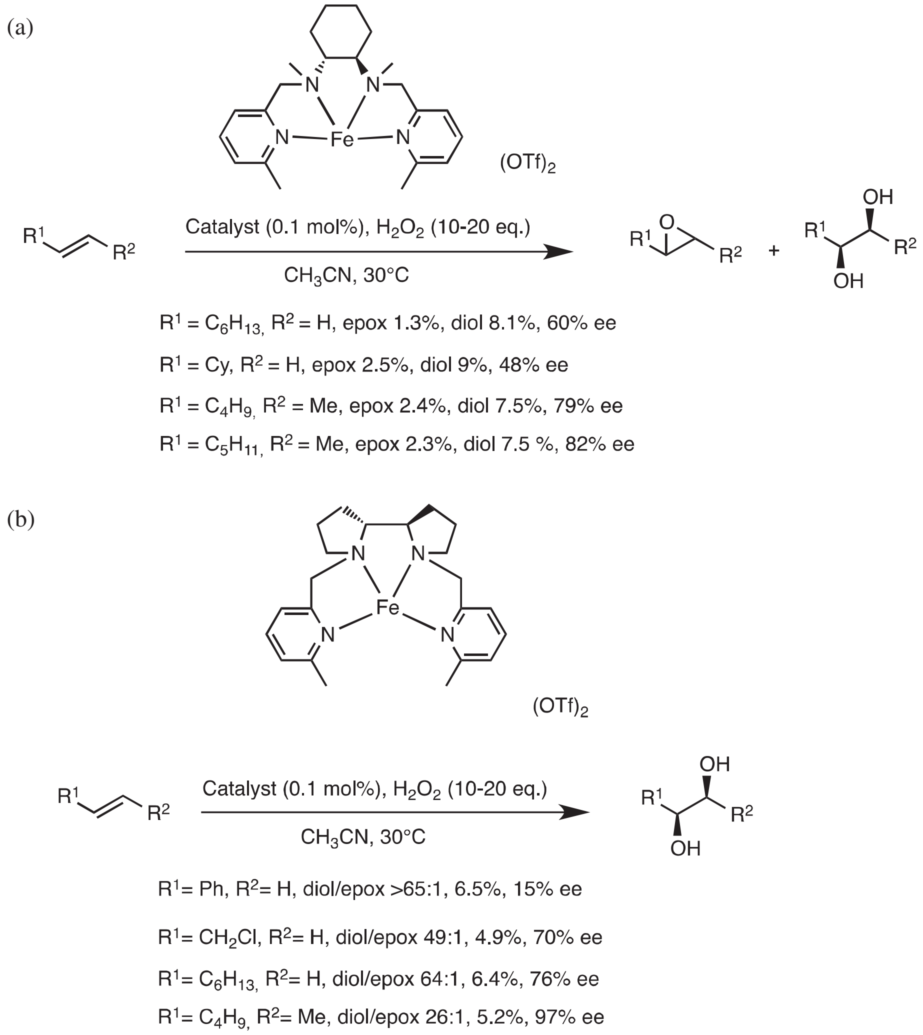


R^1 = Ph, R^2 = H, R^3 = H, 95%, 43% ee
R^1 = 4-Cl-Ph, R^2 = H, R^3 = H, 90%, 42% ee
R^1 = Ph, R^2 = H, R^3 = Me, 96%, 37% ee
R^1 = Ph, R^2 = Me, R^3 = H, 100%, 40% ee

Scheme 23.10. Asymmetric epoxidation of vinylarenes with H_2O_2 mediated by a dinuclear Fe(III) catalyst bearing a chiral poly-pyridine ligand.

the extremities, that fold like a helix coordinating two iron centers (Scheme 23.10.)[21] The dimeric complex is active and moderately stereoselective in the asymmetric epoxidation of styrenes and cis- and trans-aromatic alkenes with an ee up to 43%. The catalytic system is rather active with only 2 mol% catalyst loading working at 0°C with 1.5 equivalents of oxidant compared to the substrate.

Depending on the ligand employed, iron-catalyzed oxidation reactions of alkenes with H_2O_2 provide, in some cases, cis-diols rather than epoxides. Que and co-workers, inspired by natural dioxygenase enzymes that catalyze the cis-dihydroxylation of arene and olefin double bonds, developed tetradentate chiral ligands bearing 2,6-disubstituted pyridine and tertiary asymmetric amines that with Fe(II) metal centers and weakly coordinating anions yield low conversion into the corresponding diol, but with very interesting ee (Scheme 23.11a). Specifically, cis-disubstituted olefins afforded only 3–9% ee, 23–60% ee was achieved with terminal olefins, and trans-disubstituted olefins provided the best results with 82% ee in the oxidation of trans-2-octene.[22] Ligand optimization was performed and the replacement of the chiral 1,2-trans-cyclohexyldiamine backbone with bis-pyrrolidine led to the development of a new class of iron complexes still bearing α-methyl pyridine residues that are crucial to steer selectivity towards the formation of the cis-diol products rather than the epoxides. The level of enantioselectivity observed is the best so far reported for iron catalysts, with values up to 96% and 97% for trans-4-octene and trans-2-heptene, respectively (Scheme 23.11b).[23]



(a)

$R^1 = C_6H_{13}$, $R^2 = H$, epox 1.3%, diol 8.1%, 60% ee

$R^1 = Cy$, $R^2 = H$, epox 2.5%, diol 9%, 48% ee

$R^1 = C_4H_9$, $R^2 = Me$, epox 2.4%, diol 7.5%, 79% ee

$R^1 = C_5H_{11}$, $R^2 = Me$, epox 2.3%, diol 7.5 %, 82% ee

(b)

$R^1 = Ph$, $R^2 = H$, diol/epox >65:1, 6.5%, 15% ee

$R^1 = CH_2Cl$, $R^2 = H$, diol/epox 49:1, 4.9%, 70% ee

$R^1 = C_6H_{13}$, $R^2 = H$, diol/epox 64:1, 6.4%, 76% ee

$R^1 = C_4H_9$, $R^2 = Me$, diol/epox 26:1, 5.2%, 97% ee

Scheme 23.11. Asymmetric epoxidation of various alkenes with H_2O_2 mediated by Fe(II) catalyst bearing tetradentate nitrogen ligands.

23.3.1.5. *Ruthenium*

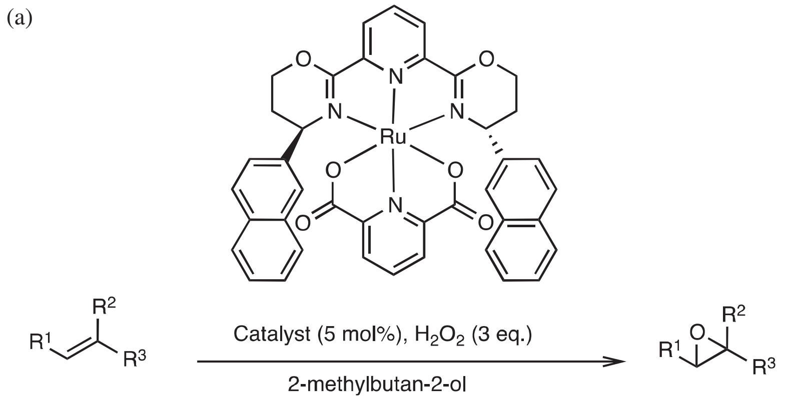
While asymmetric epoxidation reactions with Ru species bearing porphyrin, Schiff base and poly-pyridyl ligands constitute a well-documented field of research,[23] examples concerning the employment of H_2O_2 as the oxidant are less frequent. In particular, the field was opened by Nishiyama[24] and further developed by Beller[25] employing chiral tridentate nitrogen ligands generally characterized by C_2 symmetry such as Pyboxazine (2,2′-pyridine-2,6-dily-bi(5,6-dihydron-4h-1,3-oxazine), Pybox (bis(oxazolinyl)pyridine) and Pybims (bis(imidazolinyl)pyridine)[26] with an achiral pyridine-2,6-dicarboxylate as the second tridentate ligand.

One of the main advantages of this class of chiral complexes is related to the relative synthetic versatility of the chiral ligands that are based on available chiral 1,2-aminoalcohols and 1,2-diamines. This allowed the preparation of a series of complexes generally showing good catalytic activity in the oxidation of styrenes and disubstituted aromatic alkenes using an excess of H_2O_2 slowly added to the system in tert-amyl alcohol. Enantioselectivity was generally moderate, observing higher values for Pyboxazine compared to the smaller Pybox analogues on trans-substituted aromatic alkenes. For example, β,β-dimethylstyrene provided the corresponding epoxide in 84% ee (Scheme 23.12). A slightly lower level of enantioselectivity was possible using Pybims ligands which allowed ee up to 71% and quantitative yield for trans-stilbene oxidation.

The use of molecular oxygen as the terminal oxidant in asymmetric epoxidation is unusual. Katsuki and co-workers disclosed a Ru(II) complex with a second generation Salen tetradentate ligand and an apical NO molecule that enables oxygen transfer to disubstituted trans-alkenes in the presence of water as a hydrogen donor molecule and, more importantly, under visible light irradiation. The catalytic system displayed good to high enantioselectivity (76–92%) and medium to good yields (Scheme 22.13). The peculiarity of the system consists in requiring neither a proton and electron transfer system, nor the presence of a sacrificial reductant. A pivotal role is played by water which needs to be stoichiometric compared to the substrate. Water displaces the original NO ligand, coordinates the metal center and serves as a proton transfer agent for the oxygen activation process. Water is recycled and used as a proton transfer mediator during the process, favoring turnover and increasing the rate of the reaction.[27]

23.3.1.6. *Platinum*

Pt(II) complexes bearing diphosphine ligands are able to activate hydrogen peroxide and, in particular, complexes bearing strong electron-withdrawing ligands such as trifluoromethyl or pentafluorophenyl residues. They are catalytically active in the epoxidation of intrinsically poorly reactive terminal alkenes. This is based on a peculiar feature of such a catalytic system, which promotes the nucleophilic oxidation of the alkene[28] rather than a classical electrophilic pathway. While the oxidation of electron-rich alkenes with hydrogen peroxide as the terminal oxidant is performed by the vast majority of chiral organometallic complexes, the most selective towards terminal alkenes are monomeric bis-cationic Pt(II) complexes containing chiral diphosphines.[15] A set of equilibrium reactions involving the

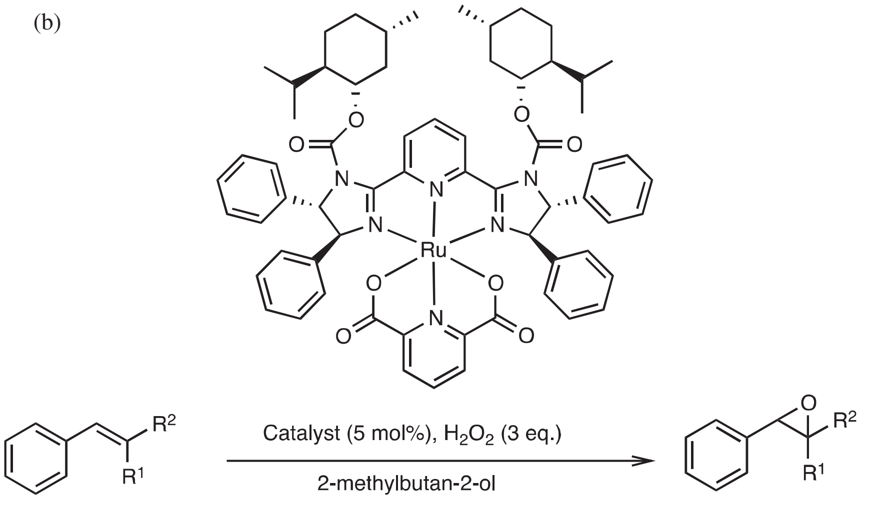


R^1 = Ph, R^2 = H, R^3 = H, 85%, 59% ee

R^1 = 2-Me-Ph, R^2 = H, R^3 = H, >99%, 64% ee

R^1 = Ph, R^2 = Me, R^3 = Me, >91%, 84% ee

R^1 = Ph, R^2 = H, R^3 = Ph, 100%, 54% ee

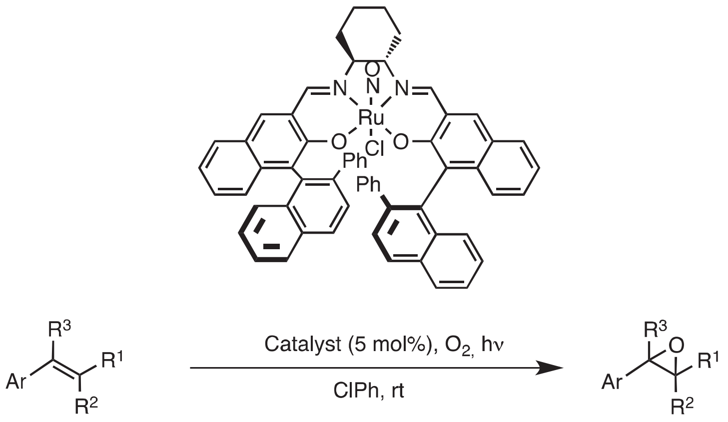


R^1 = H, R^2 = H, 76%, 42% ee

R^1,R^2 = -$(CH_2)_5$-, >99%, 54% ee

R^1 = Me, R^2 = Me, 82%, 68% ee

Scheme 23.12. Asymmetric epoxidation of vinyl arenes with H_2O_2 mediated by Ru(II) catalysts bearing Pyboxazine (a) and Pybims (b) as chiral tridentate nitrogen ligands.



Ar = 2-Naphthyl, R^1 = Me, R^2 = H, R^3 = H, 75%, 92% ee

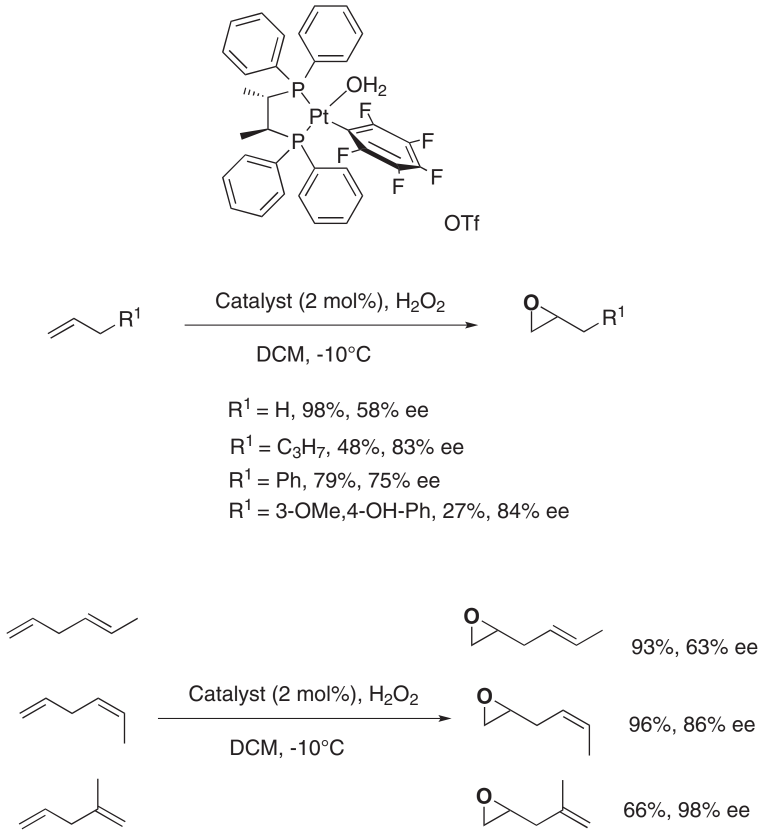
Ar = 3-Me-Ph, R^1 = Me, R^2 = H, R^3 = H, 67%, 90% ee

Ar = Ph, R^1 = Me, R^2 = H, R^3 = H, 34%, 90% ee

Scheme 23.13. Asymmetric epoxidation of vinylarenes with dioxygen mediated by a Ru(II) catalyst bearing an atropoisomeric salen ligand.

activation of hydrogen peroxide by fluorine atoms and the coordination of the alkene to the metal center precedes the rate-determining step in which a nucleophilic oxygen is transferred to the coordinated alkene. The best ligand was found to be chiraphos, yielding high conversions for linear terminal alkenes and an enantioselectivity of up to 84%. The length of the alkyl chain had a mild effect on selectivity with an increase from propene to pentene and hexene followed by a decrease for longer alkenes. Analogously, an increase in ee was observed for branched terminal alkenes when the substitution was closer to the double bond.

These data suggest the existence of a strong steric effect in the enantioselective epoxidation, as should be expected given that the active site of the complex is surrounded by aromatic rings. Allylbenzene derivatives proved to be suitable substrates, with the electron density of the aromatic ring causing a marked negative effect on the activity, but positive effect on the enantioselectivity. A maximum 87% ee was observed for safrole. The nucleophilic character of the epoxidation allowed the selective regio- and enantioselective asymmetric oxidation of substrates bearing both an internal and a terminal carbon-carbon double bond. The results reported in Scheme 23.14 are impressive: for all the three dienes investigated, the epoxidation occurred exclusively at the terminal double bond with complete regioselectivity and ee up to 98%. A greener version of the reaction was developed using water as the solvent in the presence of surfactants to mediate the solubility of both substrates and catalyst in the polar solvent (see Section 23.4.2).[29]



Scheme 23.14. Asymmetric epoxidation of terminal alkenes with H_2O_2 catalyzed by a Pt(II) chiral complex.

23.3.2. *Asymmetric sulfoxidation*

Oxidation of thioethers to the corresponding sulfides is a rather facile reaction because of the electron-rich character of the sulfur atom. Sulfoxidation can be performed with a wide range of oxidants and H_2O_2 can be easily employed exploiting simple activation with Brønsted acids or a plethora of Lewis acids. Chiral enantiopure sulfoxides are extremely interesting molecules[30] and one of the ten most sold drugs in 2003 was NexiumTM, the (S) enantiomer of omeprazole, a known anti-ulcer agent.[31] The asymmetric sulfoxidation is a benchmark test to analyze the asymmetric induction properties of newly prepared complexes.

23.3.2.1. *Titanium*

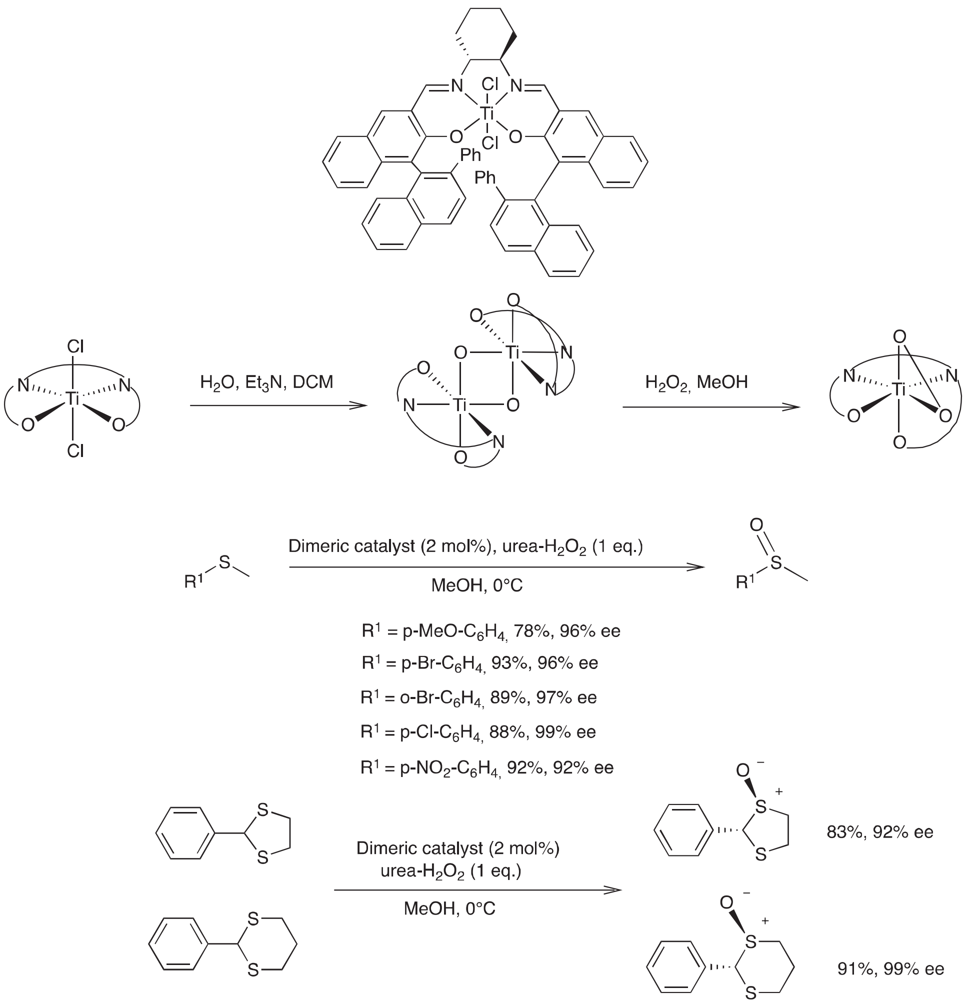
In the past, concomitant pioneering contributions came from Modena[32] using $Ti(OiPr)_4$/DET (1:4) with tert-butylhydroperoxide (TBHP) and Kagan[33] employing

$Ti(OiPr)_4$/DET/H_2O (1:2:1) with TBHP or cumylhydroperoxide (CHP), both based on a modified version of the Sharpless asymmetric epoxidation system. The use of H_2O_2 as the terminal oxidant in this reaction is a rather recent achievement. In fact the high oxophilic character of Ti(IV) complexes is in contrast with the presence of water, usually present in large amounts even in concentrated H_2O_2, because of decomposition of the original catalyst to give Ti oxides with loss of the chiral ligand. The robustness of Ti complexes for asymmetric sulfoxidation with H_2O_2 increased with the advent of tridentate O,O,N Schiff bases prepared from aminoalcohols and salicylaldehydes, and tetradentate O,N,N,O salen and salalen chiral ligands.

Asymmetric sulfoxidation with tridentate ligand Ti complexes and 30% H_2O_2 is quite efficient in terms of catalytic activity with yields of up to 96%, high selectivity to sulfoxide (90%), minimal over-oxidation to sulfone and rather low catalyst loading, usually $<1\%$ mol. Nevertheless, the enantioselectivity was not very high with a maximum ee of 60% after optimization of the chiral ligand.[34]

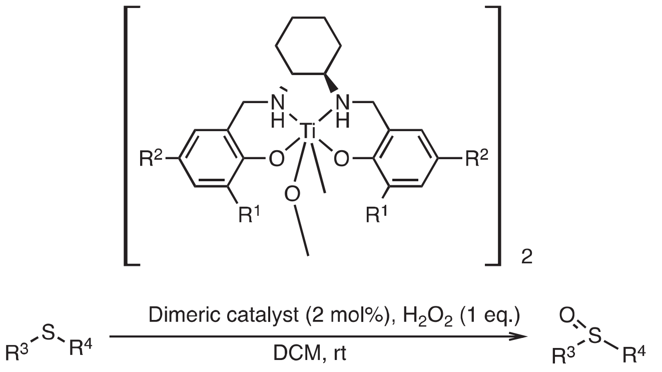
Better control on stereoselectivity was achieved with the more congested tetradentate salen ligands based on the reaction between chiral diamines with salicylaldehydes. Different coordination geometries are possible with Ti(IV) precursors, in particular, octahedral dichloro complexes did not show good enantioselectivity, while ee up to 76% with H_2O_2 and 94% with urea· H_2O_2 for methyl phenyl sulfide could be achieved with dinuclear μ-oxo bridged complexes with cis-β geometry bearing second generation salen ligands, characterized by the chiral diamine backbone and large atropoisomeric binaphthyl residues.[35] The lower stereoselectivity afforded by H_2O_2 is probably caused by the presence of several Ti-hydroperoxo equilibrium species formed by the addition of water to an original Ti-peroxo species. The asymmetric induction was high, regardless of the electronic nature of the sulfide and, surprisingly, more electron-rich substrates provided lower conversions compared to more electron-poor substrates. Detailed speciation analysis in solution confirmed that in methanol and in the presence of the oxidant, the original dimeric catalyst dissociates into monomeric species (Scheme 23.15).[36]

The same catalytic system proved to be effective and highly enantioselective towards a much less investigated class of sulfides like dithioacetals. In particular, 1,3-dithiolanes and 1,3-dithianes were converted smoothly into a single diastereoisomer with ee >90% using urea·H_2O_2 as the oxidant (Scheme 23.15). The catalytic activity and enantioselectivity were not affected by the electronic nature of the substituent in position two, but were more sensitive to steric requirements like 2-t-Bu-dithiane and dithiolane which showed lower ee.[37] The diastereoselectivity was always high and decreased slightly with alkyl or alkynyl substituents, favoring in all cases the trans isomer that was produced with the highest ee compared to the corresponding cis isomer.



Scheme 23.15. Asymmetric sulfoxidation of arylmethyl thioethers and mediated by a Ti(IV) catalyst bearing an atropoisomeric salen ligand.

Salan ligands are the reduced form of the corresponding salen derivative where imino groups have been reduced to the corresponding amino groups. First generation salan ligands bearing substituted salicylaldehyde residues provided dimeric μ-oxo-Ti(IV) complexes that allowed the asymmetric sulfide oxidation with H_2O_2 in dichloromethane.[38] The reaction, performed in the presence of 1.6 equivalents of oxidant with respect to the substrate and with as low as 0.2% mol of catalyst, allowed high conversion and ee up to 97% thanks to a tandem enantioselective oxidation of the sulfide to the sulfoxide followed by kinetic resolution of the sulfoxide to sulfone (Scheme 23.16). With the (S,S) catalyst, sulfide was preferentially formed with



R^1 = H, R^2 = H, R^3 = Ph, R^4 = CH_2Ph, SO/SO_2 = 1.07, 51%, 86% ee

R^1 = H, R^2 = H, R^3 = CH_3, R^4 = Ph, SO/SO_2 = 6.5, 78%, 45% ee

R^1 = Ph, R^2 = H, R^3 = iPr, R^4 = Ph, SO/SO_2 = 1.8, 48%, 69% ee

R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = CH_2Ph, SO/SO_2 = 3.9, 75%, 88% ee

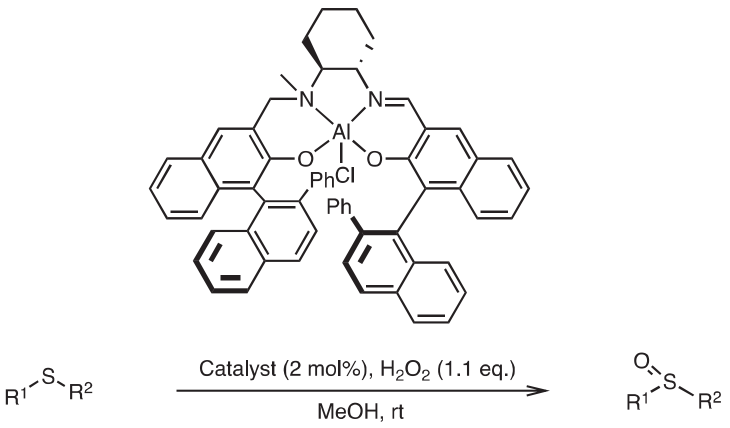
Scheme 23.16. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by dimeric Ti(salan) complexes.

the (S) configuration and the subsequent over-oxidation to sulfone preferentially consumed the (R) enantiomer leading to a further enrichment of the (S) sulfoxide.

23.3.2.2. *Aluminum*

Aluminum(III) chiral catalysts are also usually sensitive to the presence of water, but with multidentate ligands and under optimized reaction conditions Katsuki and co-workers developed a monomeric second generation salalen (semi-reduced version of salen ligands) Al(III) complex that enabled asymmetric sulfoxidation of thioethers with H_2O_2 as the oxidant in methanol and in the presence of a phosphate buffer at pH 7.4 to ensure reproducibility of the system. With mono-methylation on one amino N donor, (R) configuration on the atropoisomeric residues, and (S,S) configuration on the 1,2-cyclohexyldiamino backbone the catalyst provided minor over-oxidation to sulfone, good yields and very high asymmetric induction with ee at >97% for a series of methyl phenyl sulfides, irrespective of the position of the substituents on the aromatic ring and the electronic nature of the aryl substituents (Scheme 23.17).[39,40]

The same catalytic system enabled the kinetic resolution of sufoxides to sulfones confirming that the high ee observed is again the result of concomitant asymmetric oxidation of the sulfide, followed by kinetic resolution of the sulfoxide, both favoring the (S) enantiomer. An extensive investigation of the asymmetric oxidation of two substituted 1,3-dithianes and dithiolanes bearing alkyl, alkenyl, alkynyl and aryl groups showed that the same catalytic system was able to provide the corresponding



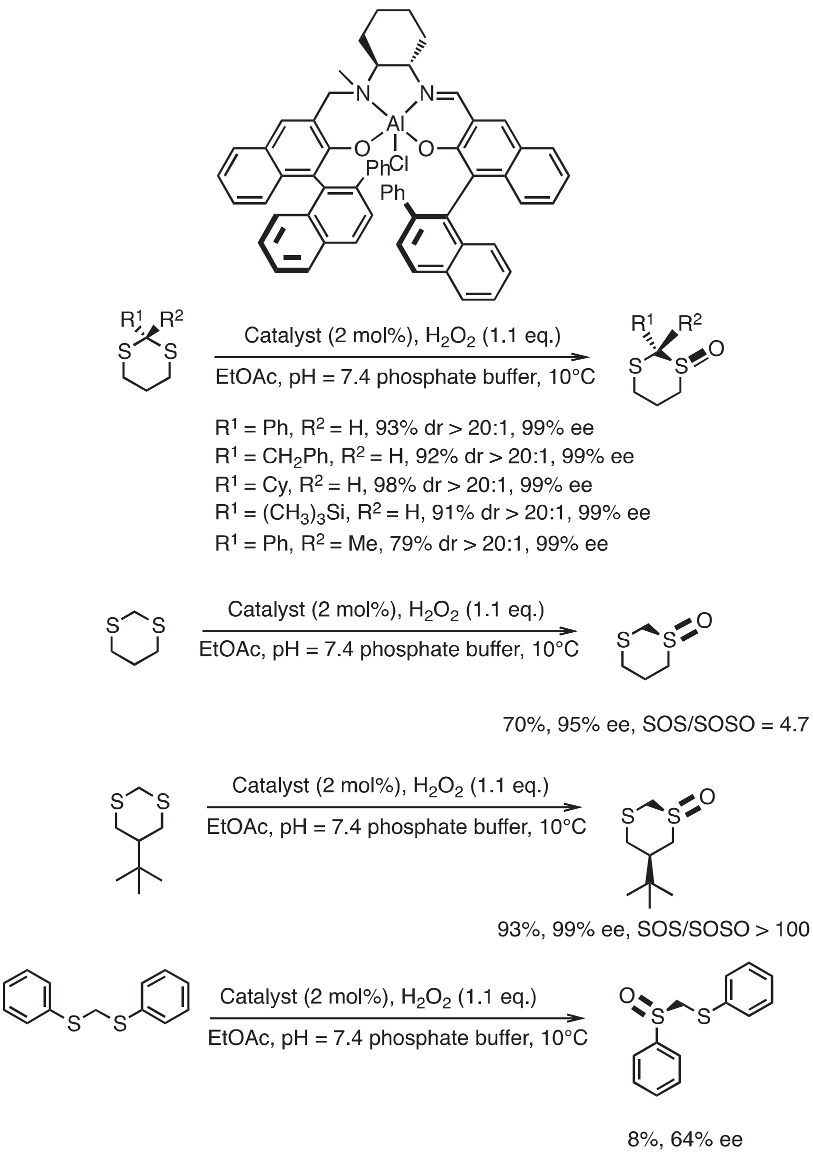
R^1 = Ph, R^2 = Me, SO/SO_2 = 9.6, 86%, 98% ee
R^1 = 4-MeO-C_6H_4, R^2 = Me, SO/SO_2 = 9.1, 82%, 97% ee
R^1 = 2-NO_2-C_6H_4, R^2 = Me, SO/SO_2 = 42, 84%, 99% ee
R^1 = Ph, R^2 = Et, SO/SO_2 = 100, 80%, 91% ee

Scheme 23.17. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by an Al(salalen) complex.

trans-monoxides in high yields with >20:1 diastereomeric ratio (dr) and 98–99% ee with H_2O_2 in ethyl acetate. Non-substituted dithianes were preferentially oxidized to the monoxide with high ee (Scheme 23.18).[41] The catalytic system is extremely selective since starting from the cyclic dithioacetals potentially four stereoisomers for the monoxide, six for the dioxide and four and one for the tri and tetraoxide are possible, respectively. Dithianes substituted in position five and two, and substituted dithiepane (seven-membered ring thioacetals) afforded high yields and ee for the corresponding monoxides, while only the sulfoxidation of acyclic thioacetals was sluggish and poorly enantioselective (Scheme 23.18).

23.3.2.3. *Vanadium*

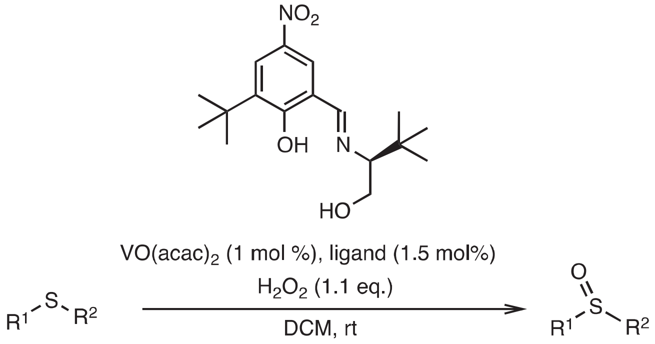
Asymmetric sulfoxidation with chiral vanadium complexes is much older than Ti and Al because this metal provides more robust catalysts which are not deactivated by the presence of water. The first contribution to the field was made by Bolm and co-workers in the second half of 1990s. These authors developed chiral catalysts formed *in situ* by the reaction of $VO(acac)_2$ with chiral enantiopure Schiff ligands bearing one stereocenter based on a t-leucinol scaffold.[42] The maximum ee achieved was 85% using low catalyst loadings (<1% mol) and without any precautions to avoid moisture or oxygen, which was unusual at that time as hydroperoxides



Scheme 23.18. Asymmetric sulfoxidation of 1,3-dithianes with H_2O_2 mediated by an Al(salalen) complex.

where the most common oxidants and strict anhydrous conditions were mandatory (Scheme 23.19).

An optimized version of Bolm's catalytic system was developed after careful variation of the substituents on the aromatic ring, observing that the di-iodo derivative reported in Scheme 23.20 allowed formation of aryl benzyl sulfoxides with ee



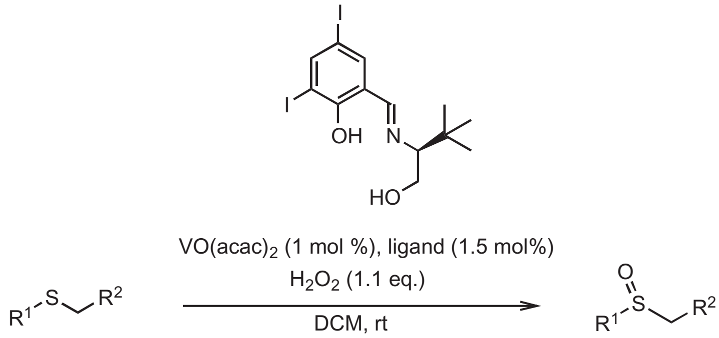
R^1 = Ph, R^2 = Me, 94%, 70% ee

R^1 = Ph, R^2 = iPr, 64%, 62% ee

R^1 = 4-NO_2-C_6H_4, R^2 = Me, 55%, 63% ee

R^1 = tBu, R^2 = CH_2Ph, 91%, 65% ee

Scheme 23.19. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by a V(IV) Schiff ligand complex.



R^1 = 4-Me-C_6H_4, R^2 = Ph, SO/SO_2 = 2.6, 48%, 94% ee

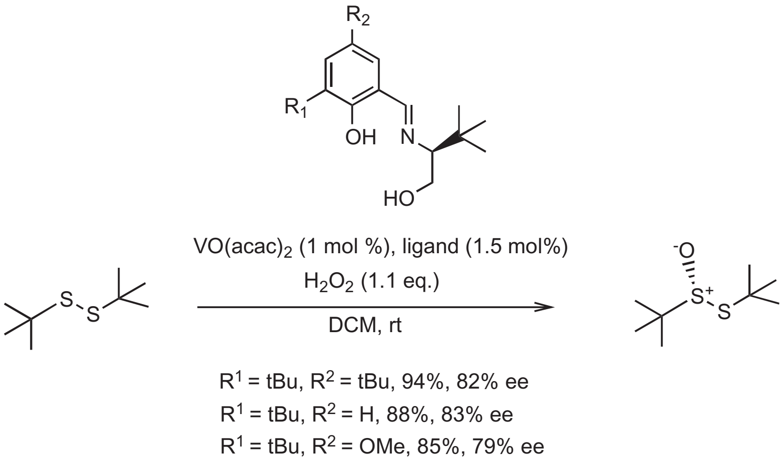
R^1 = Ph, R^2 = Ph, SO/SO_2 = 2.3, 51%, 91% ee

R^1 = 4-Me-C_6H_4, R^2 = Ph, SO/SO_2 = 1.9, 45%, 99% ee

R^1 = tBu, R^2 = Ph, SO/SO_2 = 19, 42%, 56% ee

Scheme 23.20. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by a V(IV) catalyst bearing a halogenated Schiff ligand.

typically >90% in the presence of a tandem cooperative asymmetric oxidation and kinetic resolution.[43] The kinetic resolution of sulfoxides was optimized using the *in situ* generated catalyst with 0.8 equivalents of H_2O_2 and the slow addition of the oxidant, thus obtaining good enantioselectivity with rather low conversions and selectivity factors up to 17.6 between the two enantiomers of the sulfoxide.

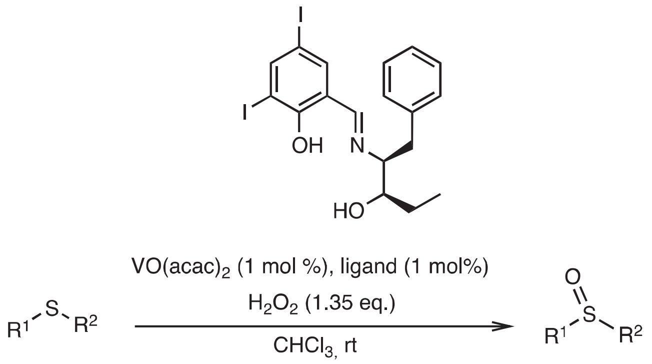


Scheme 23.21. Asymmetric sulfoxidation of alkyl disulfide with H_2O_2 mediated by a V(IV) Schiff base ligand.

The same catalytic system disclosed by Bolm was further extended by Ellman to the asymmetric oxidation of t-Bu-disulfide with H_2O_2. The corresponding tert-butyl tert-butane thiosulfinate was obtained with 91% ee and with 92% on scales as large as 1 mol with as low as 0.25% mol of V catalyst, with a Schiff base ligand and stoichiometric amount of H_2O_2 (Scheme 23.21).[44] Extensive ligand modification was necessary for the substrate of interest. In particular, it turned out that 3,5-di-tert-butyl salicylaldehyde was the best aromatic fragment, while variation on the properties of the amino alcohol confirmed the superior enantioselectivity possible with t-leucinol.

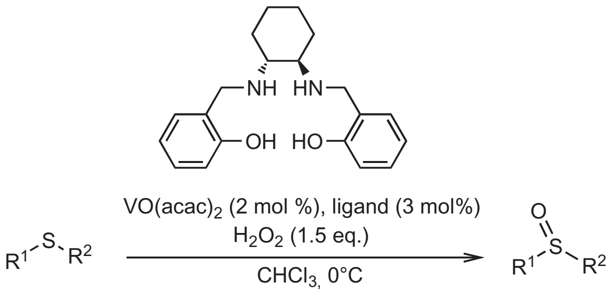
Further improvements in the asymmetric induction for the sulfoxidation of aryl methyl sulfides was achieved employing Schiff base ligands derived by condensation of salicylaldehydes with chiral aminoalcohols bearing two stereocenters.[45] In this case the best amino alcohol turned out to be the syn isomer in combination with di-iodo salicylaldehyde as previously observed.[43] Excellent enantioselectivity was possible thanks also to the partial positive kinetic resolution of the sulfoxide which was optimized using a slightly larger amount of oxidant (1.35 eq. compared to the sulfide). The catalytic system was also active towards substrates bearing longer alkyl residues without detrimental effects on either the yield and enantioselectivity (Scheme 23.22).

On the basis of the high versatility of salen and salan ligands for asymmetric oxidation with other metal centers, Zhu investigated the employment of such ligands for the *in situ* preparation of V catalysts. In particular, the first generation of salen ligands, having stereogenic centers on the 1,2-diamino backbone, showed poor asymmetric induction, while the reduced salan version surprisingly



R^1 = Ph, R^2 = Me, 81%, 99% ee
R^1 = 4-Cl-C_6H_4, R^2 = Me, 83%, 99% ee
R^1 = 4-MeO-C_6H_4, R^2 = Me, 84%, 99% ee
R^1 = 2-Naphthyl, R^2 = Me, 85%, 99% ee
R^1 = 2-Naphthyl, R^2 = n-Bu, 81%, 98% ee

Scheme 23.22. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by a V(IV) complex bearing a Schiff base ligand comprising two stereocenters.



R^1 = Ph, R^2 = Me, 81%, 95% ee
R^1 = 3-Br-C_6H_4, R^2 = Me, 83%, 92% ee
R^1 = 3-MeO-C_6H_4, R^2 = Me, 82%, 81% ee
R^1 = Ph, R^2 = CH_2Ph, 78%, 72% ee
R^1 = t-Bu, R^2 = n-Bu, 83%, 72% ee

Scheme 23.23. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by a V(IV) complexes with a salan ligand.

allowed good enantioselectivity in the oxidation of simple aryl methyl thioethers (Scheme 23.23).[46] Methylation of the amino groups of the ligand and the use of aromatic residues bearing t-Bu moieties, which are common strategies to enhance enantioselectivity in other reactions, did not improve the asymmetric induction. Better results were obtained by exploiting the partial over-oxidation of the enantioenriched sulfoxide to the corresponding sulfone (selectivity factor for methyl phenyl sulfoxide 7.3) obtaining a further enrichment in the enantiopurity of the sulfoxide.

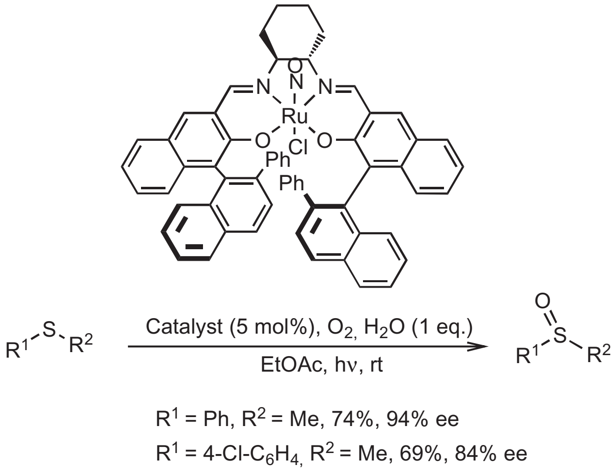
Overall, Schiff-based V complexes catalyzed asymmetric oxidation of sulfides with hydrogen peroxide represents one of the best methods in terms of high yields and enantioselectivity, low catalyst loading and simple preparation of the catalyst, as well as employment of ligands from relatively cheap chiral building blocks.

23.3.2.4. *Ruthenium*

The same Ru catalytic complex developed for asymmetric epoxidation with air proved to be active and also highly enantioselective towards asymmetric sulfoxidation.[27] Among different solvents, ethyl acetate showed the best results with 5% mol of catalyst loading at 25°C in air and visible light irradiation over 24–48 h. The oxygen transfer does not occur in the absence of visible light and no over-oxidation of the sulfoxide was observed for a series of aryl methyl sulfides and two substituted 1,3-dithianes that were successfully oxidized with ee in the range 72–98% (Scheme 23.24).

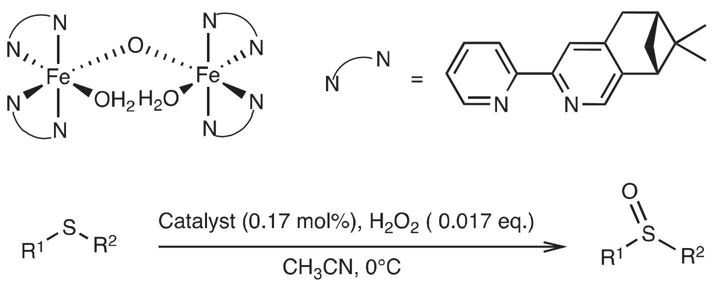
23.3.2.5. *Iron*

One of the first attempts to perform asymmetric sulfoxidation with Fe catalysts was reported by Fontecave and Ménage with mononuclear [Fe(pb)$_2$-(CH$_3$CN)$_2$] (pb=(−)4,5-pinene-2,2′-bipyridine) and the corresponding μ-oxo dinuclear system, observing that the latter was more stereoselective and active.[47] The level of



R^1 = Ph, R^2 = Me, 74%, 94% ee
R^1 = 4-Cl-C_6H_4, R^2 = Me, 69%, 84% ee
R^1 = 2-MeO-C_6H_4, R^2 = Me, 86%, 96% ee
R^1 = CH_2Ph, R^2 = Me, 26%, 75% ee

Scheme 23.24. Asymmetric sulfoxidation of thioethers with O_2 mediated by a Ru(III)salen complex.



R^1 = Ph, R^2 = Me, 90%, 21% ee

R^1 = 4-Br-C_6H_4, R^2 = Me, 90%, 40% ee

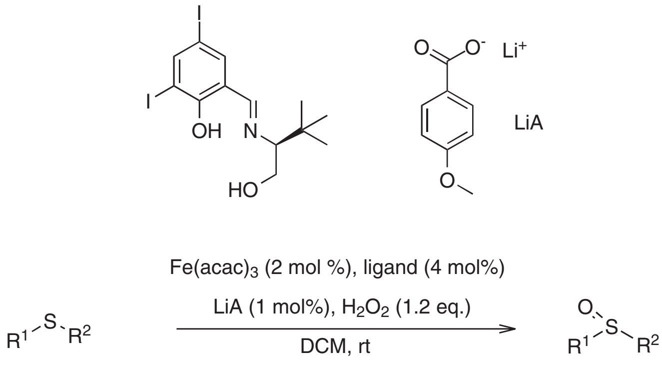
R^1 = 2-Naphthyl, R^2 = Me, 80%, 40% ee

Scheme 23.25. Asymmetric sulfoxidation of thioethers with substoichiometric H_2O_2 mediated by a dimeric Fe(III) catalyst bearing a bipyridine ligand.

asymmetric induction and the turnover ability were not high, with yields up to 90% and ee up to 40% (Scheme 23.25). It is worth noting that the catalytic system did not withstand the presence of large amounts of oxidant, in fact H_2O_2 was the limiting reactant of the reaction.

This system inspired the application of wellknown Schiff base ligands for Fecatalyzed asymmetric sulfoxidation. Bolm and coworkers investigated this area in detail, initially observing that di-iodo-substituted ligands ensured high enantioselectivity.[48] The major disadvantage was the rather low conversion of the substrate. In order to improve this aspect, a series of aromatic carboxylic acids and salts were investigated as promoters observing a marked increase in the yield of sulfoxide when employing electron-rich benzoic acids, with a further increase in the stereoselectivity. As an example, in the oxidation of phenyl methyl sulfide, the addition of 4-methoxy-benzoic acid increased the yield from 27% to 63% and ee from 26% to 90%.[49] All other substrates behaved similarly.

The effect of the acid was probably to promote the dimerization of the original complex, as confirmed by the observation of the non-linear effect[20] between the ee of the sulfoxide product and the ee of the ligand.[50] The catalytic system showed a good chemoselectivity with only marginal over-oxidation of the sulfoxide to the corresponding sulfone, with negligible effect on the stereocontrol of the reaction, which remains driven by the first oxidation step (Scheme 23.26). Overall the optimized catalytic system allowed high enantioselective oxidations (up to 96% ee) of prochiral sulfides obtained in moderate to good yields (up to 78%), under simple reaction conditions using a readily available *in situ* iron catalyst (<4 mol%) and aqueous hydrogen peroxide, using small quantities of a carboxylic acid or a carboxylate salt (1 mol%).

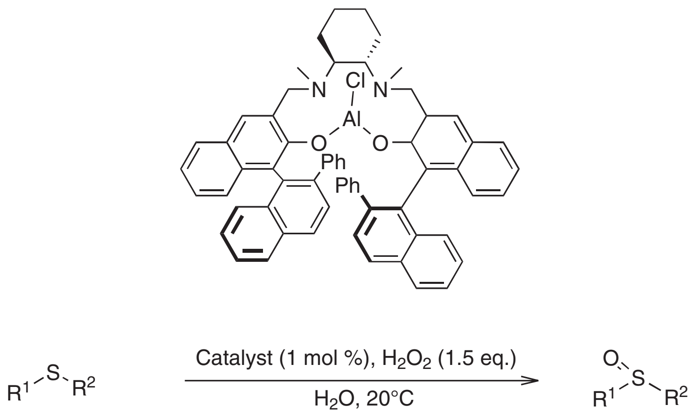


R^1 = Ph, R^2 = Me, 63%, 90% ee
R^1 = 4-NO_2-C_6H_4, R^2 = Me, 36%, 96% ee
R^1 = Mesityl, R^2 = Me, 44%, 77% ee

Scheme 23.26. Asymmetric sulfoxidation of thioethers with substoichiometric H_2O_2 mediated by a dimeric Fe(III) catalyst bearing a bipyridine ligand.

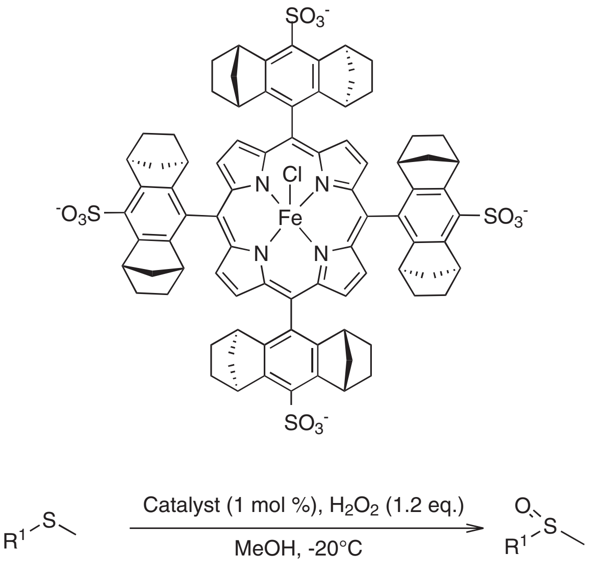
The use of Fe as metal center instead of the more oxophilic Ti and Al, associated with a more sterically demanding ligand such as salalen bearing atropoisomeric binaphthyl moieties, allowed the development of an asymmetric oxidation of sulfides with H_2O_2 in pure water.[51] The system was studied by Katsuki observing good conversion of the reagent with partial formation of sulfone and good enantioselectivity, which is only induced in the first oxidation step as kinetic resolution was poorly selective. The catalytic system was active and selective towards aryl alkyl as well as dialkyl sulfides with both high yields and ee (Scheme 23.27). Using water as the solvent, the system is biphasic, but both catalytic activity and selectivity are higher compared to the reaction in methanol, where the system is monophasic, and is an indication that hydrophobic effects[52] and "on-water conditions"[53] probably play a role.

Chiral iron porphyrin systems have been studied for asymmetric sulfoxidation usually with iodosylbenzene as the terminal oxidant. The employment of H_2O_2 is hampered by the strong tendency of the iron species to promote spontaneous decomposition of the latter oxidant, the so-called catalase reaction, with consequent catalyst destruction by hydroxyl radicals released by homolytic H_2O_2 decomposition. Very recently, it has been demonstrated that using chiral tetra-sulfonated electron-rich porphyrin Fe(II) complexes, it is possible to favor heterolytic H_2O_2 splitting when using polar solvents such as methanol. This led to the development of an efficient and enantioselective sulfoxidation reaction with very high yields and enantioselectivities in the range 76–84%, regardless of the substituents on the aromatic residue of the substrate (Scheme 23.28).[54] The addition of 10 eq. of 2-methylimidazole



R^1 = 4-Me-Ph, R^2 = Me, 91%, 96% ee
R^1 = 2-Cl-C_6H_4, R^2 = Me, 97%, 96% ee
R^1 = CH_2Ph, R^2 = Me, 93%, 87% ee
R^1 = $C_{12}H_{25}$, R^2 = Me, 82%, 94% ee

Scheme 23.27. Asymmetric sulfoxidation with H_2O_2 mediated by an Al(III) salan ligand.



R^1 = Ph, R^2 = Me, 100%, SO/SO_2 = 95:5, 85% ee
R^1 = 4-NO_2-C_6H_4, R^2 = Me, 90%, SO/SO_2 = 95:5, 85% ee
R^1 = 2-Bu-C_6H_4, R^2 = Me, 98%, SO/SO_2 = 98:2, 87% ee

Scheme 23.28. Asymmetric sulfoxidation with H_2O_2 mediated by an Fe(III) porphyrin ligand.

compared to the catalyst led to the coordination of the N-containing heterocycle to the Fe(II) center, resulting in a less active but more enantioselective catalyst (for thioanisole with 2-methylimidazole: yield 61%, $SO/SO_2 = 92:8$, 90% ee; without 2-methylimidazole: yield 100%, $SO/SO_2 = 95:5$, 85% ee).

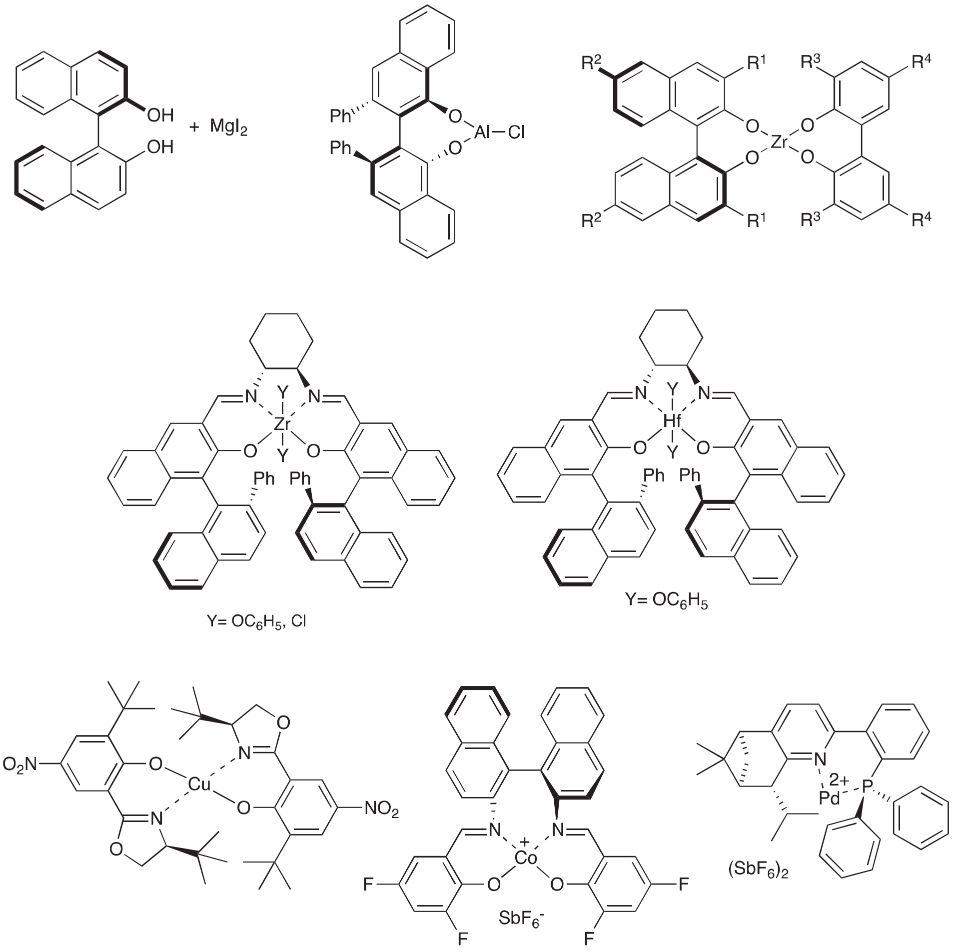
23.3.3. *Asymmetric Baeyer–Villiger*

The Baeyer–Villiger (BV) oxidation reaction is a very old chemical transformation that converts ketones into the corresponding esters or lactones by inserting an oxygen atom from the oxidant between the carbonyl carbon and the one next to it. The first report on the asymmetric BV oxidation appeared about fifteen years ago thanks to the pioneering work of Bolm[55] and Strukul.[56] These authors independently demonstrated, with two different catalysts and oxidant combinations, that a certain degree of stereocontrol of the process was possible, with ee up to 92% on chiral cyclobutanones and 58% in the kinetic resolution of chiral-substituted cyclohexanones, respectively. After these seminal contributions, a series of different catalysts have been proposed.

Most catalytic systems are active towards four-membered ring ketones leading to the corresponding substituted γ-butyrolactones. Pt(II) complexes modified with chelating diphosphines turned out to be the most efficient in catalyzing the BV oxidation of a wide range of substrates, including cyclohexanones and acyclic ketones that can be converted into the corresponding esters, albeit with low turnover.

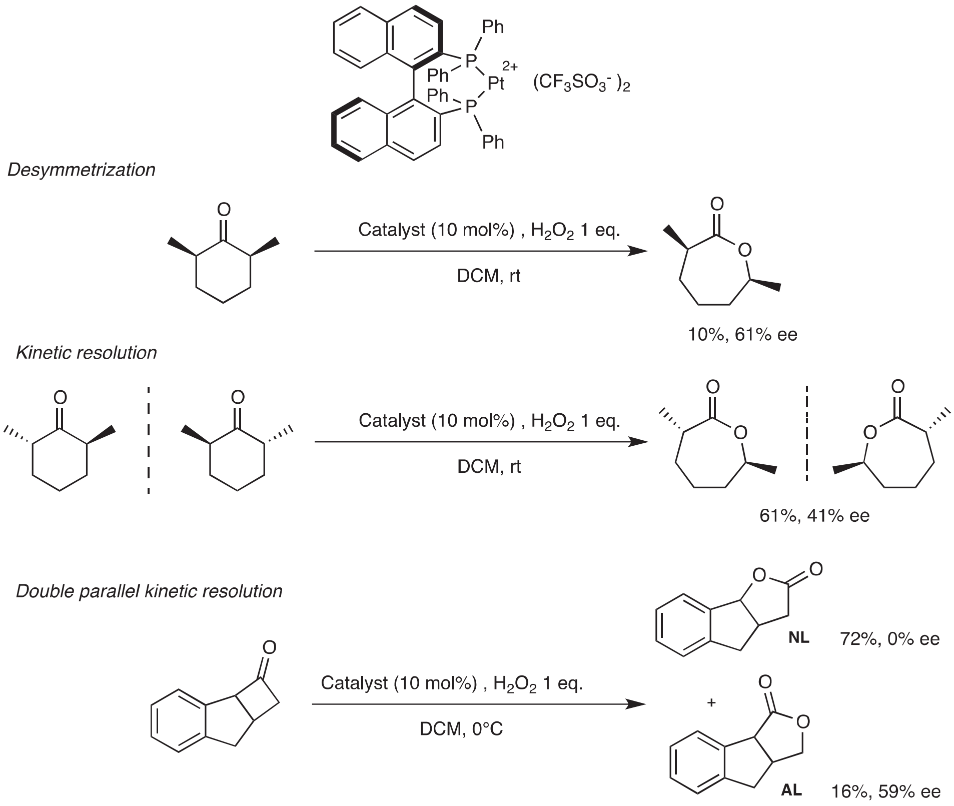
Worthy of mention is that catalysts based on Co,[57] Cu,[58] Pd,[59] Pt,[20,60] Zr[61] and Al[62] are all active towards meso or chiral cyclobutanone substrates, which are intrinsically much more reactive than larger cyclic ketones. Some representative examples are reported in Scheme 23.29. However, only biocatalytic BV oxidations[63] performed with isolated enzymes, or whole cells containing cyclohexanone monooxygenases (CHMOs) or BV monooxygenases (BVMOs) showed good conversions as well as enantioselectivity above 95% ee with cyclohexanone as the substrate.[64]

Recently, Strukul investigated the employment of bis-cationic Pt(II) complexes bearing chiral diphosphines for the asymmetric BV oxidation of six- and four-membered ring cyclic chiral and meso ketones (Scheme 23.30).[65] Atropoisomeric complexes proved to be the best in terms of asymmetric induction in the oxidation of 2,6-dimethyl cyclohexanones which exists in two diastereoisomers, one meso and one chiral compound. The reaction occurs in a stereoselective fashion, with complete retention of configuration of the migrating carbon atom, which is a common observation for the BV reaction. All catalysts are much more active towards the chiral trans-isomer than the meso cis-isomer, in particular, binaphthyl ligands imparted both higher activity and higher enantioselectivity.



Scheme 23.29. Examples of chiral orgsnometallic catalysts developed for the asymmetric BV oxidation cyclic ketones.

When an intrinsically more reactive substrate such as the chiral cyclobutanone reported in Scheme 23.30 was investigated, the interaction between the substrate and the chiral enantiopure catalysts led to substrate kinetic resolution, while the insertion of the oxygen atom between the carbonyl moiety and the adjacent C atom provides two possible diastereoisomeric five-membered ring lactones. Overall, the reaction is a double parallel kinetic resolution and high ee of products in combination with high conversions are possible. The normal lactone (NL) was the predominant product of the reaction in agreement with the migratory aptitude for BV reactions. In particular, catalysts bearing a biaryl ligand reacted with the cyclobutanone-substrate more reactive enantiomer to give both NL and the abnormal lactone (AL) at a greater



Scheme 23.30. Asymmetric Baeyer–Villiger oxidation of meso, chiral and four-membered ring cyclic ketones with H_2O_2 mediated by a Pt(II) catalyst bearing an atropoisomeric diphosphine ligand.

rate than the corresponding reaction on the less reactive enantiomer. On the contrary, the other catalysts characterized by larger bite angles showed a small degree of regiodivergent parallel kinetic resolution.

At present, chiral Pt(II) complexes represent the most efficient catalytic system in terms of activity and enantioselectivity for poorly reactive meso and chiral cyclohexanones, with important improvements observed when working in water, as reported in the following sections.

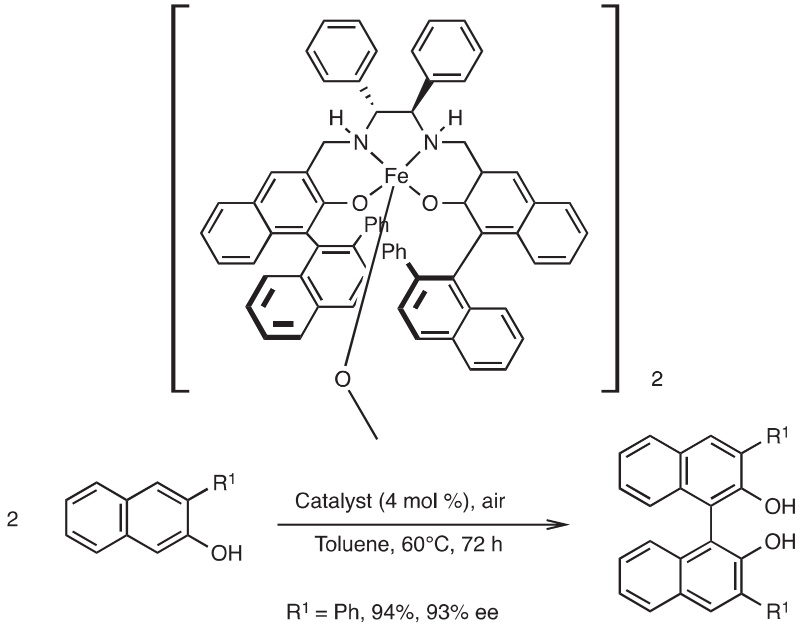
23.3.4. *Other asymmetric oxidations*

The atropoisomerism of binaphthol ligands has been extensively exploited for the preparation of enantiopure bidentate ligands. These are usually produced in racemic mixtures and subsequently treated with a resolving agent. Alternative pathways for the direct synthesis of enantioenriched binaphthols are based on the oxidative dimerization of 2-naphthol derivatives which directly provides the chiral ligand. This asymmetric oxidation can be performed with different methods. In the following, two procedures will be discussed based on the use of molecular oxygen as the terminal oxidant.

We have already discussed the use of iron-based chiral complexes in asymmetric oxidation reactions with H_2O_2. In order to employ O_2 as the terminal oxidant it is necessary to choose the correct ligand to suitably reduce its oxidation potential. Salan ligands, bearing two phenolic and two amino donor atoms, provide the necessary requirements to promote the aerobic oxidation of 2-naphthols to the corresponding bi-naphthols, which are invaluable chiral precursors and ligands. Katsuki observed that first generation chiral dimeric μ-oxo-Fe(salan) complexes were poorly active, while second generation Fe(salan) with a chiral 1,2-diphenyl backbone and atropoisomeric bi-naphthalene substituents allowed substantial asymmetric induction. Once optimized, the catalytic system allowed the dimerization of 2-naphthols with 4% mol catalyst at 60°C in toluene under air as the terminal oxidant, with yields in the range 77–94% and 77–96% ee.[66] In particular, 2-naphthols substituted in position six provided lower asymmetric induction compared to substrates substituted in position three (Scheme 23.31).

An alternative approach to the asymmetric synthesis of binaphthols via biaryl coupling in the presence of molecular oxygen as the terminal oxidant was disclosed by Kozlowski using chiral diamine ligands, in particular, using (S,S)-1,5-diaza-cis-decalin with Cu(II).[67] The peculiarity of the system is to work efficiently (2.5–10% mol of catalyst) with high yields and high enantioselectivity (>90%) exclusively for 2-naphthols bearing ester, ketone, phosphonyl and sulfonyl derivatives in the R^1 position (Scheme 23.32). The role of such functional groups in that position is manifold: they play a pivotal role in regulating the oxidation potential of the substrate, they provide a coordination site for the Cu(II) metal center, in association with the phenolic OH, and they enable turnover ability of the catalyst. Electron-rich 2-naphthols lacking the substituents in position three provide good catalytic activity but with much lower enantioselectivity because of the less rigid monodentate coordination to the metal center. The mechanism of the reaction was investigated in detail[68] observing that the aerobic oxidation of the catalyst is the turnover limiting step of the reaction.

This catalytic system operating on less electron-rich 2-naphthols complements well more traditional systems working on highly electron-rich naphthols, which have been employed in the synthesis of chiral perylenequinones-based derivatives that are potent protein kinase C inhibitors and are promising agents for photodynamic cancer therapy.[69]



R^1 = Ph, 94%, 93% ee

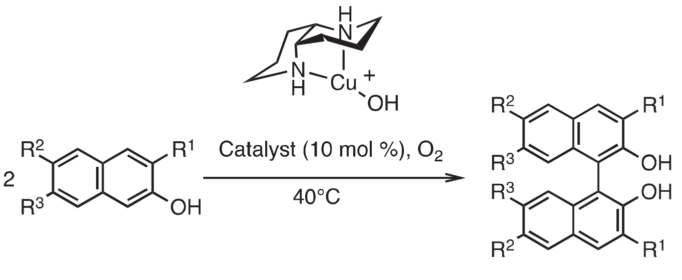
R^1 = 2-naphthyl, 91%, 94% ee

R^1 = Cl, 82%, 94% ee

R^1 = I, 77%, 96% ee

R^1 = Me, 89%, 77% ee

Scheme 23.31. Asymmetric oxidation of naphthols with air to provide atropoisomeric binaphthols mediated by a dimeric Fe(III) salan catalyst.



R^1 = COOMe, R^2 = Br, R^3 = H, 27%, 92% ee

R^1 = $CONEt_2$, R^2 = H, R^3 = H, 48%, 72% ee

R^1 = $CO(C_6H_4)$-p-NMe_2, R^2 = H, R^3 = H, 84%, 94% ee

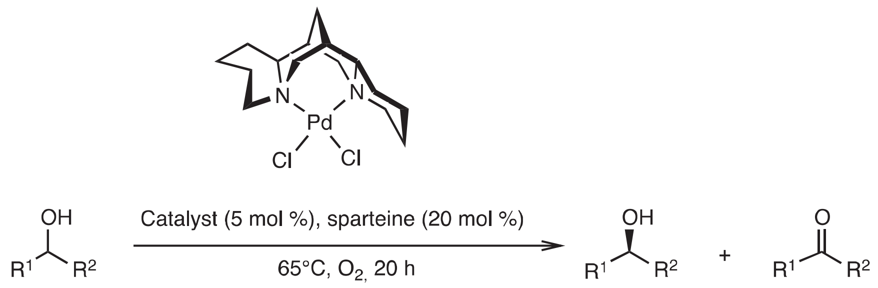
R^1 = $CO(C_6H_4)$-p-OMe, R^2 = H, R^3 = H, 93%, 90% ee

Scheme 23.32. Asymmetric oxidation of naphthols to atropoisomeric binaphthols with O_2 mediated by a dimeric Cu(II) cornplex bearing a diamine ligand.

23.3.5. *Resolution of chiral secondary alcohols via asymmetric oxidation*

23.3.5.1. *Palladium*

Despite its high value in the synthesis of chiral natural products and pharmaceutical drugs, the asymmetric kinetic resolution of secondary alcohols via oxidation to the corresponding ketones is a much younger reaction than other asymmetric oxidations, just a little more than ten years old. The major problem that hampered its development was the choice of oxidant[70] which can participate in the general mechanism based on the substrate oxidation by Pd(II) species followed by re-oxidation of the Pd(0) species by the terminal oxidant (Wacker-type oxidation). The seminal work of Uemura[71] on the achiral version of the reaction based on the employment of $Pd(OAc)_2$ with pyridine and O_2 as the oxidant under anhydrous conditions was independently extended to the use of chiral ligands by Sigman[72] and Stoltz[73] when in 2001 they selected (−)-sparteine as the best ligand for the reaction. The two groups identified similar catalytic systems based on different Pd precursors, solvents and bases. In particular, Sigman's system is based on the employment of 5% mol of Pd[(−)-sparteine]Cl_2 with an extra 20% mol of ligand that acts as a base in t-butanol as the solvent at 65°C, for 20−24 h with oxygen, and it is active and selective with K_{rel} (K_R/K_S) between 10 and 20 for a wide range of secondary benzylic and aliphatic alcohols, as well as for meso 1,3-diols (Scheme 23.33) with possible extension up to 10 mmol scale.[74] The catalytic system optimized by Stoltz uses 5% mol of [Pd(nbd)Cl_2] (nbd = norbornadiene) with 12% of (−)-sparteine in chloroform,



R^1 = 4-Me-Ph, R^2 = Me, 61.6%, 98.5% ee, K_{rel} = 19

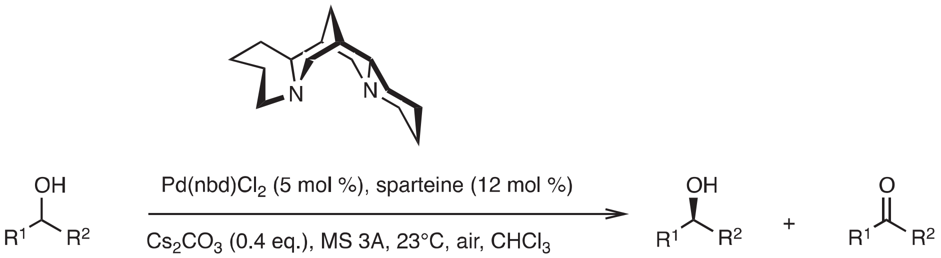
R^1 = 2-naphthyl, R^2 = Me, 55.9%, 90.2% ee, K_{rel} = 17.7

R^1 = 2-furyl, R^2 = Me, 65.2%, 99.3% ee, K_{rel} = 16.3

R^1 = t-Bu, R^2 = Me, 60.9%, 97.2% ee, K_{rel} = 17.3

R^1 = Cy, R^2 = Me, 53%, 61% ee, K_{rel} = 6.1

Scheme 23.33. Kinetic resolution of secondary alcohols via oxidation with O_2 mediated by a Pd(II) catalyst bearing a bidentate amine ligand.



R^1 = 4-Me-Ph, R^2 = Me, 62.3%, 99.8% ee, K_{rel} = 25.7

R^1 = 2-naphthyl, R^2 = Me, 55.5%, 98.0% ee, K_{rel} = 37.3

R^1 = Ph, R^2 = Et, 56.8%, 94.9% ee, K_{rel} = 21.7

R^1 = 4-F-C_6H_4, R^2 = Me, 56.7%, 93.0% ee, K_{rel} = 19.5

Scheme 23.34. Kinetic resolution of secondary alcohols via oxidation with air mediated by a Pd(II) bearing (−)-sparteine ligand.

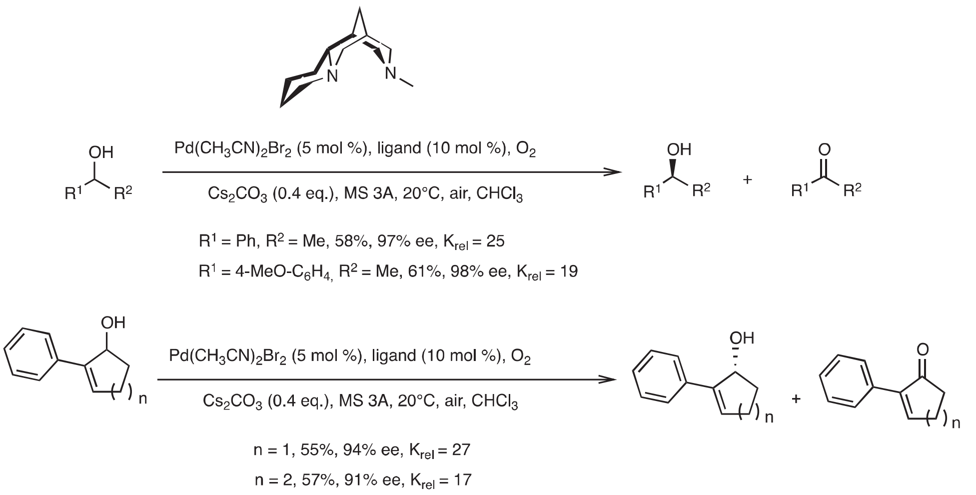
with Cs_2CO_3 as the base under anhydrous conditions at room temperature and with air as the oxidant.[75] This system works under milder experimental conditions and allows K_{rel} between 10 and 30, in particular, for benzylic alcohols (Scheme 23.34).

In spite of its high selectivity, the intrinsic limitation of the Pd(−)-sparteine catalytic system is related to the natural origin of the chiral ligand which is only available in one enantiomeric form. This restricts the stereochemistry of the enantioenriched secondary alcohol recovered after the kinetic resolution to one enantiomeric series. Stoltz overcame the problem by selecting another chiral diamine ligand[76] derived by (−)-cytisine that shares three of the four cyclic rings present in the structure of (−)-sparteine. The new ligand, in the presence of $[Pd(CH_3CN)_2Br_2]$ as the metal precursor, allowed the enantiomers of the secondary alcohols usually achieved with (−)-sparteine to be obtained (Scheme 23.35).

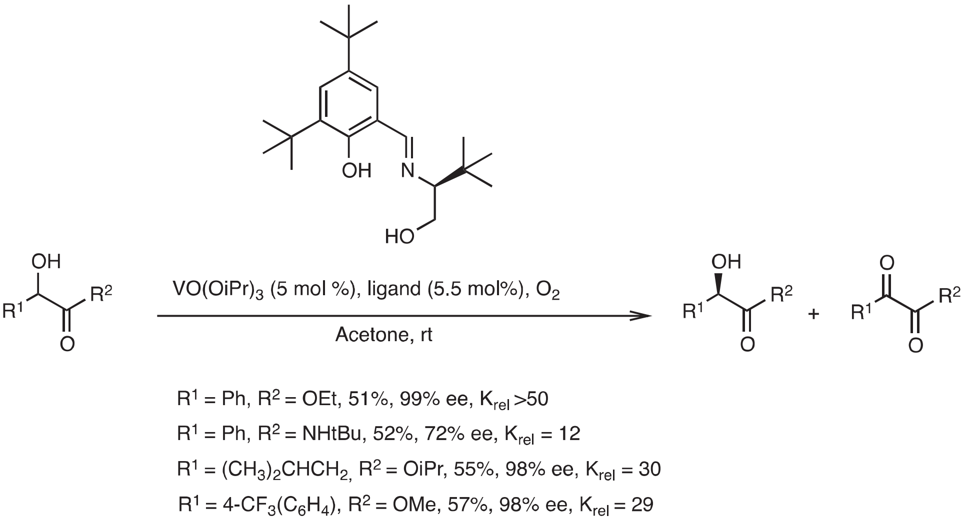
Both ligands with the appropriate Pd precursors have been recently implemented in the enantioselective synthesis of alkaloids[77] and pharmaceutical building blocks,[78] showing potential applicability to high-value molecules as well as the possible scale-up of the reaction.

23.3.5.2. *Vanadium*

Asymmetric secondary alcohol oxidation can also be performed with other metal complexes, in particular Toste showed that traditional Schiff based V catalysts prepared *in situ* from the corresponding ligand and VO(O-*i*Pr)$_3$ allowed the kinetic resolution of α-hydroxy esters in acetone under mild experimental conditions and with 1 atm of O_2 (Scheme 23.36).[79] The reaction works well for both benzylic and



Scheme 23.35. Kinetic resolution of secondary alcohols with a Pd(II) catalyst bearing a bidentate N ligand that provides the opposite enantiomers compared to (−)-sparteine.



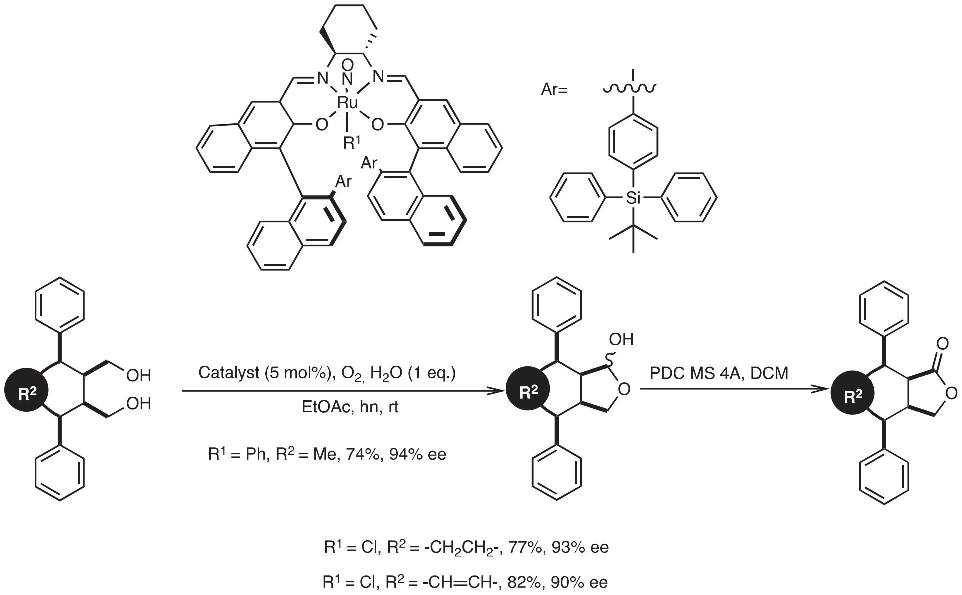
Scheme 23.36. Kinetic resolution of secondary α-keto alcohols with O_2 mediated by a V(V) with a Schiff base ligand.

non-benzylic substrates, in the latter case longer reaction times being necessary. Although V complexes are known to efficiently promote the epoxidation of alkenes, the present catalytic system is highly chemoselective and also provides the carbonyl product in the presence of alkene residues which remain unchanged. The selectivity factor, which correlates the ee of the reagent and conversion, is in most cases >10 and up to more than 50 for ethyl mandelate.

23.3.5.3. *Ruthenium*

Ruthenium complexes bearing nitroxyl apical ligands, in conjunction with second generation salen ligands, were developed by Katsuki and showed good catalytic activity in the aerobic oxidation of secondary alcohol under visible light irradiation. The catalytic system was accurately tuned in terms of chirality of the ligand and it was subsequently applied to the desymmetrization of meso diols to give optically active lactols.[80] In particular, each substrate, ranging from acyclic diols to monocyclic diols, needs the catalytic system tailored in order to attain high enantioselectivity (up to 93%) with a peculiar role played by the apical ligand that affects not only the enantioselectivity, but also the kinetics of the desymmetrization reaction (Scheme 23.37).

Subsequent implementation of the knowledge developed in this work enabled the application of the Ru(salen)(nitrosyl) complexes to the oxidative aerobic kinetic resolution of secondary alcohols, modifying the original catalyst by the addition of 1,3-bis(p-bromophenyl)propane-1,3-dione as a bidentate ligand whose effect was to steer the coordination geometry of the Ru(III) center to a cis-β configuration.[81] This allowed a highly enantioselective catalyst which, under mild conditions (air at room temperature), converts chiral racemic secondary benzylic, allylic, propargylic and aliphatic alcohols with K_{rel} between 14 and 30 (Scheme 23.38).



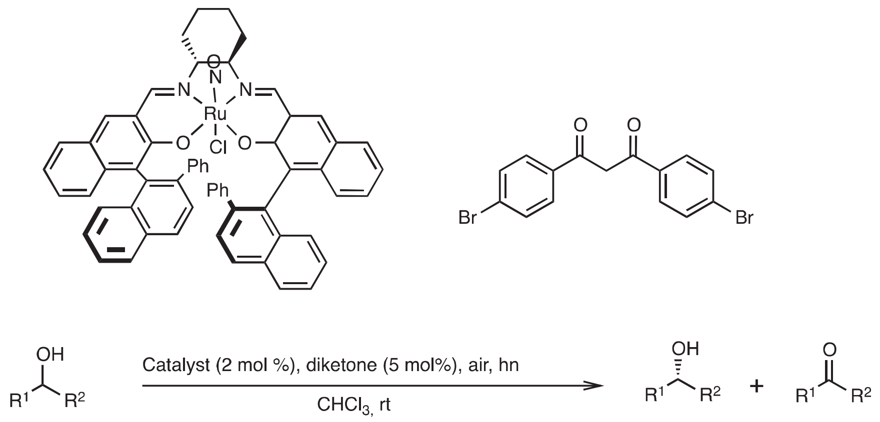
R^1 = Cl, R^2 = -CH_2CH_2-, 77%, 93% ee

R^1 = Cl, R^2 = -CH=CH-, 82%, 90% ee

R^1 = OH, R^2 = -CH_2CH_2-, 58%, 83% ee

R^1 = OH, R^2 = -CH=CH-, 99%, 81% ee

Scheme 23.37. Desymmeterization of primary diols with O_2 mediated by a Ru(III) salen complex.



R^1 = Ph, R^2 = Me, 61%, 98% ee, K_{rel} = 19

R^1 = PhCC, R^2 = Me, 58%, 99% ee, K_{rel} = 30

R^1 = 4-Cl(C_6H_4), R^2 = Me, 57%, 95% ee, K_{rel} = 23

R^1 = $PhCH_2$, R^2 = Me, 41%, 55% ee, K_{rel} = 15

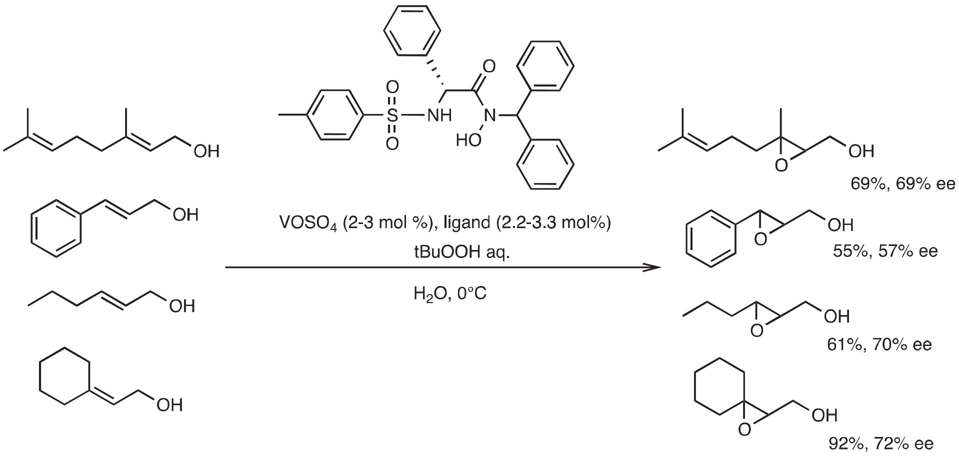
Scheme 23.38. Kinetic resolution of secondary alcohols with air mediated by Ru(III) salen complex.

23.4. Water as the Reaction Medium

Water is the medium where all biological reactions take place, including oxidation reactions, but it is a rather unfamiliar solvent for chemists who tend to avoid it, often in an over-prudent approach. When H_2O_2 and O_2 are used as oxidants, water is present as a by-product and this prompted the investigation of catalytic asymmetric oxidation reactions in water. The hydrophobic effect,[52] which consists of the tendency for organic species to self-assemble in water, is the most peculiar effect of this solvent and operates both on apolar catalysts and organic substrates. This overall "squeeze out" effect produces, in several cases, positive effects on both the catalytic activity and the enantioselectivity of asymmetric reactions, as described in the following examples of stereoselective oxidation.

23.4.1. *Water as solvent*

The vanadium-catalyzed epoxidation reaction of allylic alcohols with bidentate chiral hydroxamic acids is, similar to several other oxidation reactions, an example of ligand-decelerated catalysis when comparing the original V-alkoxide precursor and the V-ligand complex for reactions performed in organic media. In water the effect is reversed, with the chiral ligand accelerating the reaction if compared to the original V precursor for a ratio of up to 1:1 ligand to metal. The epoxidation reaction with



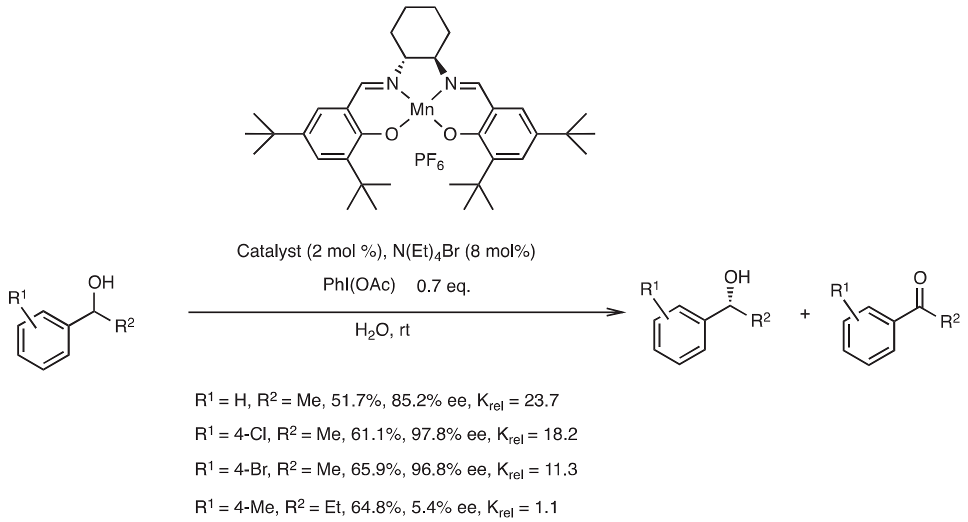
Scheme 23.39. Asymmetric epoxidation of allyl alcohols with tBuOOh in water mediated by a V(IV) with a NO bidentate ligand.

t-BuOOH as the oxidant occurs in the organic phase formed by the poorly soluble substrate where the catalyst is confined by the hydrophobic effect. This catalytic system does not suffer from epoxide ring-opening caused by the presence of water, and a series of allyl alcohols can be efficiently oxidized with 41–92% yield and 57–72% ee (Scheme 23.39).[82]

More impressive results were observed in two other asymmetric reactions both based on the use of well-known catalysts developed for other transformations that turned out to perform well in new reactions, thanks to the beneficial use of water as solvent. One case is based on the oxidative kinetic resolution of secondary alcohols with chiral Mn(salen) complexes using $PhI(OAc)_2$ as the oxidant (Scheme 23.40). The reaction is poorly enantioselective in dichloromethane (2% ee $K_{rel} < 1.1$), while in water, in the presence of tetraethylammonium bromide as the phase transfer agent, the reaction is fast (63.4% conversion in 2 h) and highly enantioselective (85.2% ee with K_{rel} 23.7).[83]

23.4.2. *Micellar catalysis*

As exemplified above, the use of water as the solvent for organometallic catalysis is hampered by the low general solubility of both substrates and catalysts in this medium. Possible approaches to solving this are based on i) the use of polar co-solvents that often decrease the green character of the catalytic system or ii) the employment of surfactants that form micelles in water as apolar nano-environments where substrates and catalyst get together and react, often with enhanced activity and selectivity.[84] Micelles are self-assembled devices arising from neutral, anionic

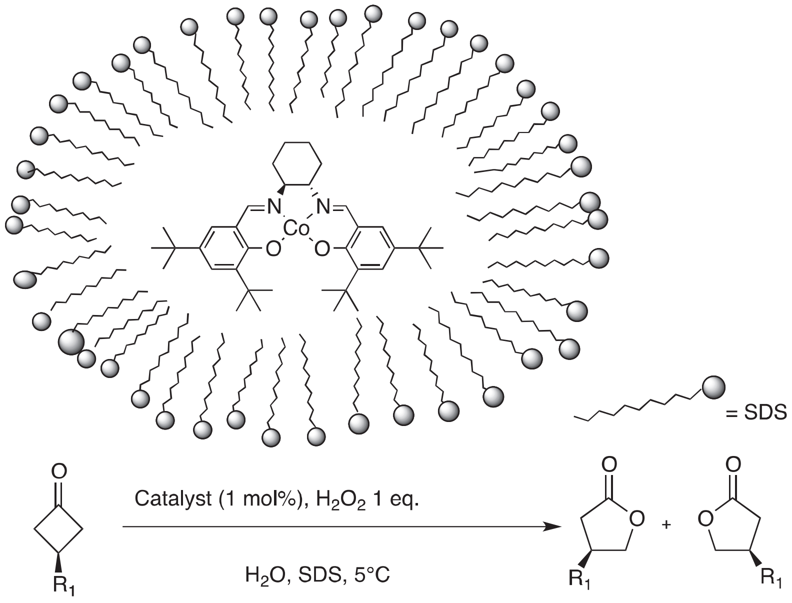


Scheme 23.40. Kinetic resolution of secondary alcohols with PhI(OAc)$_2$ in water mediated by the Mn(II)salen complex.

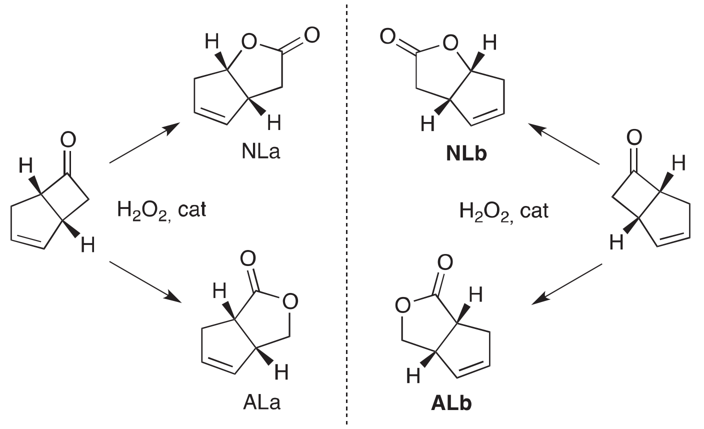
or cationic amphiphilic molecules exposing the polar heads to water and aligning the hydrophobic tails in the core. Because of this structure, ongoing from the surface to the core of a micelle, a polarity gradient is present. Asymmetric oxidation reactions, such as Baeyer—Villiger epoxidation and sulfoxidation reactions, all showed better performances when carried out in water under micellar conditions rather than with the use of organic chlorinated solvents.

One remarkable example is based on a Co(salen) complex that was employed as the catalyst for the Baeyer–Villiger oxidation of cyclic meso ketones with H_2O_2 as the oxidant. The complex was not active in organic media with poor yields and no enantioselectivity, but when tested in micellar media the system became active and selective (Scheme 23.41).[85] After optimizing the experimental conditions, the Co(salen) catalyst in the aqueous micellar medium allowed high yields (up to 98%) in normal lactone, with high diastereoselectivity (up to 86%) and high ee (up to 90%) in the double parallel kinetic resolution of chiral cyclobutanones via asymmetric Baeyer—Villiger oxidation. It is worth noting that when this catalytic system operates in water the exceptional increase in activity and selectivity is solely due to the micelles where both catalyst and substrate are dissolved.

Using water as the solvent also increased the selectivity in the asymmetric Baeyer–Villiger oxidation of cyclic six- and four-membered ring ketones. In particular, the use of surfactants under micellar conditions allowed i) the direct solubilization of otherwise water insoluble complexes and ii) the increase of



R^1 = Ph, 20%, 13% ee (CH_2Cl_2 2%, 0% ee)
R^1 = Bu, 12%, 26% ee (CH_2Cl_2 1%, 0% ee)
R^1 = Cy, 24%, 14% ee (CH_2Cl_2 2%, 0% ee)



Solvent	TON NL+AL	NL/AL	ee (%) NL
CH_2Cl_2	15	34	0
H_2O/TritonX100	48	74	51
H_2O/TritonX114	60	70	90

Scheme 23.41. The asymmetric Baeyer–Villiger oxidation of 3-substituted cyclobutanones chiral cyclobutanones with H_2O_2 mediated by a Co(II)salen catalyst benefits greatly from the employment of micellar media instead of common organic media.

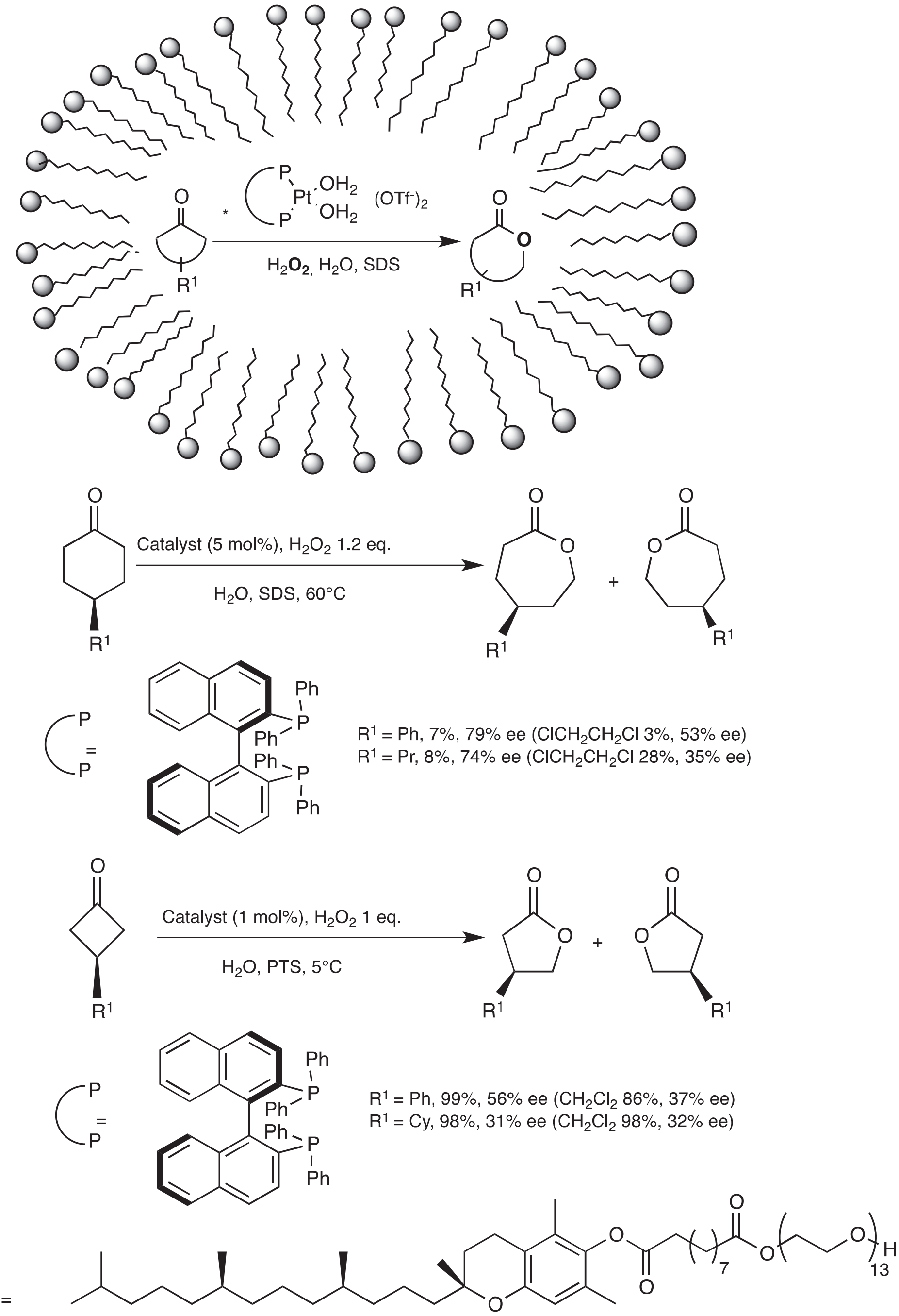
enantioselectivity and green character compared to the same reaction carried out in common chlorinated organic solvents.[86]

Scarso and Strukul observed that anionic micelles based on sodium dodecylsulfate (SDS) efficiently solubilized Pt bis-cationic complexes and ketones in the apolar core of the micelles. This favored the contact between substrate and catalyst and, more importantly, led to a higher steric control of the asymmetric reaction thanks to the more ordered nano-environment present in the micelles compared to bulk organic solvents. Each substrate required the dedicated optimization of the catalyst, the surfactant and the experimental conditions since the distribution of the substrates and catalysts is greatly affected by the kind of surfactant and aggregate considered (Scheme 23.42). Overall, in all the cases tested, an increase in enantioselectivity was observed for the asymmetric BV oxidation of meso-4-substituted cyclohexanones with bis-diphenylphoshinobinaphthyl (BINAP) as the ligand and SDS as the surfactant. A different scenario was present in the kinetic resolution of chiral cyclobutanones or with meso cyclobutanones where an increase of enantioselectivity was observed with the neutral polyoxyethanyl-α-tocopheryl sebacate (PTS) surfactant (Scheme 23.42).

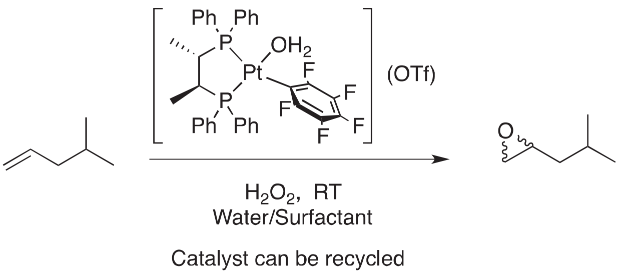
Overall, the use of surfactants in water for the studied BV reactions implies the partition of all reaction partners (substrate, oxidant and catalyst) between the micelle, bulk water and the interphase between the two. As a consequence, the lipophilicity of all species is crucial to rationalize their positioning in the micellar system, and as a general observation, more hydrophilic substrates worked well in neutral surfactants while more lipophilic ones worked well in anionic micelles.

Asymmetric epoxidation of terminal alkenes with hydrogen peroxide was optimized with electron-poor chiral Pt(II) complexes bearing a pentafluorophenyl residue, as described in Section 23.3.1.6. The same catalytic system was made more sustainable by the employment of water as the solvent under micellar conditions. Surfactant optimization revealed the preferential use of neutral species like Triton-X100 to solubilize both the catalyst and substrates. In several cases an increase of the asymmetric induction was observed (Scheme 23.43).[29] The use of an aqueous phase and the strong affinity of the catalyst for the micelle allowed the recycling of the catalytic system by means of phase separation and extraction of the reaction products using an apolar solvent (hexane). The aqueous phase containing the catalyst was reused for up to three cycles with no loss of activity or selectivity.

In addition, asymmetric sulfoxidation could benefit from the use of aqueous micellar systems. In the reaction catalyzed by dimeric chiral Pt(II) species, both the chemoselectivity (chiral sulfoxide vs achiral sulfone) and the enantioselectivity of the former product increased, moving from dichloromethane as the organic solvent to water/SDS forming anionic micelles where the bis-cationic catalyst interacts via ion pairing (Scheme 23.44).[87]



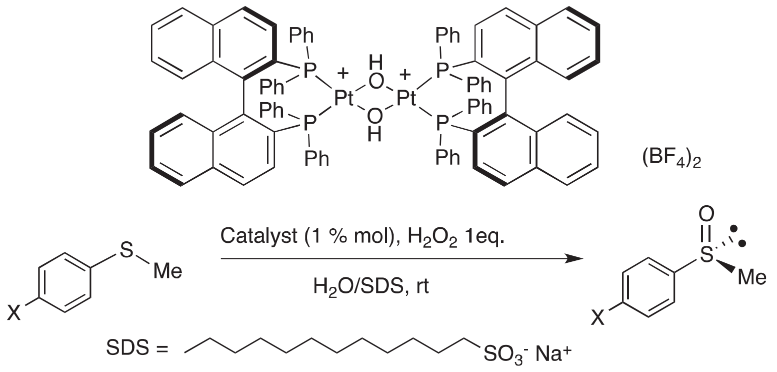
Scheme 23.42. The asymmetric Baeyer–Villiger oxidation of meso cyclohexanones and cyclobutanones with H_2O_2 mediated by a Pt(II) diphosphine catalyst in water with surfactant addition.



Yield (%)	EE (%)	Medium
56	58	DCE
51	84	H_2O/Triton-X100

Cycle	Yield (%)	EE (%)
1	26	75
2	26	72
3	33	77

Scheme 23.43. Asymmetric epoxidation of terminal alkenes with H_2O_2 mediated by electron-poor Pt(II) catalysts bearing diphosphine ligands.



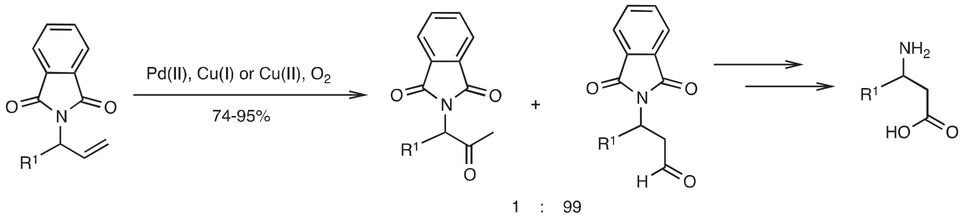
R^1 = H, 98%, 40% ee (CH$_2$Cl$_2$, 99%, 16% ee)
R^1 = CN, 68%, 63% ee
R^1 = NO$_2$, 63%, 88% ee

Scheme 23.44. Asymmetric sulfoxidation of thioethers with H_2O_2 mediated by a dimeric Pt(II) catalyst in micellar media.

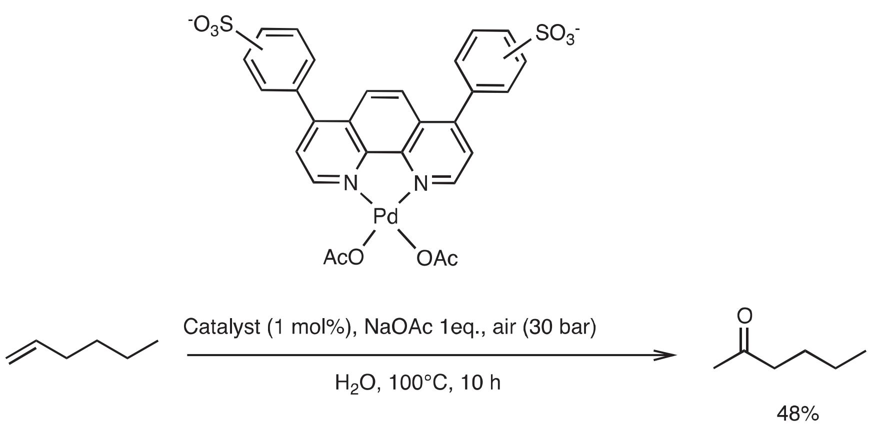
23.4.3. *Wacker oxidation of alkenes*

In the Wacker oxidation reaction that converts alkenes into the corresponding carbonyl compounds, the terminal oxidant is usually molecular oxygen, but the real oxidation steps are carried out by the redox chemistry of the Pd(II) centers. The classical system requires Cu(II) as a co-catalyst to re-oxidize Pd(0) to Pd(II) and O_2 as the terminal oxidant to re-oxidize Cu(I) to Cu(II). The oxygen atom transferred to the substrate comes from water. Because of the role played by H_2O, recent updates on Wacker-type oxidations are described below. The mechanism of the general oxidation with $PdCl_2$, $CuCl_2$ and O_2 has also been reviewed recently, and different pathways are possible as a function of the different concentrations and other experimental conditions.[88] The oxidation reaction usually follows the Markovnikov rule, but important exceptions are known. In particular, heteroatoms in allylic positions tend to mitigate the preference for the formation of methyl ketones. This effect can be exploited in order to selectively form the aldehyde when using allylamines as substrates protected with a phthalimide functional group that ensures quantitative oxidation and >99:1 preference for the aldehyde (Scheme 23.45).[89] The catalyst used in this case is $PdCl_2$ with stoichiometric CuCl in DMF/H_2O as the solvent, using O_2 as the oxidant; the reaction is compatible with the presence of stereocenters on the substrate. In fact, enantioenriched allylic phthalimides maintain their chirality and provide chiral aldehydes which are precursors of β-aminoacids.

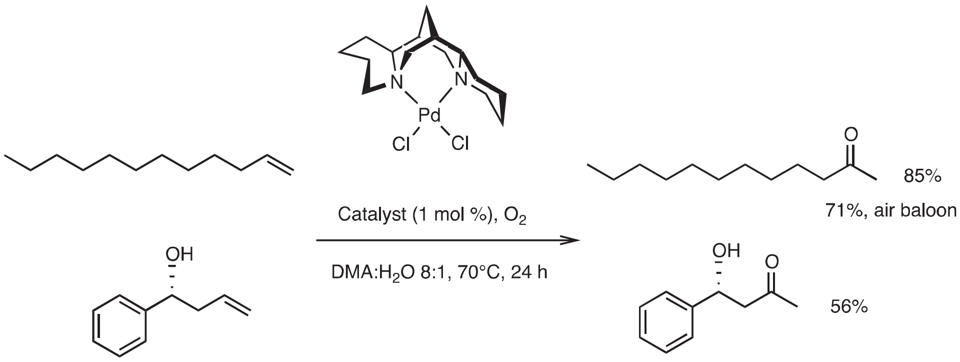
Recent trends in Wacker oxidation[90] involve the avoidance of Cu salts as co-catalysts, which implies the direct re-oxidation of Pd(0) species by O_2. This requires the presence of the correct ligands stabilizing the reduced form of the catalyst avoiding zerovalent metal aggregation, which is the main deactivation pathway hampering catalyst turnover. The use of tailored ligands for Pd(II) centers is also in contrast with the presence of Cu species because of possible ligand exchange during catalysis. An original approach toward this goal was proposed by Sheldon when using water-soluble phenanthroline ligands in water to prevent Pd(0) aggregation and contextually decrease the redox potential of Pd(II)/Pd(0), thereby reducing catalyst



Scheme 23.45. Aldehyde selective Wacker oxidation of terminal alkenes bearing a phthalimide substituent with O_2.



Scheme 23.46. Wacker oxidation of terminal alkenes with air in water with a water-soluble Pd(II) catalyst bearing a sulfonated phenanthroline ligand.



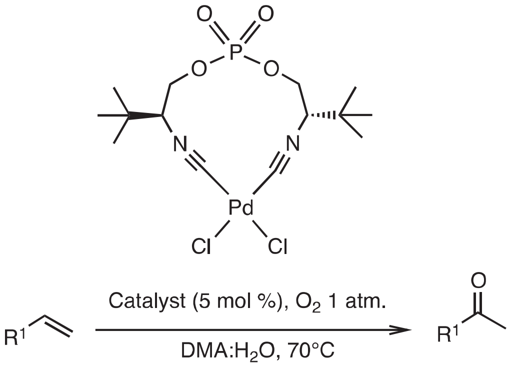
Scheme 23.47. Wacker oxidation of alkenes with O_2 mediated by a (−)-sparteine Pd(II) catalyst.

decomposition (Scheme 23.46).[91] Both terminal and internal alkenes were oxidized to ketones at 100°C and 30 bar of air. Using water as the solvent, catalyst recycling was achieved by means of a simple extraction of the organic product and reuse of the aqueous phase.

A more active system working under less harsh conditions was obtained using (−)-sparteine as a bidentate ligand for Pd(II).[92] A lower concentration of O_2 can be used and the possible isomerization of terminal olefins is suppressed with the exclusive formation of terminal methyl ketones (Scheme 23.47). Enantiomerically-enriched protected alcohols bearing terminal alkenes provided the corresponding chiral methyl ketones without racemization, further emphasizing the potential synthetic utility of the oxidation method.

Very recently, Reiser[93] showed that a bis(isonitrile) ligand forms robust Pd(II) complexes for the direct Wacker oxidation of alkenes without Cu co-catalysts under 1 atm of O_2 at 70°C. The catalytic system showed good activity towards terminal aliphatic alkenes, but also styrene substrates, which are usually more challenging substrates for this kind of oxidation because of the competitive double-bond cleavage under oxidative conditions reacting readily, favoring the acetophenone products and concomitant formation of benzaldehydes as side products in 4–20% yield (Scheme 23.48).

An extremely simple solution for the direct use of O_2 in the Wacker reaction was achieved by switching to N,N-dimethylacetamide (DMA) as the water co-solvent because of its intrinsic properties that promote the re-oxidation of Pd(0) species. Efficient and regioselective oxidation on C_2 of terminal alkenes was possible using $PdCl_2$ as the catalyst at 60°C with 6 atm of O_2.[94] If the reaction is carried out under anhydrous conditions in the presence of NaOAc and acetic acid with DMA as the solvent, the reaction provides selective oxidation of the terminal alkene on C_1 leading to the corresponding allyl acetates (Scheme 23.49). The catalytic system is also active towards internal alkenes that are efficiently converted into the corresponding ketones, showing good tolerance for the presence of other functional groups in the substrate such as alcohol, nitrile and allyl ether.[95]



$R^1 = C_6H_{13}$, 98%

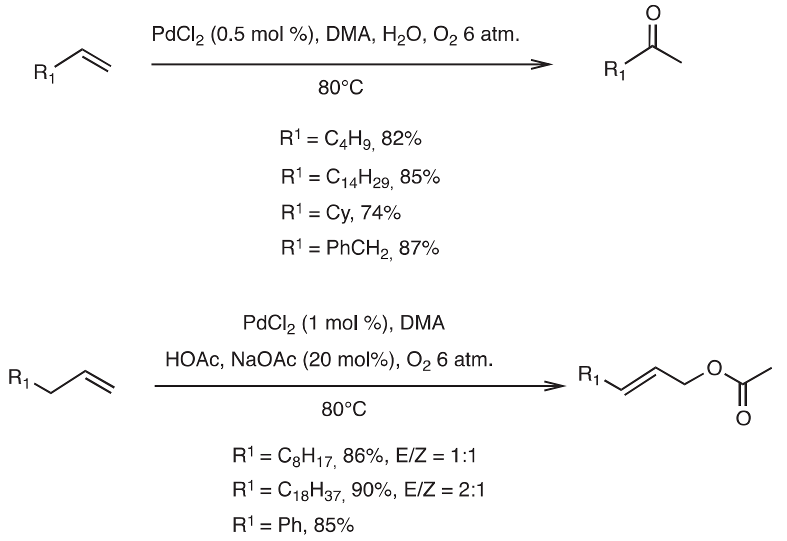
$R^1 = PhCH_2$, 75%

R^1 = Cy, 84%

R^1 = 4-MeO-Ph, 99%, ket./ald. = 21

R^1 = Ph, 84%, ket./ald. = 17

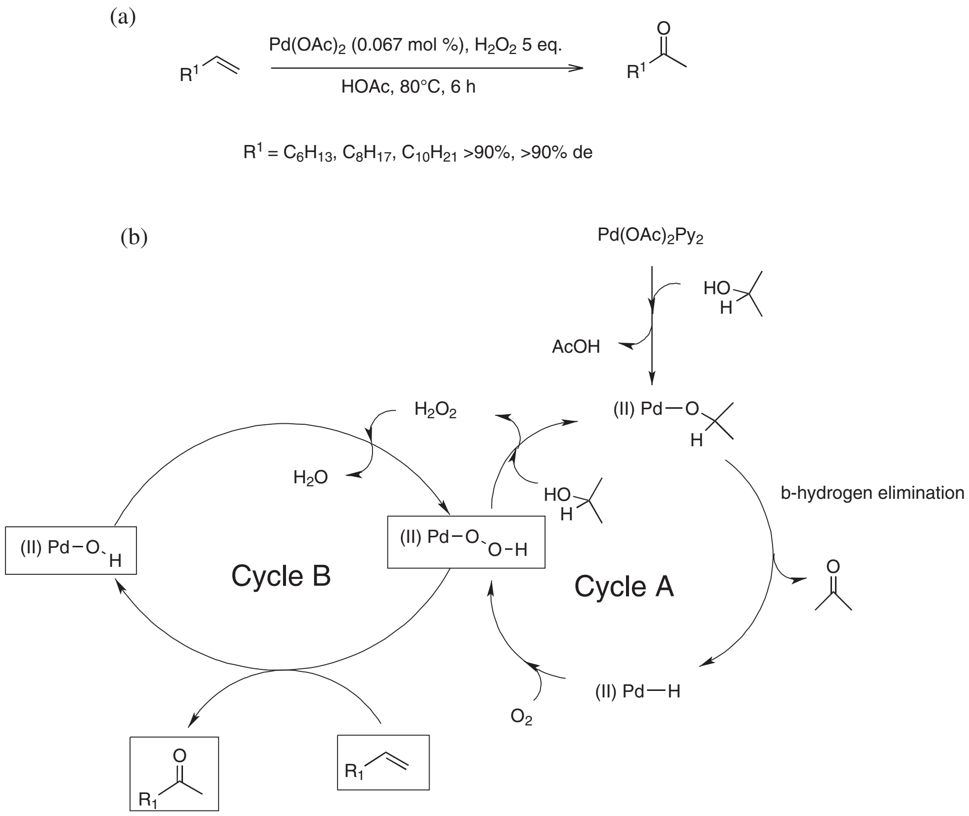
Scheme 23.48. Wacker oxidation of terminal alkenes with O_2 mediated by a Pd(II) catalyst bearing a bidentate isonitrile ligand without a Cu(I) co-catalyst.



Scheme 23.49. Wacker oxidation of terminal alkenes with O_2 in DMA with a $PdCl_2$ without Cu(I) co-catalyst provides the corresponding methyl ketones or, in the presence of HOAc and NaOAc, allyl acetates.

An alternative approach to the Wacker reaction, excluding the use of Cu(II), is based on the use of oxidants alternative to O_2. Early examples dating back to the 1980s for the reaction using H_2O_2 instead of O_2 were reported by Mimoun using five equivalents of oxidant in acetic acid.[96] The reaction is highly selective, forming the corresponding methyl ketone for a series of terminal alkenes from C_8 to C_{12}, while it does not work on internal double bonds or alkenes with heteroatoms in the allylic position (Scheme 23.50a). A more recent example is based on the *in situ* formation of H_2O_2 from O_2 using $Pd(OAc)_2$ as the catalyst, with pyridine as the ligand in the presence of i-PrOH. This system efficiently provides methyl ketones from terminal alkenes but it was inactive towards internal ones. A plausible mechanism of the reaction is based on alcohol oxidation that forms the Pd-hydride species that further react with molecular oxygen leading to Pd-hydroperoxo species that eventually transfer the oxygen of the activated oxidant directly to the substrate (Scheme 23.50b).[97]

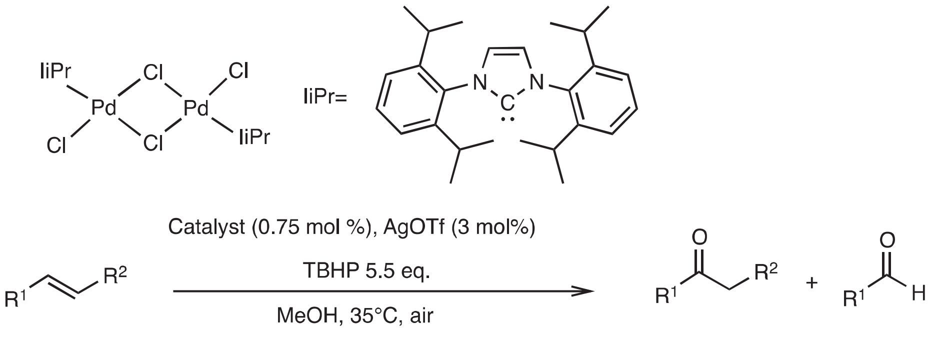
In 2005 Sigman disclosed that the dimeric $[Pd\text{-}(I\text{-}i\text{-}Pr)Cl_2]_2$ complex bearing a carbene ligand with AgOTf to replace the chlorine ligand, was able to activate t-butyl hydroperoxide towards the oxidation of styrene to acetophenone in methanol under mild conditions.[98] Conversion was high with a wide range of styrene substrates regardless of the electronic nature of the substituents in the aromatic ring, with all cases exhibiting an extremely high regioselective Markovnikov oxidation of the double bond (Scheme 23.51). Mechanistic investigation and isotopic



Scheme 23.50. (a) Wacker oxidation of terminal alkenes to methyl ketones with H_2O_2 mediated by Pd(II) in acetic acid; (b) Mechanistic hypothesis.

labeling experiments ensured that the oxidant provides the oxygen atom transferred to the substrate and the hydrogen atoms present on styrene are maintained in the product in agreement with a 1,2-hydride shift mechanism wherein an enol is formed.

Very recently, Sigman extended the substrate scope of the oxidation with hydroperoxides. With a bidentate ligand belonging to the Quinox family comprising a quinoline and an oxazoline N donor, it was possible to achieve extreme regioselective oxidation of protected allyl alcohol derivatives with t-butyl hydroperoxide to the corresponding methyl ketones (Scheme 23.52), while the same substrates under classical Wacker conditions provide the aldehyde as the preferred product.[99] The chelating nature of the ligand plays a key role by allowing the simple and efficient conversion of styrene and other terminal alkenes exclusively towards the corresponding methyl ketones (Scheme 23.52). Chiral protected allyl alcohols can be transformed into the methyl ketone with retention of configuration and enantiomeric



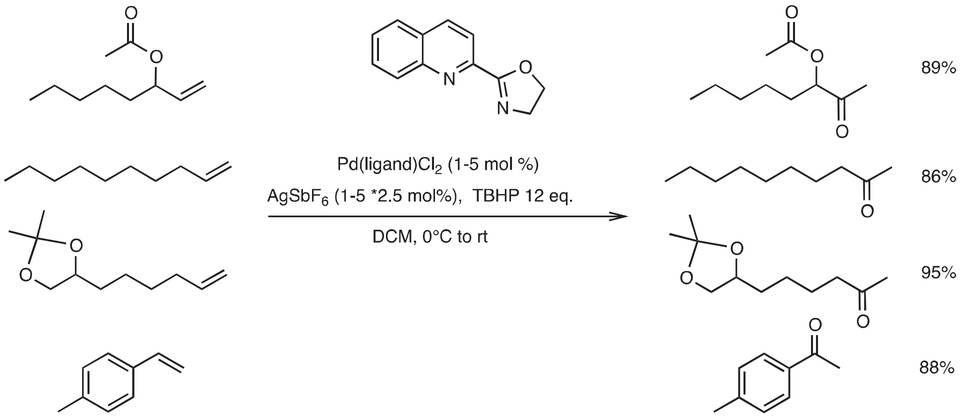
R^1 = Ph, R^2 = H, 75%, ket./ald. > 130:1

R^1 = 4-Me(C_6H_4), R^2 = H, 86%, ket./ald. = 22:1

R^1 = Ph, R^2 = Ph, 42%, ket./ald. = 42:35

R^1 = Ph, R^2 = Me, 97%, ket./ald. = 2.3:1

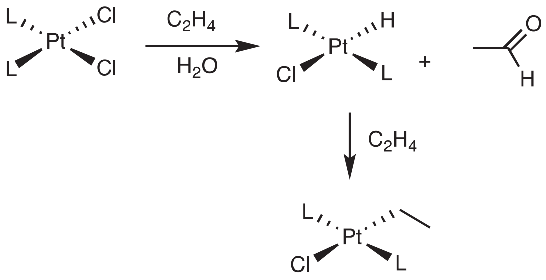
Scheme 23.51. Wacker oxidation of alkenes with t-BuOOH mediated by a Pd(II) catalyst bearing a NHC (N heterocyclic carbene ligand) leading to ketones and aldehydes.



Scheme 23.52. Wacker oxidation of terminal alkenes with t-BuOOH mediated by a Pd(II) catalyst bearing a bidentate N,N ligand.

excess of the molecule. Even highly aldehyde orienteering substrates such as allylic phthalimides led to the Markovnikov oxidation, and the reaction showed analogous regioselectivity for other protected chiral and achiral allylamines.[100]

Wacker oxidation is not an exclusive characteristic of Pd(II) complexes. In 2004, Atwood reported an example of the conversion of ethylene to acetaldehyde mediated by a water-soluble Pt(II) complex of general formula cis-Pt(Cl)$_2$(TPPTS)$_2$ bearing intrinsically water-soluble monophosphines (TPPTS = triphenylphosphine



Scheme 23.53. Wacker oxidation of alkenes and O_2 mediated by a Pt(II) catalyst.

trisulfonate).[101] The reaction is stoichiometric at low temperature but up to 90 turnovers are possible when the reaction temperature is raised to 95°C and Cu(II) salts as co-catalysts remain absent. This behavior is probably due to the higher stability imparted by the phosphine ligands to the Pt(II) metal center (Scheme 23.53).

23.5. The Use of Less Toxic Metals as Active Ingredients

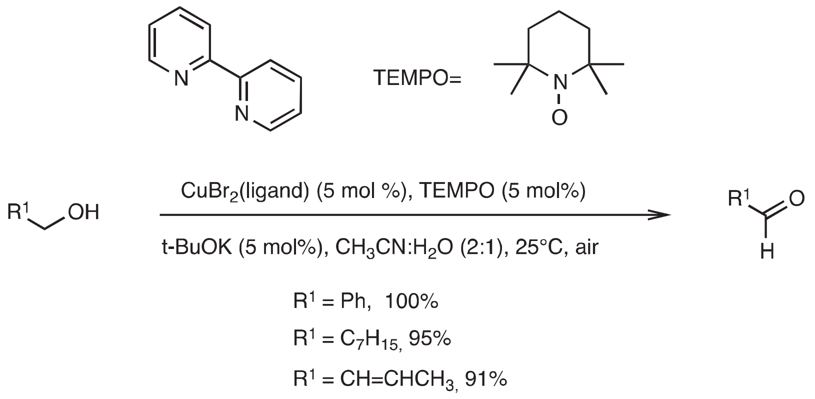
In recent years the stringent regulations on the maximum content of heavy metals allowed in pharmaceutical and agrochemical products, together with the steady increase in the cost of precious metals used in catalysis has prompted the development of new catalytic methods based on non-toxic and more economic transition metals, in particular iron and copper. These are both in abundant supply, they have accessible redox potentials and nature has developed several classes of enzymes to perform catalytic oxidations based on these metal centers. This observation spurred investigations on both the mechanism of action of the enzymes and the development of new biomimetic catalytic systems that are inspired by increasing knowledge acquired on natural catalysts.[102]

Copper is present in nature within oxidases and oxygenases.[103] Both classes of enzymes are characterized by the use of O_2 as the terminal oxidant but only in the latter class is it directly incorporated into the product. Oxidases are active mainly towards alcohols and amines, and oxygenases towards aromatic residues and ketones, thus requiring a wide variety of active sites bearing different structures and numbers of metal atoms. Notable examples are galactose oxidase which contains a copper-tyrosyl radical unit to perform two-electron redox chemistry, and tyrosinase and catechol oxidase which contain a dicopper(I) active site. As far as iron is concerned, enzymes can be classified in two main families based on either the heme ligand, as in the well-known cytochromes P450 family that lead to the hydroxylation of aliphatic C–H bonds and epoxidation of C=C double bonds, or non-heme ligands. Examples of enzymes belonging to the latter class are the di-iron methane monoxygenases which convert methane to methanol, and Rieske dioxygenases that provide cis-dihydroxylation on aromatic rings and contribute to the biodegradation of such substrates in the soil. All these enzymes use dioxygen as the terminal oxidant and all synthetic bio-inspired complexes reported below make use of O_2 as a green oxidant, making the overall oxidation systems sustainable, at least in principle.

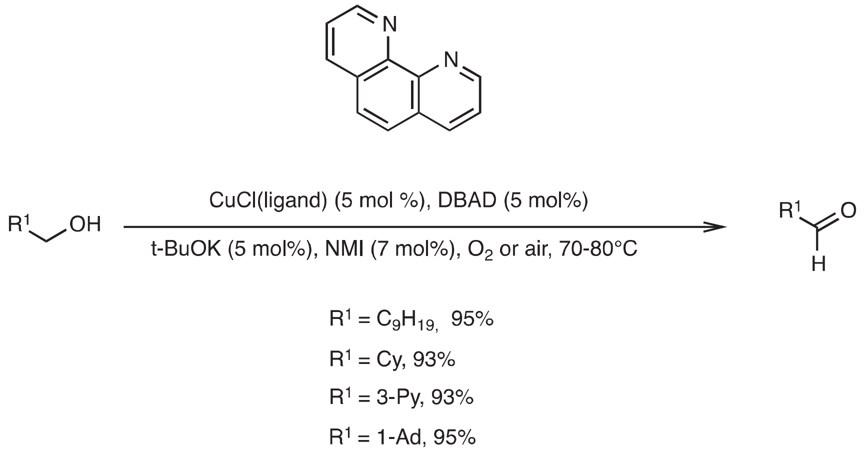
23.5.1. *Bio-inspired systems*

Among the recently developed wide range of copper-based oxidation methods, several are related to alcohol oxidation to the corresponding aldehydes and ketones using O_2 as the oxidant and releasing H_2O_2 as a by-product, mimicking galactose oxidases and sharing with the latter the presence of ligands containing phenol residues via the intermediacy of Cu(II)-phenoxyl radical species.[102] A conceptually related system was proposed by Sheldon based on copper salts with nitrogen containing ligands such as bipyridine and 2,2,6,6-tetramethyl-1-piperidinyloxyl radical (TEMPO) as the radical intermediate species.[104] The catalytic system converts primary alcohols efficiently under mild conditions, but it is completely inactive towards secondary substrates (Scheme 23.54).[105]

A similar system was proposed by Markó based on CuCl, phenanthroline, di-tert-butyl azodicarboxylate (DBAD) and N-methylimidazole (NMI) as additives showing efficient oxidation of both primary and secondary alcohols to carbonyl compounds, with molecular oxygen or air as the oxidant releasing water as the sole by-product.[106] The catalytic system exhibits good tolerance of the presence of electron-rich alkenes, thioethers and pyridine moieties, which could be involved in other oxidation reactions but remain unaffected by the catalyst. In the case of



Scheme 23.54. Oxidation of primary alcohols with air and TEMPO radical mediated by a Cu(II) complex bearing a phenanthroline ligand.

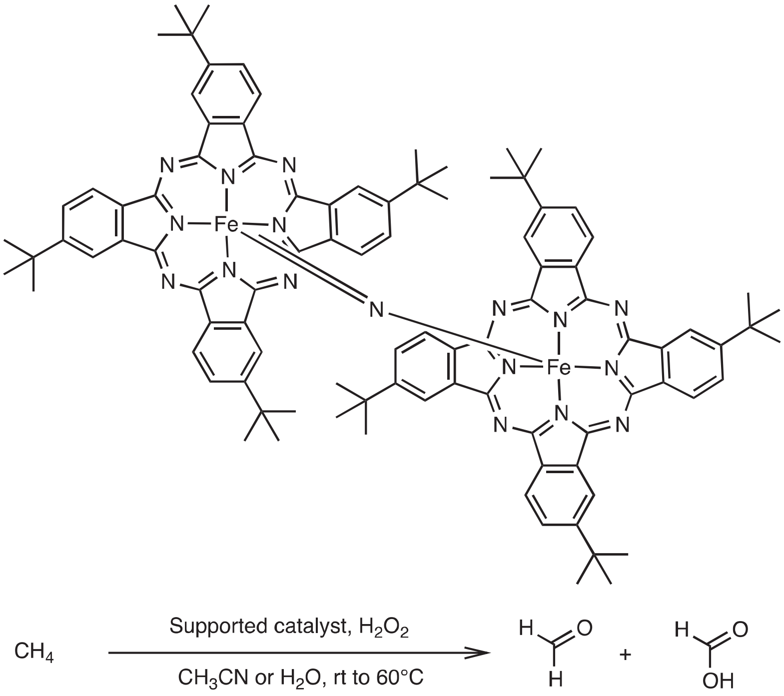


Scheme 23.55. Oxidation of primary alcohols to the corresponding aldehydes with O_2 mediated by a Cu(I) catalyst in the presence of N-methylimidazole and di-tert-butyl azodicarboxylate.

primary alcohols as substrates the reaction is extremely chemoselective and no over-oxidation of the aldehyde to the corresponding carboxylic acid is observed (Scheme 23.55).

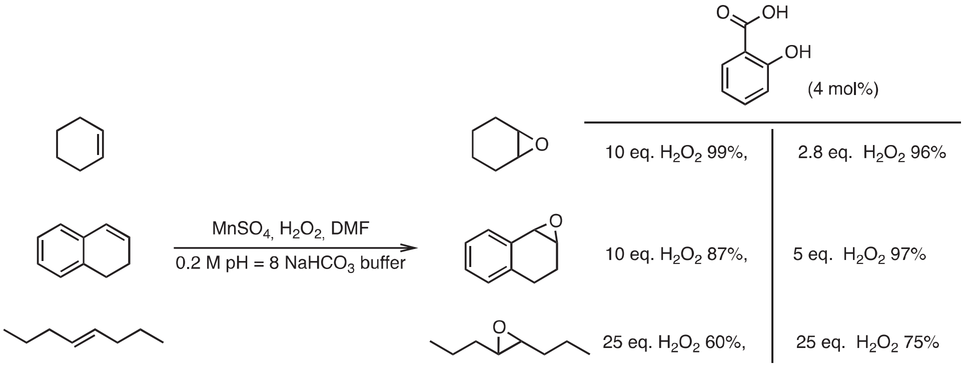
As mentioned before, methane monoxygenases are enzymes capable of the direct oxidation of methane. Only recently, a synthetic catalyst reminiscent of the heme structure of that enzyme was introduced by Sorokin. It is based on a μ-nitrido bridged di-iron phthalocyanine structure showing methane oxidation activity with H_2O_2 as the terminal oxidant.[107] It operates in acetonitrile with partial oxidation of the latter, but it can also work in water as a green inert medium by means of heterogenization on silica. The optimized catalytic system shows both formaldehyde and formic acid as oxygenated products, 15 turnover at room temperature and more than 430 at 60°C, demonstrating the robustness of the di-iron structure and the sustainable character of the process coming from the use of water and H_2O_2 as the solvent and oxidant (Scheme 23.56).

Mn-based oxidation systems have recently been developed. Burgess, via a high throughput screening, evidenced that simple $MnSO_4$ can activate hydrogen peroxide towards alkenes leading to epoxides in dimethylformamide (DMF). The key role in this case is played by bicarbonate which is converted into the corresponding percarboxylic acid which forms either a Mn(II)-peroxocarbonato or Mn(IV)=O species responsible for the oxygen transfer to the substrate.[108] The presence of simple additives such as sodium acetate (in t–BuOH) and salicylic acid (in DMF) enhanced the rate of the epoxidation reaction, enabled the use of bicarbonate in a catalytic amount, required less hydrogen peroxide and shorter addition times, and favored the epoxidation of less electron-rich alkenes (Scheme 23.57).



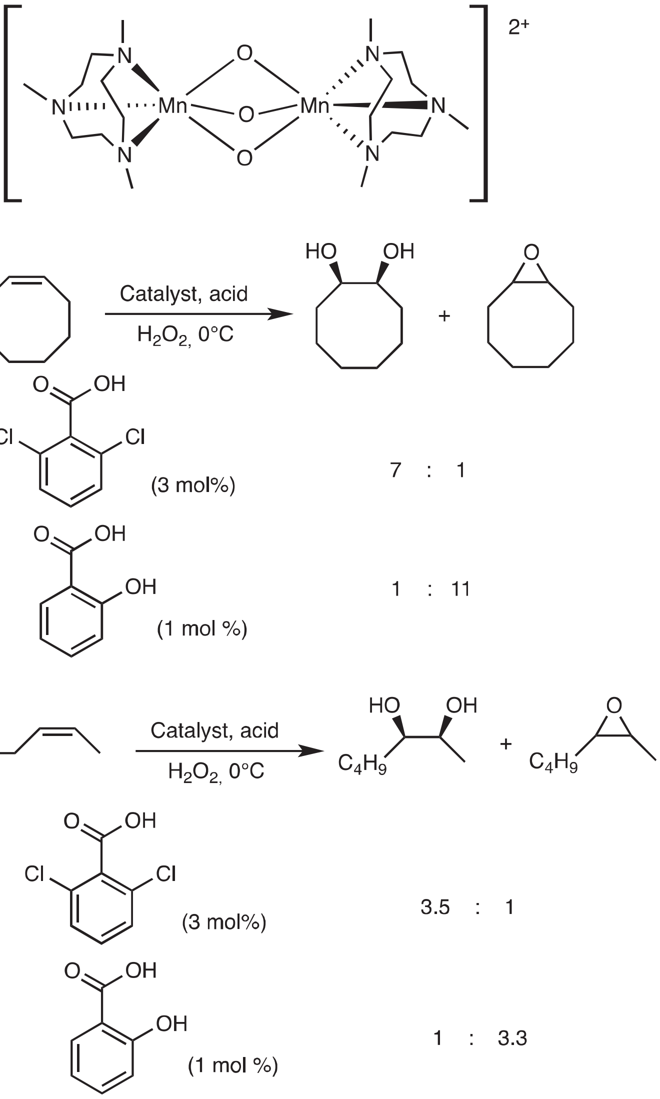
TON HCOOH = 135, TON HCOH = 17, Total TON = 437

Scheme 23.56. Oxidation of methane to formaldehyde and formic acid with H_2O_2 mediated by a dimeric Fe(III) catalyst.



Scheme 23.57. Epoxidation of alkenes with H_2O_2 mediated by a Mn(II) catalyst in the presence of $NaHCO_3$.

In 2005, Feringa disclosed a dinuclear Mn-based catalyst bearing a trimethyl triazacyclononane ligand which efficiently converted alkenes into the corresponding epoxides and cis-diols, with H_2O_2 as the oxidant under mild conditions. In this case too, the presence of carboxylic acids as additives is extremely important. Their role is *in primis* to suppress the decomposition of the oxidant, a common problem with Mn species, but also to influence the ratio between the possible oxygenated products, as shown in Scheme 23.58, where complete reversal of chemoselectivity



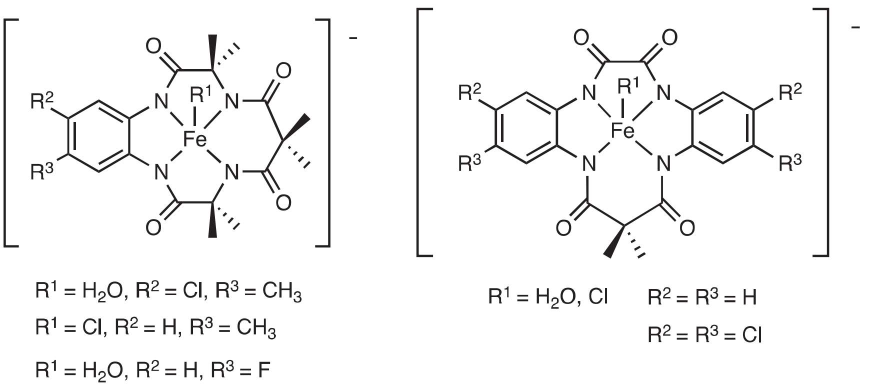
Scheme 23.58. Oxidation of alkenes to cis-diols and epoxides with H_2O_2 mediated by a dimeric Mn(III) catalyst bearing a tridentate cyclic ligand.

is possible using either 2,6-dichlorobenzoic acid which promotes diol formation or salicylic acid that favors the epoxide.[109] Overall the catalytic system is very active providing up to 2,000 turnover numbers for cis-cycloctane diol representing a real, green non-toxic alternative to Os-based oxidation systems.

23.5.2. *Iron complexes*

The well-known Fenton chemistry involves the oxidation process activated by Fe(II) salts in the presence of H_2O_2, which generates radical species in solution and oxidizes a wide range of organic substrates with high activity but generally poor selectivity. The main drawbacks of these systems are the tendency to decompose the oxidant, which implies the need for over-stoichiometric amounts of H_2O_2, the difficult control of the coordination geometry and the oxidation state of the metal leading to the coexistence of several parallel oxidation processes, all of which have limited the development of iron-based oxidation methods for years. On the contrary, the very low cost of this metal compared to others, in combination with its poor toxicity, support its employment in homogeneous catalysis,[110] and in oxidation processes in particular.

One landmark example was developed by Collins and Lenoir based on a Fe(III) metal center coordinated to a tetra-amido macrocyle which coordinates the metal with four anionic amide groups. The complex is highly active in the activation of H_2O_2 as the terminal oxidant towards the complete degradation of different species in aqueous solution such as dyes, water effluents from paper industries and resistant chlorinated phenol derivatives. The catalysts operate under μM concentrations and mild experimental conditions allowing hundreds to thousands of cycles within minutes before coming to a stop (Scheme 23.59).[111] More importantly, among the decomposition products of pentachlorophenol or trichlorophenol, dioxines were not



Scheme 23.59. Structure of Fe(III) catalysts developed for waste water treatment.

detected; instead a mixture of small biodegradable organic acids and CO, CO_2 and HCl were present when working under basic conditions, clearly showing the high environmental compatibility of this catalytic system which soon found practical applications. Further optimization of the ligand structure led to the development of a second generation of tetramide systems showing high activity at pH 5–8, which makes the new class of catalysts even more suitable for purifying environmental waters. The endocrine disrupting activity of the new Fe(III) tetramide complexes was checked by observing their absolute compatibility with aquatic life[112] as a further confirmation of the green character of this oxidation method.

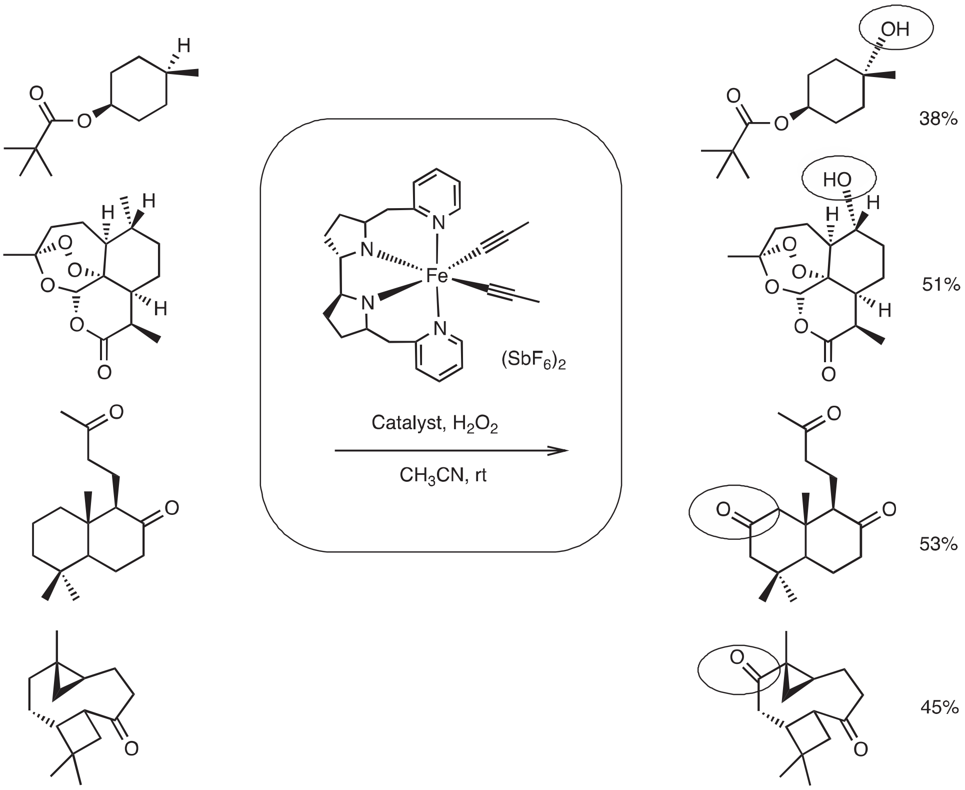
Among the possible oxidation reactions, the direct CH selective functionalization of alkanes to oxygenated compounds is both a highly valuable and challenging transformation. White recently reported two important contributions concerning Fe(II)-mediated oxidation of tertiary and secondary CH bonds to tertiary alcohols[113] or carbonyl compounds,[114] respectively, by using H_2O_2 as the oxidant under mild experimental conditions. A pivotal role in this catalytic system is played by the tetradentate ligand employed bearing two pyridines and two pyrrolidines as donor atoms, whose effect is to greatly increase both the catalytic activity and the selectivity of the iron catalyst. In particular, the catalyst is more active towards tertiary CH bonds if these are sterically accessible and if no electron-withdrawing groups are in close proximity. This allows extremely regioselective functionalization of elaborated organic structures such as in the cases reported in Scheme 23.60.

In the absence of tertiary CH groups or if these do not meet the above described criteria, the catalytic system operates on secondary methylene residues with high selectivity, again with preference for CH_2 groups that are sterically accessible and with greater conversion if electron-activating groups such as cyclopropyl or ether moieties are present (Scheme 23.60).

Overall, despite the high catalyst loading required and the generally low turnover number of this Fe(II) catalytic system, the use of H_2O_2 under mild conditions, in combination with the highly valuable selective functionalization of CH bonds and high predictability on the basis of electronic and steric considerations, makes this catalytic system extremely important and valuable. In fact, the possibility to specifically insert oxygen atoms in certain positions in complex structures at a late stage of synthesis represents an alternative streamline approach compared to classical synthesis, thereby reducing unproductive chemical manipulations associated with carrying them through a sequence.

23.6. Heterogenization of Homogeneous Systems

The quest for separation and recycling has always been a key issue in homogeneous catalysis in general. This is why methods have been devised to anchor the



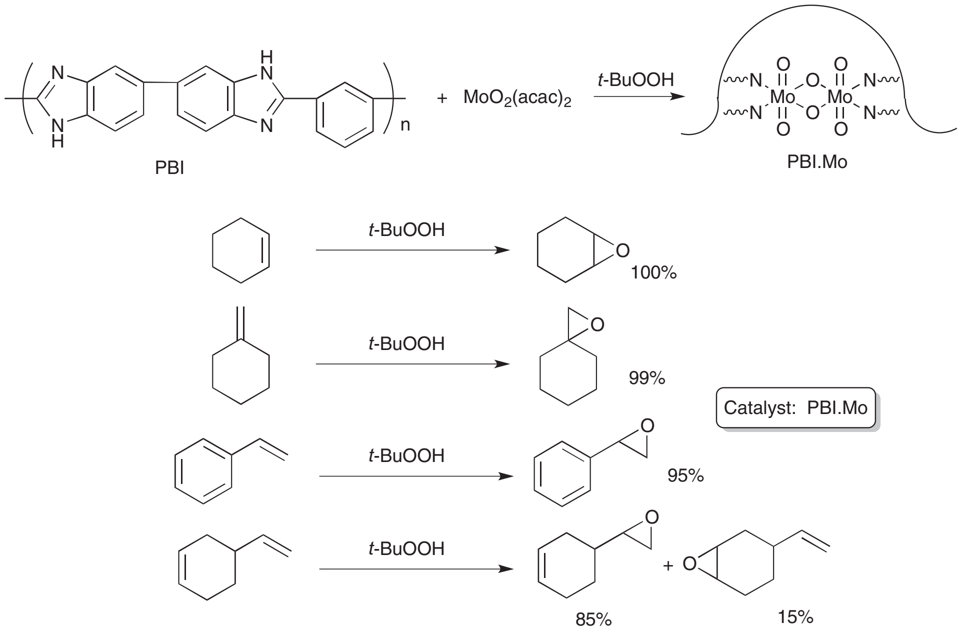
Scheme 23.60. Selective CH oxidation of complex molecules with H_2O_2 mediated by a Fe(II) catalyst bearing a tetradentate N ligand.

most interesting soluble catalysts to suitable solid phases. The possibility of easily separating the catalyst from the reaction mixture without harming its catalytic properties (activity, selectivity) is an important step forward towards possible commercialization, increasing the overall exploitable turnover number, minimizing metal contamination of the products, simplifying the process engineering, saving energy, etc., and generally moving towards a more sensible and sustainable use of costly materials and primary resources. Over the years the topic has been reviewed several times, so throughout this section, reference to these reviews will be provided, while only some selected examples taken from those among the most interesting and/or recent papers will be overviewed, emphasizing those aspects that are most relevant to sustainability.

23.6.1. *Polymer-based systems*

The use of commercial polymers to immobilize homogeneous catalytic species dates back to the early 1970s. Initial supports were in most cases commercial ion exchange resins that could immobilize ionic metal complexes or the Merrifield resin containing benzylchloride residues that could be easily functionalized to introduce potential ligands to anchor metal catalysts. These supports were all based on styrene-divinylbenzene copolymers. The major limitation of these early systems was the moderate stability of the catalysts upon recycling due to the leaching of significant amounts of metal into solution in the majority of cases. Critical evaluations of these early systems were reported several times.[115]

In the field of oxidation, given the commercial importance of the Halcon–Arco process using soluble Mo complexes for the epoxidation of propylene with t-BuOOH, epoxidation has been by far the most studied reaction. Early attempts in this area focused on the immobilization of soluble Mo^{VI} catalysts on polymer supports by anion or cation exchange, or by modifying the polymer with suitable functional groups capable of acting as possible ligands towards molybdenum.[116] Sherrington pioneered this field developing aminated polystyrene, polymethacrylate, polybenzimidazole (PBI) and polysiloxane to immobilize Mo^{VI} epoxidation catalysts.[117] The most successful catalyst (PBI.Mo) was obtained by reacting PBI with $MoO_2(acac)_2$ (Scheme 23.61) and proved to be highly active in generating the active species. It showed a remarkable aging behavior over 10 recycles in the epoxidation of propylene with the yield of epoxide increasing from 59% at the first



Scheme 23.61. Preparation of PBI.Mo and its use as an epoxidation catalyst.

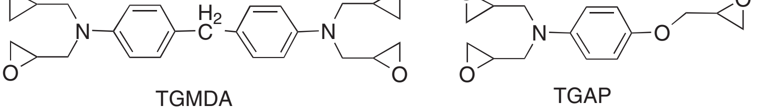
cycle to 99.8% at the tenth. Furthermore, apart from the first catalytic run, there was negligible leaching of Mo from PBI.Mo. It also proved to be very useful in the epoxidation of a range of alkenes (Scheme 23.61).

Using cyclohexene as a model substrate and TBHP as the oxidant, Cu, Mn, Fe, Ru and Ti have all been shown to be catalytically active when supported on PBI. PBI.Cu, PBI.Mn and PBI.Fe are all potentially useful allylic oxidation catalysts; PBI.Ru offers an opportunity in dihydroxylation, and perhaps not surprisingly, PBI.Ti shows significant selectivity towards epoxidation.[118]

Attempts to switch to more appealing oxidants, such as hydrogen peroxide, by immobilizing simple tungstate anions on poly(methacrylate)-based aminophosphorilated resins to carry out epoxidation were only moderately successful because of significant metal leaching into solution with consequent loss of activity.[119]

Remarkably stable Mo catalysts have been obtained with the use of epoxy resins for their immobilization.[120] The epoxy monomers are shown in Scheme 23.62. Tetraglycidyl-4,4′-methylenedianiline (TGMDA) was treated with either a series of metal acetylacetonates ($TiO(acac)_2$, $VO(acac)_2$, $MoO_2(acac)_2$) or metal alkoxides ($Ti(O\textit{i}Pr)_4$, $VO(O\textit{i}Pr)_3$, $Mo(OEt)_5$). Metal contents of 1.5 wt% were adjusted by dispersing the corresponding amount of metal complex in the resin. The resins were cured in aluminum molds at temperatures between 120 and 230°C and thin plates with about 1 mm thickness were obtained. The thermosets thus obtained were tested as epoxidation catalysts. Outstanding long-term catalyst activities and selectivities were observed for Mo-containing resins in the epoxidation of cyclohexene with tert-butyl hydroperoxide. Mechanistic investigations indicate the true heterogeneity of the system with an extremely low metal leaching that depends on the catalyst preparation mode. The catalysts were employed batchwise in up to 60 consecutive runs exceeding an application period of 50 days. They were applied without any reconditioning or loss of activity, thus offering promising perspectives for industrial applications in continuously operating processes.

Methyltrioxorhenium (MTO) has perhaps been the most successful homogeneous catalyst for the epoxidation of simple olefins with hydrogen peroxide,[121] however, attempts to modify the catalyst to achieve enantioselective epoxidation or anchoring to a solid support have met with only moderate success, probably because



Scheme 23.62. Monomers used for the preparation of epoxy resins to be used as catalyst supports.

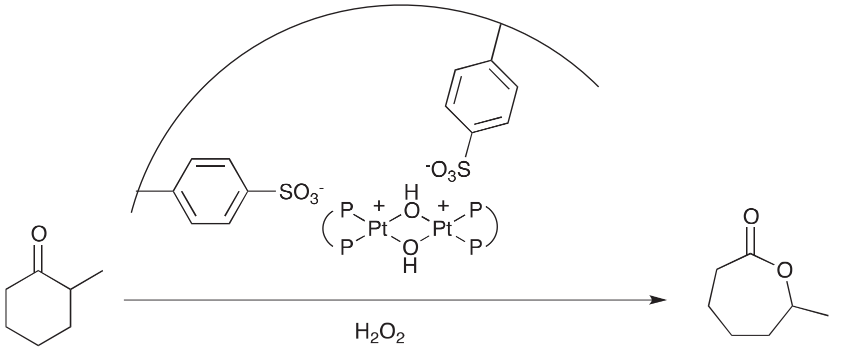
these modifications change the electronic properties of the metal center generally decreasing its catalytic activity.

Heterogenization could be achieved using either simple poly-4-vinylpyridine polymers,[122] exploiting the donor porperties of pyridine to create a six-coordinate surface species or simple encapsulation in polystyrene. Both heterogenized catalysts could be used for the conversion of monoterpenes such as carene, limonene, geraniol and nerol to their corresponding epoxides using H_2O_2 or its urea adduct (UHP) as the oxygen atom donors.[122] Heterogeneous catalysts were stable systems for at least four recycling experiments. The oxidation of geraniol and nerol proceeded selectively at the more electron-rich 6,7-double bond in accordance with the electrophilic character of the oxidant. A comparison between molecular solvents and ionic liquids as reaction media showed that the latter enhance the reaction rates and improve the regioselectivity of epoxidation.

Outside epoxidation a significant contribution was reported on the Baeyer–Villiger oxidation of ketones with hydrogen peroxide catalyzed by $[(\text{P-P})\text{Pt}(\mu\text{-OH})]_2^{2+}$ cationic complexes immobilized on ordinary sulfonated styrene-DVB anionic resins (Scheme 23.63) via simple electrostatic interaction.[123]

Polymer swelling was found to be a critical factor and EtOH was the best solvent to ensure a better mixing of reactants (ketone and hydrogen peroxide) in proximity to the active sites. In any case the activity observed was lower than the same system used in solution.

The latter example emphasizes a major problem encountered when using organic polymers to heterogenize homogeneous systems. While easy to modify chemically, in order to construct the proper bonding interaction between solid phase and soluble



	Yield %
Anchored catalyst	12
Free catalyst	65

Scheme 23.63. Platinum complex anchored on an ion exchange resin and its use as a BV oxidation catalyst.

catalyst, insoluble organic polymers can introduce severe diffusion problems related to the swelling of the organic matrix that hamper the reaction under study, because a good solvent for the polymer may be a bad one for the reaction and *vice versa.*

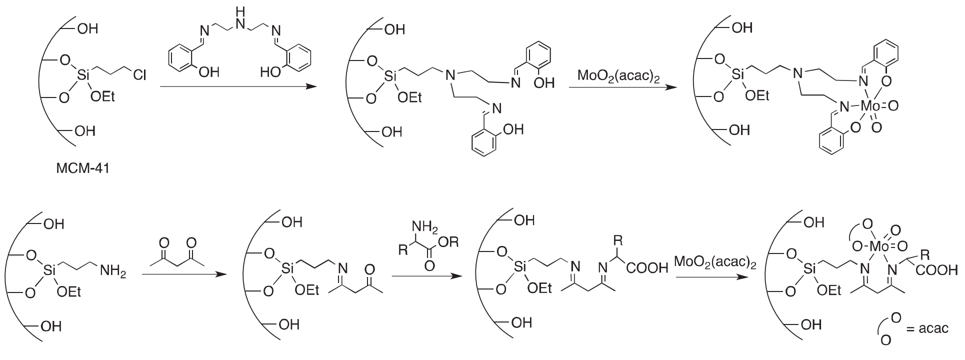
23.6.2. *Silica-based systems*

The problems associated with organic polymers account for why, in the past 10–15 years, major attention has been paid to mesoporous inorganic oxides (especially ordered silicas) that do not suffer from such limitations, and plenty of work has been devoted to organic-inorganic nanocomposites obtained by surface modification. Grafting has been the method of choice to introduce into physically inert inorganic oxides with suitable porosity, additional properties such as (i) the functional groups necessary to bind the complex catalyst component; (ii) the desired philicity (inorganic oxides are generally hydrophilic) to facilitate reactant diffusion and (iii) the ability to maintain single-site catalysts preventing undesired dimerization reactions that may lead to deactivation. As an alternative method for heterogenizing homogeneous catalysts, encapsulation of large soluble complexes into the cages of microporous oxides e.g. zeolites has met with considerable success. In general, if the bonding interaction between the solid support and catalyst is sufficiently strong and no ligand dissociation is involved, or if the size of the support pores is smaller than the diameter of the catalyst (ship-in-the-bottle concept), then the major problem of catalyst leaching can be avoided.[124]

Again epoxidation remains the most investigated reaction in this area with a dominant role for Mo- and W-based catalysts. The use of heterogenized complexes in epoxidation has been recently reviewed.[125] Because of the molecular simplicity of the Mo species involved in Halcon chemistry, early studies exploited the ligand ability of surface hydroxyls present on inorganic oxides such as MCM-41 to bind simple precursors such as $MoO_2Cl_2(solvent)_2$ to produce single-site catalysts capable of epoxidizing alkenes such as cyclooctene, 1-octene, norbornene, styrene, etc., with t-BuOOH obtaining moderate to good yields.[126] However, the grafted species are essentially atomically dispersed Mo oxides with a pronounced tendency to coalesce into clusters during operation, thus leading to loss of activity and metal leaching into solution.

The creation of a robust metal ligand interaction has been the preferred strategy to prevent metal leaching. As a typical example worthy of note, recent work by Masteri-Farahani reported the synthetic approach shown in Scheme 23.64 for the synthesis of Mo complexes on functionalized MCM-41 materials.[127]

As can be seen, stepwise synthesis of robust chelating ligands allows a strong anchoring of the metal center on the silica surface. Studies on the epoxidation of different olefins with t-BuOOH as the oxygen source indicated the following reactivity

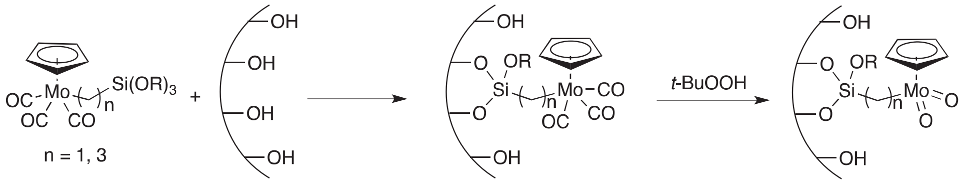


Scheme 23.64. Synthesis of Mo(VI) complexes anchored on MCM-41 to be used as catalysts for the epoxidation of alkenes.

order: cyclooctene > cyclohexene > 1-hexene > 1-octene and the catalyst could be recycled without loss of activity and selectivity after hot filtration,[128] indicating the heterogeneous nature of the reaction.

Cyclopentadienyl molybdenum carbonyl complexes are stable precursors to achieve (Cp)Mo(O)$_2$Cl by *in situ* oxidation with t-BuOOH. The latter complexes are perhaps the most active catalysts for the epoxidation of alkenes with turnover frequencies (TOF) as high as 21,000 h^{-1} in the case of cyclooctene.[129] Kühn and co-workers reported the direct grafting of (Cp)Mo(CO)$_3$Cl on mesoporous MCM-41, MCM-48 and their aluminum-substituted analogues by simple exchange of the chloro ligand with the surface hydroxyls. These materials were excellent catalyst precursors for the selective epoxidation of cyclooctene with t-BuOOH, with TOFs exceeding 4,000 h^{-1}, similar to the homogeneous system under identical conditions, thus demonstrating the absence of diffusional limitations induced by the mesoporous material.[130] The observed higher yield and activity in the case of Al-containing mesoporous molecular sieves was attributed either to the higher Lewis acidity of Mo in these systems or to the activation of t-BuOOH by the Al sites.[131] After reaction, used catalysts were washed several times with dichloromethane to remove the physisorbed molecules (coke) and reused. Catalysts were found to be quite active even after four catalytic runs. However, the catalytic activities decreased in all examined cases to about two thirds of the original activities after four runs. The observed activity decrease was attributed — at least partially — to an increasing number of chemisorbed organic molecules on the surface of the materials. Leaching was proved to be negligible demonstrating the true heterogeneity of the system.

The same authors grafted (Cp)Mo(CO)$_3$ moieties onto MCM-41/48, starting from complexes functionalized with trialkoxysilane groups connected to the Mo center via a hydrocarbon chain (Scheme 23.65).[132] The new materials retained the original mesoporosity of the siliceous supports and proved to be active and robust



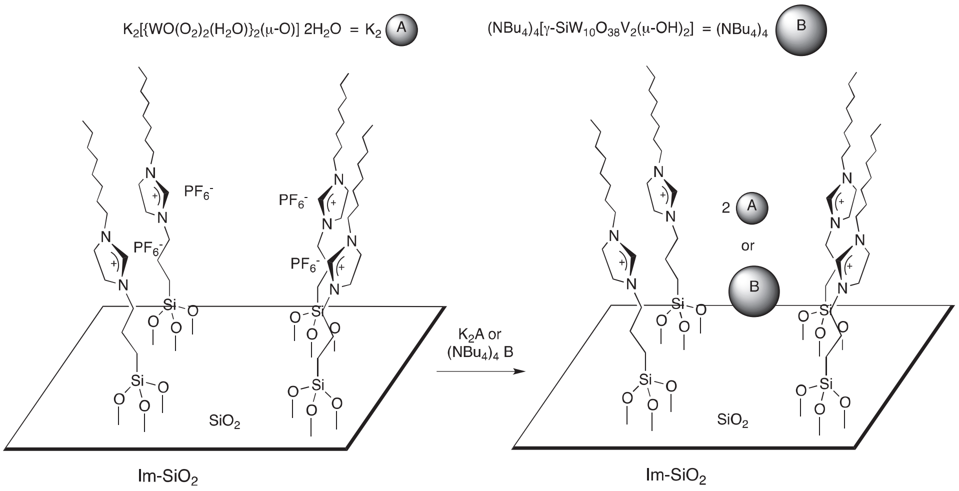
Scheme 23.65. Grafting and activation of catalytically active Mo complexes.

catalysts for the selective epoxidation of cyclooctene with t-BuOOH (TOF: 2,900–10,200 h^{-1}, selectivity: 73–100%). The formation of the Mo=O species upon treatment with t-BuOOH was confirmed by Fourier transform infrared spectroscopy (FTIR) analysis. It was found that the material containing the longer chain between molybdenum and the silica surface displayed higher catalytic activity, because the Lewis acidity of the Mo center is less influenced by the donor ability of the surface. The catalyst can be successfully recycled four times, although again some loss of activity was experienced and attributed to coke formation.

Polyoxometalates (POMs) constitute a large family of anionic metal-oxygen clusters of early transition metals and have stimulated many current research activities in many fields of science such as catalysis, materials and medicine, because their chemical properties such as redox potentials, acidities and solubilities in various media can be finely tuned by choosing constituent elements and counter cations. In addition, POMs are thermally and oxidatively stable in comparison to organometallic complexes and enzymes. The use of POMs in oxidation catalysis has received much attention and has been reviewed several times.[133]

Recently, Mizuno and co-workers have successfully developed highly atom efficient, catalytic green oxidation systems with H_2O_2 or O_2 as the oxidants by precise design and synthesis of novel POM-based molecular catalysts.[133] Hybrid supports have been synthesized by covalently anchoring N-octyldihydroimidazolium cation fragments onto SiO_2 and the catalytically active peroxotungstate and POM anions, such as A and B, can be immobilized on the modified support via simple anion exchange (Scheme 23.66).[134]

The structure of polyanions was preserved after the anion exchange process. The supported catalysts A/Im–SiO_2 and B/Im–SiO_2 showed high catalytic performance for epoxidation and sulfoxidation with H_2O_2.[134] The catalyst A/Im–SiO_2 showed high yields (>90%) in the conversion of a variety of alkenes and allylic alcohols to the corresponding epoxides, and its activity could be compared with that of the corresponding homogeneous n-dodecyltrimethylammonium salt of A under the same conditions.[135] Similarly, B/Im–SiO_2 also proved very active towards the epoxidation of different alkenes and in the sulfoxidation of a variety of substituted thioanisoles.[135] The catalyzed epoxidation of 3-methyl-1-cyclohexene was highly

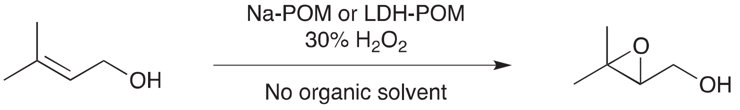


Scheme 23.66. Immobilization of POM catalysts onto hybrid organically-modified silica.

diastereoselective and gave the corresponding epoxide with the oxirane ring trans to the substituent (anti-configuration). Furthermore, the epoxidation of trans-1,4-hexadiene gave only 1,2-epoxide. These unusual diastereo- and regioselectivities were very close to those for the homogeneous epoxidation.[135] These facts indicate that POM-based homogeneous molecular catalysts can be heterogenized with retention of their intrinsic catalytic performance (reaction rates, chemo-, regio- and diastereoselectivities). After filtration, no POM species could be found in the filtrate ruling out any contribution from leached species. In addition, the catalysts could be reused several times without loss of their catalytic performance.

A still unanswered problem with POMs is related to the inherent acidity of these catalysts and the use of aqueous H_2O_2 as the oxidant (the commercial solution is acid stabilized), as they may cause hydrolysis of the epoxide. Many approaches such as the addition of basic pH-adjusting additives,[136] insufficient amount of aqueous H_2O_2,[136] the use of phase transfer catalysts[136, 137] and organic solvents[136, 137, 138] have been applied to overcome this problem. Given these limitations, the development of heterogeneous POM catalysts that can suppress the acid-catalyzed hydrolysis of epoxide without the need for any additives has long been a challenge.

Recently Liu *et al.* reported[139] on a series of self-assembled polyoxotungstates modified with heteroatoms such as Zn, Co, Mn, that were directly immobilized into hydrotalcite-like layered double hydroxides (LDH) by a selective ion exchange method. Sandwich-type POM species were found to be more favorable than Keggin-type POM for the direct immobilization in LDH, because strict pH control was not needed and the LDH hosts can be kept intact. The resulting LDH–POM catalysts



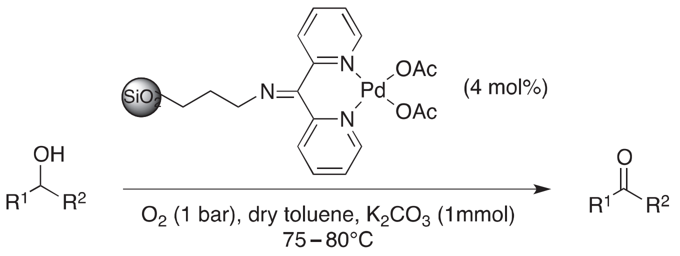
	Conv.(%)	Sel. (%)
Na-POM	92–98	15–27
LDH-POM	85–95	81–98

Scheme 23.67. Epoxidation of allylic alcohols with free and hydrotalcite-immobilized POM catalysts.

were evaluated in the epoxidation of allylic alcohols with aqueous H_2O_2 as the oxidant without using any organic solvents. The heterogeneous LDH–POM catalysts show much higher epoxide selectivity than the corresponding homogeneous Na–POM catalysts (Scheme 23.67), which was attributed to the beneficial effect of the basic LDH host suppressing the acid-catalyzed epoxide hydrolysis. The cooperation between the POM guest and the LDH host can lead to 98% epoxide selectivity, 95% H_2O_2 efficiency and 37,200 h^{-1} TOF without the need of base additives and pH control, and the host–guest catalysts can be readily recycled with no apparent loss of catalytic performance.

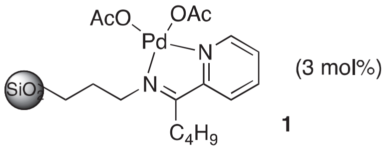
The selective oxidation of alcohols to aldehydes and ketones is a highly desirable and much sought after transformation, in both industrial chemistry and organic synthesis, due to the wide-ranging utility of these products as important precursors and intermediates for many drugs, vitamins and fragrances.[140] A palladium catalyst covalently anchored onto the surface of silica gel for the selective oxidation of alcohols to carbonyl compounds has been reported by the group of Clark.[141] This is a quite efficient and reusable supported palladium catalyst for the selective oxidation of alcohols to carbonyl compounds using molecular oxygen (Scheme 23.68). This catalyst can be used for the oxidation of primary benzylic alcohols using atmospheric air, but is less effective for aliphatic and secondary alcohols. Although it requires relatively long reaction times (4–14 h), it was quite stable and could be recycled at least three times without appreciable loss of activity.

An improved series of catalysts bearing N–N, N–S and N–O chelating ligands has been reported by the same group.[142] The most active catalyst (Scheme 23.69) was used for the oxidation of a series of primary and secondary alcohols to carbonyl compounds. The reactivity was improved with respect to the previous example and no significant differences were observed between primary and secondary alcohols. The catalyst is highly selective and no over-oxidation products were detected. Catalyst 1 in Scheme 23.69 can also be used for the oxidation of primary



R^1	R^2	Time (hr)	Yield (%)
Ph	H	8	100
Ph	Et	12	100
4-Me-C_6H_4	H	5	100

Scheme 23.68. Oxidation of alcohols with a silica-anchored Pd catalyst.



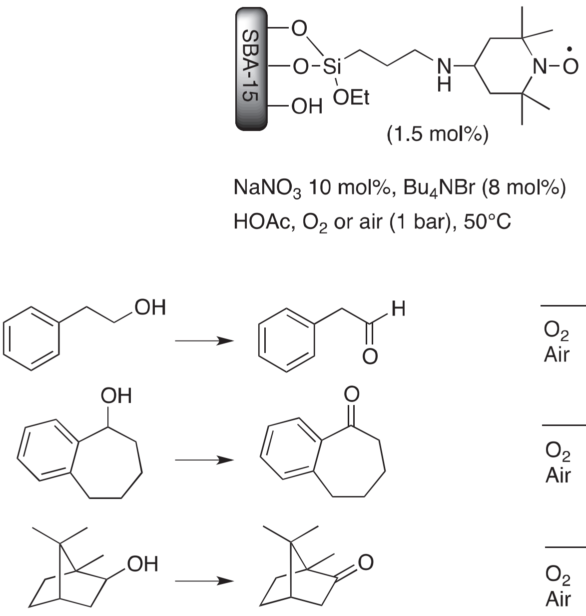
K_2CO_3 1 mmol, 90°C

Alcohol (1 mmol)	Oxidant (1 bar)	Time (hr)	Yield (%)
Benzyl alcohol	O_2	2.5	95
2-Butanol	O_2	5	82
Benzyl alcohol	Air	7	100

Scheme 23.69. Evolution of the catalyst reported in Scheme 23.68.

benzyl alcohols to carbonyl compounds with comparable yields in the presence of atmospheric air.

The selective oxidation of alcohols to carbonyl compounds has recently been achieved through the use of the stable nitroxyl radical TEMPO, in combination with transition metals such as Ru[143] and Cu[144] using molecular oxygen or air under mild reaction conditions. Toy and co-workers have developed an attractive multipolymer reaction system for the aerobic oxidation of alcohols using poly(ethylene glycol) monomethyl ether (MPEG)-supported TEMPO and MPEG-supported bipyridine to bind Cu^{II}. Both TEMPO and the Cu^{II} complex could be recovered at the same time and recycled.[145] However, this method is only effective for the aerobic oxidation of highly active primary benzylic alcohols after prolonged heating (18 h) in CH_3CN-H_2O solvent mixtures.



NaNO$_3$ 10 mol%, Bu$_4$NBr (8 mol%)
HOAc, O$_2$ or air (1 bar), 50°C

	Yield (%)	Time (hr)
O$_2$	95	2
Air	94	3

	Yield (%)	Time (hr)
O$_2$	100	3
Air	100	4.5

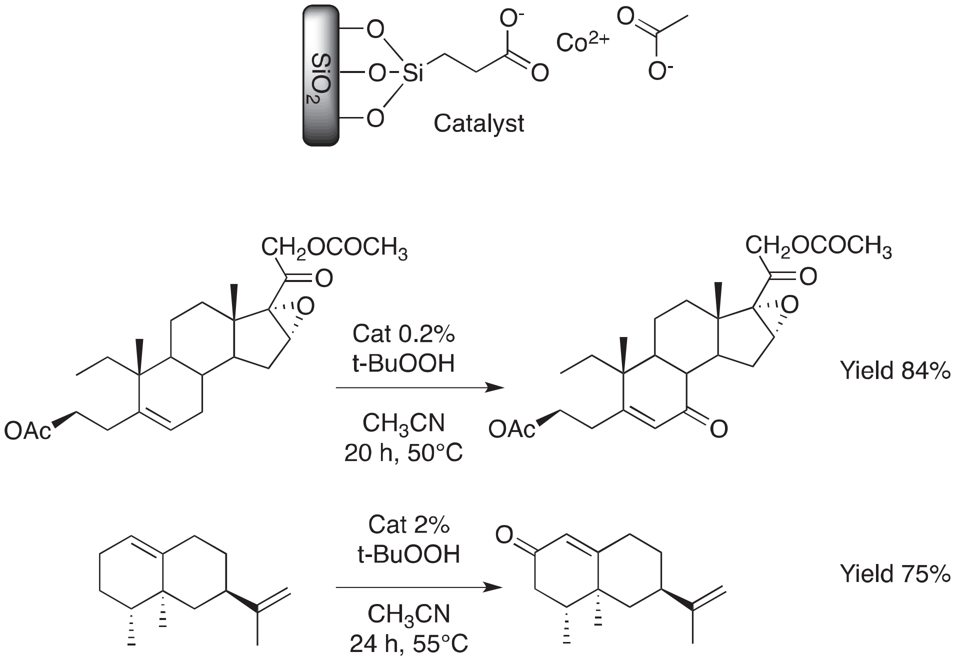
	Yield (%)	Time (hr)
O$_2$	100	10
Air	99	11

Scheme 23.70. Oxidation of alcohols with air using a SBA-15-supported TEMPO catalyst.

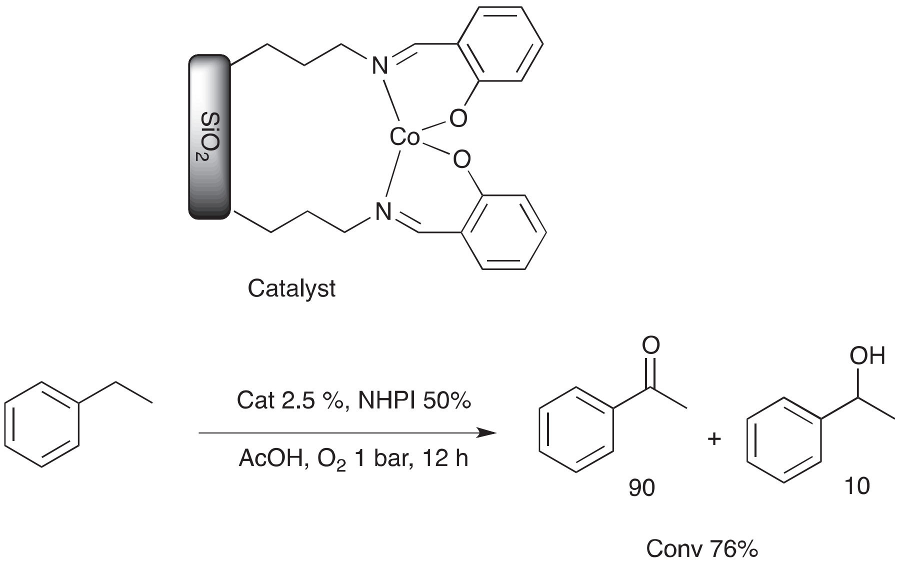
More recently Clark and co-workers have reported the use of a stable version of supported TEMPO grafted on SBA-15 as an efficient and selective heterogeneous catalyst for the aerobic oxidation of a wide range of primary, secondary, and even sterically-hindered alcohols (Scheme 23.70) in the absence of any transition-metal-containing co-catalyst.[146] Air can be conveniently used instead of pure oxygen without affecting the efficiency of the reaction. Benzyl alcohol was tested in a catalyst recycling experiment and, over 14 subsequent runs, a total turnover number (TON) of over 1,00 was observed. Detailed spectroscopic analyses of the catalyst, prior to and after, the 14th reaction cycle showed that neither the anchored organic group nor the nanometer-scale voids and channels of the parent SBA-15 are significantly affected by prolonged use in the reaction system.

The same group also reported the selective allylic oxidation of unsaturated steroids and valencene by a series of metal complexes based on Co(II), Cu(II), Mn(II) and V(II) immobilized on mesoporous silica using a synthetic strategy similar to that reported in Scheme 23.71. The catalysts could be recycled with only minor loss of activity.[147]

With a similar synthetic approach, a cobalt (II) salen complex catalyst has been supported on silica and successfully employed in the aerobic oxidation of alkyl aromatics at atmospheric pressure in the presence of N-hydroxyphthalimide (NHPI). The reaction is particularly selective for the oxidation of the benzylic CH$_2$ group and the major product obtained was ketone (Scheme 23.72). The immobilized catalyst



Scheme 23.71. Use of a silica-anchored Co catalyst for the allylic oxidation of an unsaturated steroid and valencene.

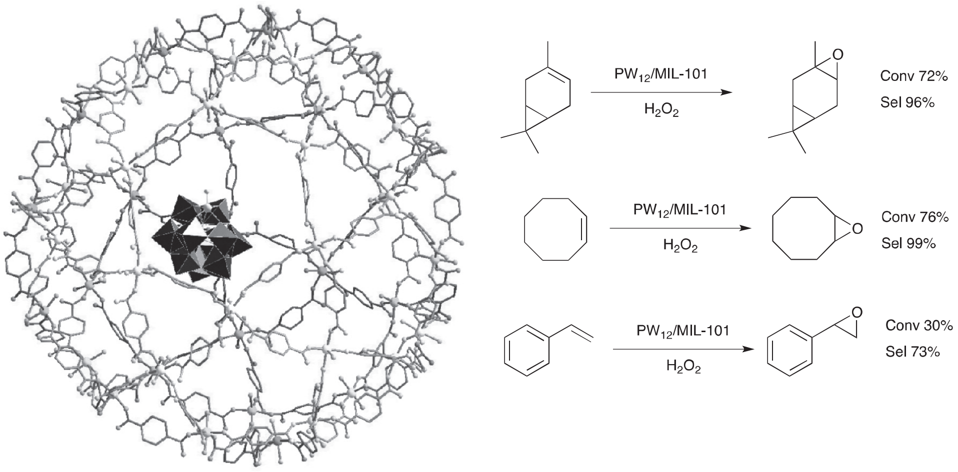


Scheme 23.72. A silica-immobilized Co(salen) complex and its use as a catalyst for the oxidation of ethylbenzene.

can be easily recovered and reused for at least four reaction cycles without any significant loss of its catalytic activity.[148]

23.6.3. *Ship-in-the-bottle systems*

Koldeeva and co-workers recently reported the encapsulation of phosphotungstates $[PW_4O_{24}]^{3-}$ $[PW_{12}O_{40}]^{3-}$ and their titanium- and cobalt-monosubstituted heteropolyanions $[PW_{11}CoO_{39}]^{5-}$ and $[PW_{11}TiO_{40}]^{5-}$ into the cages of the chromium terephthalate polymer matrix MIL-101 via electrostatic binding.[149] MIL-101 is a metal organic framework, zeolite-type innovative material with a large pore size (14.5 x 16 Å hexagonal windows) and very high surface area (4,500–5,500 m^2/g) obtained from terephthalic acid and chromium nitrate.[150] The MIL-supported polyoxometalate catalysts (Scheme 23.73) were characterized by elemental analysis, x-ray diffraction XRD, N_2 adsorption and FTIR spectroscopy. The catalytic performance of both MIL-101 and the novel composite materials M-POM/MIL-101 (M = Ti, Co) was assessed in the oxidation of three representative alkenes −α-pinene, caryophyllene and cyclohexene — using molecular oxygen and aqueous hydrogen peroxide as oxidants, observing poor to moderate selectivities in allylic oxidation and epoxidation. On the other hand, operating under mild conditions ($[H_2O_2]$ = 0.1–0.2 M, 50°C, MeCN), the unmodified phosphotungstates (PW_4, PW_{12}) demonstrated fairly good catalytic activities and selectivities in the epoxidation of various alkenes (3-carene, limonene, R-pinene, cyclohexene, cyclooctene,



Scheme 23.73. MIL-101-encapsulated POM catalyst and its use in the epoxidation of alkenes.

1-octene), with conversions close to the corresponding ones achieved with homogeneous PW_x (Scheme 23.73).

For the oxidation of substrates with aromatic groups (styrene, cis- and trans-stilbenes), a higher level of olefin conversion was attained using PW_{12}/MIL-101. Moreover, confinement of PW_{12} within MIL-101 nanocages allowed the realization of higher epoxide selectivities at higher alkene conversions. The hybrid PW_x/MIL-101 materials were stable to leaching, behaved as true heterogeneous catalysts, were easily recovered by filtration and were reused several times without sustaining a loss of activity or selectivity.

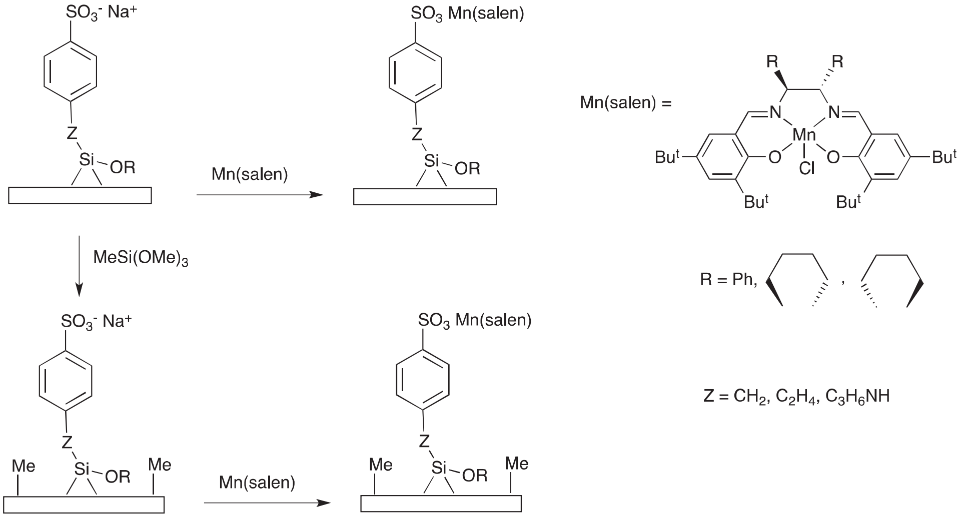
The ship-in-the-bottle approach to heterogenization just exemplified has also been frequently investigated in oxidation. Two recent papers reported the use of complexes of Fe(III), Mn(III), V(VI), Cu(II), Ni(II) modified with salen-type ligands entrapped into the cages of zeolite Y.[151,152] Typically, the complexes were formed *in situ* by stepwise introduction of the different components (a suitable transition metal precursor, followed by the ligand or *vice versa*) so that the assembly of the small components into a complex larger than the zeolite pores can take place in the relatively large cages of the support. Catalysts were tested in the epoxidation of styrene, but only with t-BuOOH as the oxidant; moderate to good selectivities were observed (60–71% in the case of the V and Cu derivative).[151] In the oxidation of cyclohexane, cyclohexanol and cyclohexanone were observed with excellent combined yields (>90%), but high TOFs ($220\,h^{-1}$) were detected only in the case of the Cu derivative with hydrogen peroxide as the oxidant. The oxidation of thioanisol with hydrogen peroxide yielded 93% conversion with 96% selectivity to sulfoxide in the presence of the VO(salen)/Y catalyst.[151]

The implementation of enantioselectivity issues in heterogenized oxidation catalysts has been a key strategy for a number of years which has been successful only with certain classes of catalysts. For example, molybdenum and rhenium catalysts are among the most efficient in epoxidation reactions, however, attempts to modify them with chiral ligands in order to achieve enantioselective transformations, either in solution or anchoring the resulting species on solid supports such as the MCM family, has met with only moderate success. The activity is generally decreased and only poor to moderate enantioselectivities have been observed in some cases. This topic has been recently reviewed.[153]

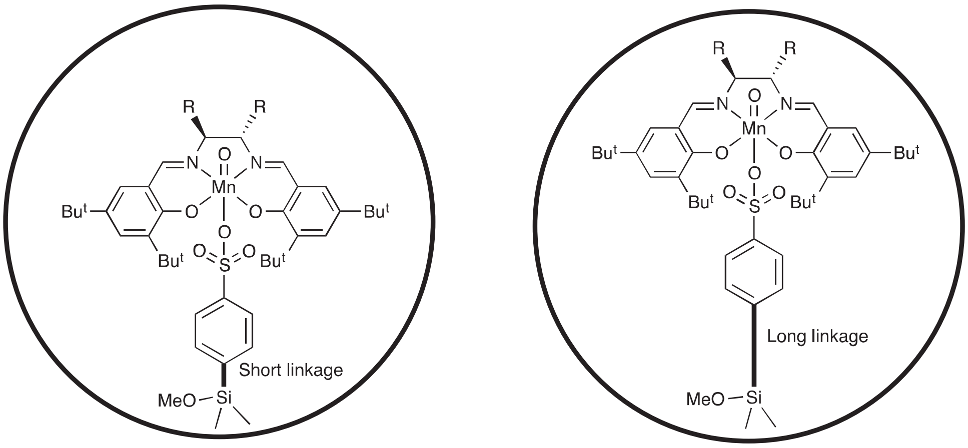
In 2004 Can Li published a seminal review in which the weak interactions between the surface of the support and the heterogenized catalyst were analyzed with respect to their influence on the transition state of the enantioselective transformation, exploiting the concept of the confinement effect.[154] A series of examples were considered including a variety of epoxidation systems such as the Sharpless Ti catalyst for the epoxidation of allylic alcohols or the Jacobsen family of catalysts for the epoxidation of simple alkenes, all prepared by grafting, encapsulation and intercalation. The confinement effect has been initially proposed by Thomas *et al.*[155] to explain some surface effects on enantioselectivity in heterogeneous asymmetric hydrogenation, and subsequently by Hutchings *et al.*[156] in the asymmetric aziridination of styrene and the hydrogenation of carbonyl- and imino-ene compounds. The confinement effect is a consequence of the change in transition states induced by weak interaction in pores or on surfaces, such as hydrogen bonding, physical adsorption and electronic interaction, in addition to the chemical bonding between the catalysts and the surfaces. It may increase the enantioselectivity (positive effect) or decrease the enantioselectivity (negative effect) depending on how the interaction changes the transition states of the chiral products.

Li and co-workers reported that chiral Mn(salen) complexes can be successfully immobilized onto inorganic mesoporous materials such as activated silica (pore size 9.7 nm with sharp pore distribution), SBA-15 (pore size 7.6 nm) and two MCM-41 (pore sizes 2.7 and 1.6 nm) via a phenyl sulfonic group, and that these catalysts have higher ee values than the corresponding homogeneous ones for the asymmetric epoxidation of some olefins.[157] The anchoring phenyl sulfonic group is bound to silica through chains of different length and the influence of the latter on the reaction performance was investigated comparing the behavior of immobilized chiral Mn(salen) complexes either into the nanopores or onto the external surface of mesoporous materials (Scheme 23.74).

Increasing the linkage length inside the nanopores caused an increase in the ee values (e.g. ee from 14% to 64%) but had practically no effect on the external



Scheme 23.74. Anchoring/encapsulation of a chiral Mn(salen) complex on a mesoporous silica support.



Scheme 23.75. Steric effect on a Mn(salen) complex covalently immobilized on a porous support as a function of the length of the tether.

surface (e.g. 47% to 44%). When comparing the same catalyst inside the pores or anchored on the external surface ee values also decreased (e.g. 58% vs 40%). The modification of the nanopore surface by methyl groups further improves the reaction performance for the asymmetric epoxidation (e.g. ee 62% non-methylated vs 70% methylated). In the epoxidation of 1-phenyl-cyclohexene the effect of pore size is to decrease the conversion (86% to 71% on going from activated silica (9.7 nm) to MCM-41 (2.7 nm)) while increasing the enantioselectivity (15% to 25% for the same supports).

As illustrated in Scheme 23.75, all these results show that because of the space available on top of the catalyst where the oxo moiety to be released to the substrate resides, the confinement effect originating from nanopores can not only enhance the chiral recognition of chiral catalysts, but also restrict the rotation of intermediates, resulting in increasing ee values with the increasing length of linkage groups for the catalysts immobilized in the nanopores. For the same reason, a similar behavior is observed changing the pore size of the support and no effect is observed when the catalyst resides on the external surface.

23.6.4. *Conclusion*

In this overview we have tried to highlight some of the major advances reported in the heterogenization of oxidation catalysts emphasizing those aspects (where present) that can add extra properties to the heterogeneous system with respect to the homogeneous counterpart. The examples cited have tried to cover the major strategies that have been developed to achieve heterogenization in a stable manner preserving the catalysts' original activity and selectivity properties. The two major issues, i.e. recyclability and absence of metal leaching, have been addressed by all researchers involved in this area, although they have been fulfilled in a satisfactory manner only in a minority of cases. In all the examples cited in this overview, according to the authors, catalysts have been recycled at least four times without appreciable loss of metal. In very few examples has the stability been proven for longer times. In general, while this may not be sufficient to replace existing technologies on a large-scale, and based on low-cost simple homogeneous species, it can otherwise constitute a sustainable alternative for small-scale processes based on costly catalysts (e.g. in enantioselective transformations) where an easy catalyst recovery and/or prolonging catalyst lifetime can be important issues to decrease process costs.

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