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Ruthenium catalyzed epoxidations: mechanistic and synthetic aspects

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Abstract

The mechanisms of ruthenium-catalyzed oxygen transfer processes are discussed and an overview is given of the synthesis and application of ruthenium complexes as catalysts for epoxidations, including enantioselective epoxidations.

Keywords: Enantioselectivity; Epoxidation; Oxygen transfer ; Ruthenium

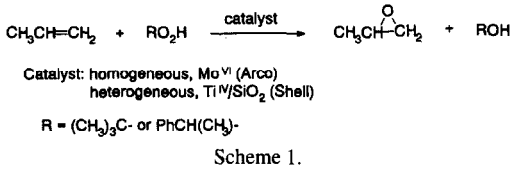
1. Introduction

The catalytic epoxidation of olefins is both an important industrial technology and a useful synthetic method [1–4]. For example more than a million tons of propylene oxide is produced annually via the liquid phase epoxidation of propylene with an alkyl hydroperoxide (Scheme 1).

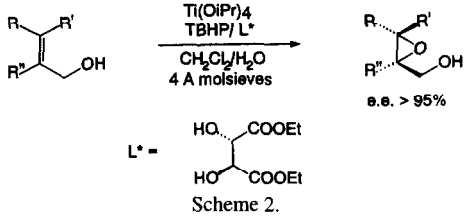
In the ARCO process a homogeneous, molybdenum(VI) catalyst is used [5] while the Shell process employs a heterogeneous, titanium(IV)–silica catalyst [1–3]. More recently, Enichem scientists showed [6] that the redox molecular sieve, titanium(IV)–silicalite (TS-1) is a very effective catalyst for epoxidations with 30% aqueous hydrogen peroxide.

Currently there is also considerable interest in the development of effective catalytic systems for the enantioselective epoxidation of prochiral olefins [7,8]. The well-known Katsuki–Sharpless reagent [9,10] for the asymmetric epoxidation of allylic alcohols, for example, employs an alkyl hydroperoxide in conjunction with a homogeneous titanium(IV)–dialkyl tartrate catalyst (Scheme 2). This system is not effective, however, with simple, unfunctionalized olefins.

Following the report by Kochi and coworkers [11] that the cationic (salen)manganese(III) complex (**1**) (Fig. 1) is an efficient catalyst for the epoxidation of olefins with iodosylbenzene the groups of Jacobsen [12,13] and Katsuki [14]



Scheme 1.



Scheme 2.

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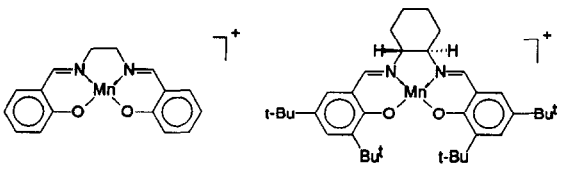


Fig. 1.

investigated the enantioselective epoxidation of unfunctionalized olefins with NaOCl or ArIO in the presence of analogous chiral manganese(III) Schiff's base complexes. An important feature of the salen-based catalysts is the closer proximity of the stereogenic centre(s) to the metal center, compared to chiral porphyrin-based systems (see later), which allows for better stereochemical control in the epoxidation step. Indeed, the manganese(III) complex of the Jacobsen ligand (**2**) has proven to be a highly effective catalyst for enantioselective epoxidations of unfunctionalized aromatic olefins [13].

In vivo, the enantioselective epoxidation of olefins is mediated by the ubiquitous cytochrome P450-dependent monooxygenases [15,16], in which the prosthetic group comprises an iron porphyrin (heme) complex. The active oxidant is believed to be a high-valent oxoiron porphyrin species (see later) [17].

Based on its juxtaposition to iron and manganese in the Periodic Table, and its ability to form a variety of high-valent oxo complexes, ruthenium is also a potentially interesting epoxidation catalyst. Compared to iron and manganese, however, relatively little attention has been devoted to ruthenium as an epoxidation catalyst. Indeed, a recent review of catalytic asymmetric epoxidation [7] contained no mention of ruthenium. Hence, the subject of this review comprises the use of ruthenium complexes as catalysts for the selective epoxidation of olefins and enantioselective epoxidation in particular. To provide a mechanistic framework for discussion of ruthenium-catalyzed processes we shall first delineate the mechanisms of metal-catalyzed oxygen transfer processes in general.

2. Mechanisms of catalytic oxygen transfer

Catalytic systems for oxygen transfer processes, such as olefin epoxidation, can be divided into two major mechanistic categories, involving peroxometal and oxometal species as the active oxidant, respectively [18–21]. The peroxometal mechanism is generally observed with early transition elements whereby high-valent peroxometal complexes of, e.g. Mo^{VI}, W^{VI}, V^{V}, Ti^{IV}, etc. are the active oxidants (pathway (a) in Fig. 2). The ARCO, Shell and Enichem processes and the Sharpless asymmetric epoxidation method discussed above all proceed via peroxometal mechanisms.

Catalysis by later and/or many first-row transition elements (Cr, Mn, Fe), on the other hand, involves the intermediacy of high-valent oxometal species, formed via reaction of the metal catalyst with a single oxygen donor (pathway (b) in Fig. 2). A characteristic feature of this second category is that the olefin epoxidation is often only observed in the presence of organic ligands that modulate the activity of the oxometal intermediate (this is certainly the case with ruthenium). In cytochrome P450-dependent monooxygenases, for example, a porphyrin ligand stabilizes a formally oxoiron(V) intermediate [15,17]. In vivo the active oxoiron(V)porphyrin is formed by reaction of iron(III) with dioxygen in the presence of a cofactor (NADH), which acts as a sacrificial reductant according to the stoichiometry in Scheme 3.

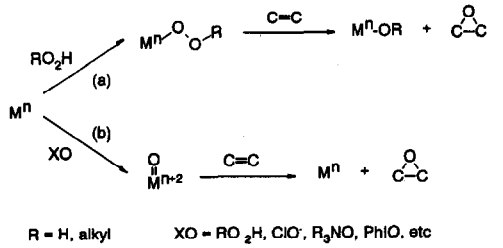


Fig. 2. Peroxometal (a) and oxometal (b) mechanisms for olefin epoxidation.

$$S + DH_2 + O_2 \longrightarrow SO + D + H_2O$$

S = substrate; DH_2 = reduced cofactor

Scheme 3.

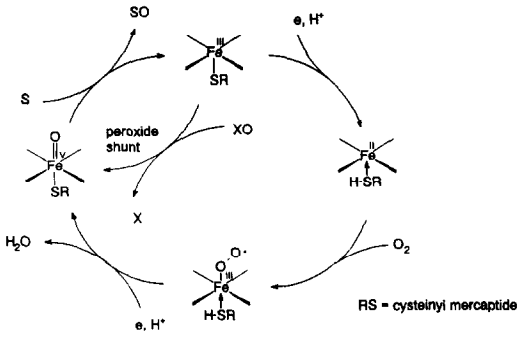


Fig. 3. Mechanism of cytochrome P450-mediated oxidation.

Scheme 4.

In vitro, the need for a sacrificial reductant can be circumvented by using a single oxygen donor, such as RO_2H, ClO^-, IO_4^-, R_3NO or PhIO, in the so-called peroxide shunt pathway (see Fig. 3). In this context it should be noted that although it is often tacitly assumed that oxidations with ClO^-, IO_4^-, R_3NO, PhIO, etc., involve oxometal intermediates, alternative mechanisms involving a metal–oxidant complex, analogous to the peroxometal intermediate, can be envisaged (e.g. M–OCl, M←O=NR_3, etc.).

When an oxometal mechanism is operative one would expect to observe similar results with different oxygen donors, as is the case with in vitro experiments with cytochrome P450 (see above). When a metal–oxidant complex is the active species, in contrast, different oxygen donors should give different results.

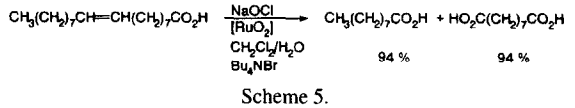
For the sake of completeness we note that the Group VIII metals Pt and Pd appear to catalyze epoxidation with H_2O_2 via a different type of peroxometal mechanism. The key step (Scheme 4) involves bimolecular reaction of a hydroperoxoplatinum(II) complex, with a platinum(II) olefin complex [22], i.e. the metal activates both the substrate and the oxidant.

3. Ruthenium as an (ep)oxidation catalyst

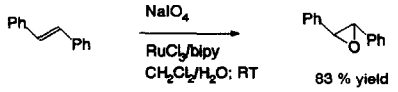
Their ability to form compounds in eleven different oxidation states, ranging from $-II(d^{10})$ to $+VIII(d^0)$, makes ruthenium and osmium unique in the Periodic Table [23]. Their rich redox chemistry is dominated by their propensity for the formation of high-valent complexes containing the strongly σ- and π-donating oxo (O^{2-}) ligand. In ruthenium, a second-row transition element, the outer 4d electrons are more tightly held than is the case with the 5d electron of osmium. Consequently for agiven oxidation state, ruthenium is a more powerful oxidant than osmium, e.g. the E_0 for RuO_4/RuO_4^- is +0.99 V whereas for OsO_4/OsO_4^- it is +0.22 V. These features make ruthenium an extremely versatile catalyst for oxidation reactions. Moreover, not unimportantly, ruthenium is much cheaper than osmium.

The most well-known ruthenium oxidant is the tetroxide, RuO_4, which effects a comprehensive range of oxidative transformations [24,25]. Reaction of RuO_4 with olefins leads to oxidative cleavage of the double bond, affording carboxylic acids. The reaction can be made catalytic by employing RuO_4, $RuCl_3$ or RuO_2 in conjunction with oxygen donors, e.g. NaOCl [26], $NaIO_4$ [27] or CH_3CHO/O_2 [28], as the primary oxidant. The use of NaOCl, in a two-phase, CH_2Cl_2/H_2O system, with RuO_2 or $RuCl_3$ constitutes a mild and convenient method for the oxidative cleavage of double bonds (Scheme 5) [26].

Balavoine and coworkers [29,30] reasoned that the small amounts of epoxide, that were sometimes observed as byproducts in these reactions, could probably be enhanced by employing an electron donating ligand to moderate the oxidizing power of RuO_4. This indeed proved to be the case: reaction of olefins with $NaIO_4$ or NaOCl, in the presence of catalytic amounts of $RuCl_3$ and bipyridyl or substituted phenanthrolines, afforded the corresponding epoxide as the major product



Scheme 5.



Scheme 6.

[29,30]. The reaction was stereospecific for both *cis* and *trans* alkenes, consistent with a heterolytic mechanism, as depicted in Scheme 6.

Interestingly, the epoxidation of styrene with dioxygen or TBHP in the presence of catalytic amounts of $RuCl_2(Ph_3P)_3$ was described more than 10 years earlier by Turner and Lyons [31].

The major byproducts observed in ruthenium catalyzed epoxidations (see later) are the products of oxidative cleavage of the double bond. A sine qua non for the development of efficient ruthenium-based systems is a thorough understanding of the nature of the active (oxo)ruthenium species responsible for epoxidation and oxidative cleavage. In this context it should be emphasized that the accessibility of several oxidation states makes ruthenium a versatile oxidation catalyst but, by the same token, makes elucidation of reaction pathways difficult. Moreover, the exact nature of the active oxidant will almost certainly be influenced by the nature of the primary oxidant and the electronic and steric properties of the ligand surrounding the ruthenium. The rest of this review will be devoted to a discussion of these aspects.

4. The mechanism of epoxidation vs. oxidative cleavage

The mechanism of oxidative cleavage of olefins by RuO_4 is generally believed [25], but not proven, to involve a [3+2] cycloaddition of the *cis*-dioxo moiety to the double bond, to give a ruthenium(VI) monoglycolate ester which rapidly decomposes to RuO_2 and cleavage products (Fig. 4). The first step is presumably rate limiting and the putative cyclic ester intermediate cannot be isolated. Osmium(VI), in contrast, is a much less powerful oxidant than ruthenium(VI) and an analogous dimeric osmium(VI) glycolate has been isolated and characterized [32]. Alternatively, the glycolate ester could be formed via a [2+2] cycloaddition followed by rearrangement of the resulting metallaoxetane intermediate (Fig. 4).

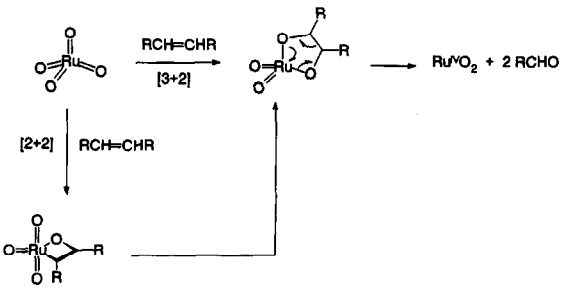
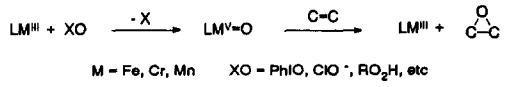


Fig. 4. Mechanism of oxidative cleavage of olefins by RuO_4.



Scheme 7.

Catalysis of epoxidation by salen [11,13,33,34] and/or porphyrin complexes of iron(III), manganese(III) and chromium(III), with various oxygen donors such as PhIO, NaOCl and TBHP, have been shown to involve the corresponding oxometal(V) complexes as the active oxidant (Scheme 7).

Similarly, epoxidation with PhIO, ClO^-, RO_2H, etc. in the presence of cobalt(II) [35] or nickel(II) [36] salen complexes, respectively, involves the corresponding oxometal(IV) complex as the active oxidant. In the presence of electron donating N, O and P ligands, ruthenium also catalyzes olefin epoxidation with a variety of oxygen donors (see later). However in the case of ruthenium the exact nature of the active oxidant is less clear. The active oxidant is undoubtedly an oxoruthenium complex but various candidates can be envisaged. Moreover, oxidative cleavage is generally observed as a competing side reaction and different species may be responsible for epoxidation and oxidative cleavage. A further complicating factor is that the nature of the putative oxoruthenium intermediate may depend on the oxygen donor used (see later). Drago [37–39] has presented evidence in favour of a monooxoruthenium(IV) complex being responsible for epoxidation and a *cis*-dioxoruthenium(VI) species for competing epoxidation and oxidative cleavage (Fig. 5).

Monooxoruthenium(IV) and *cis*-dioxoruthenium(VI) complexes containing the 2,9-dimethyl-1,10-phenanthroline (dmp) ligand were

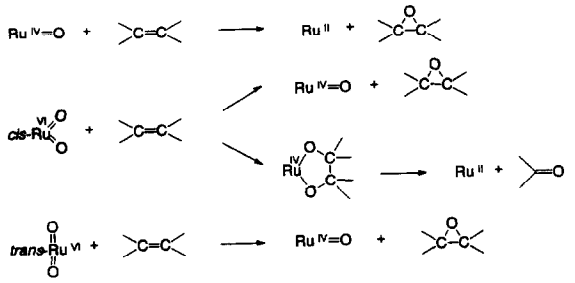
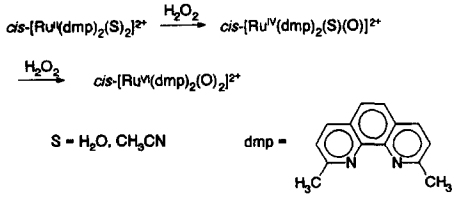


Fig. 5. Reactions of oxoruthenium species with olefins.



Scheme 8.

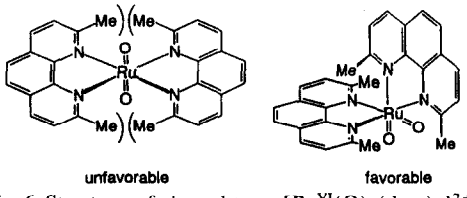


Fig. 6. Structures of *cis*- and *trans*-$[Ru^{VI}(O)_2(dmp)_2]^{2+}$.

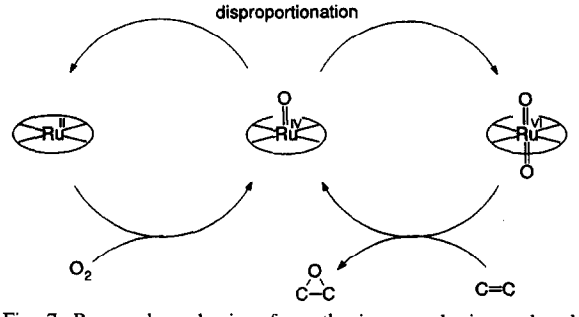
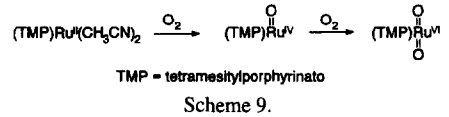


Fig. 7. Proposed mechanism for ruthenium porphyrin catalyzed epoxidations.



Scheme 9.

synthesized by sequential oxidation of the $(dmp)_2$ruthenium complex with H_2O_2 (Scheme 8) [38]. Reaction of the monooxoruthenium(IV) complex with norbornene afforded the epoxide in quantitative yield.

Another factor which can be expected to play a role in ruthenium-catalyzed (ep)oxidations is the relative reactivity of the *cis*- and *trans*-dioxoruthenium complexes. Assuming that oxidative cleavage involves initial [3+2] cycloaddition of the olefin to a dioxoruthenium(VI) moiety, one would expect this to be precluded when the two oxo ligands are disposed in a *trans* fashion. Hence, epoxidation should prevail in this case. Moreover, as pointed out by Drago [37,38], the *trans*-dioxoruthenium(VI) complexes are more stable and weaker oxidants than the corresponding *cis* complexes. In the $(dmp)_2$dioxoruthenium(VI) mentioned above steric crowding of the dmp ligands enforces the *cis*-conformation [38] (Fig. 6).

In ruthenium porphyrin complexes, in contrast, a *trans* disposition of oxo ligands is enforced by the coplanarity of the metal with the porphyrin ring. Indeed, ruthenium(II) complexes of sterically hindered porphyrins, such as tetramesitylporphyrin (TMP), catalyze the epoxidation of olefins with dioxygen [40–42], iodosylbenzene [43] or pyridine-*N*-oxides [44]. Groves [40] proposed the mechanism shown in Fig. 7 to account for the observed catalytic epoxidation with dioxygen.

A sterically hindered porphyrin is required in order to prevent the formation of unreactive μ-oxo dimers of the type LRu–O–RuL. A solution of sterically hindered tetramesityl porphyrin $Ru^{II}(TMP)(CH_3CN)_2$ in benzene-d_6 was shown [41], by NMR spectroscopy, to react with air at ambient temperature to form the corresponding oxoruthenium(IV) complex. On longer standing the corresponding *trans*-dioxoruthenium(VI) complex was formed as the final oxidation product (Scheme 9).

Titration of the dioxoruthenium(VI) complex, under anaerobic conditions, with one equivalent of triphenylphosphine afforded the oxoruthenium(IV) complex, indicating that $Ru^{VI}(TMP)(O)_2$ is a much more powerful oxo-transfer agent than $Ru^{IV}(TMP)(O)$. Hence, it was proposed [40] that in the aerobic epoxidation of olefins, initial formation of $Ru^{IV}(TMP)(O)$ is followed by its disproportionation to $Ru^{II}(TMP)$ and $Ru^{VI}(TMP)(O)_2$ and that the latter species transfers oxygen to the olefin to regenerate Ru(TMP)(O) (see Fig. 7). An alternative was

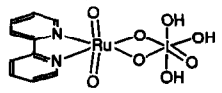


Fig. 8. Structure of $RuO_2bipyIO_3(OH)_3 \cdot 1.5H_2O$

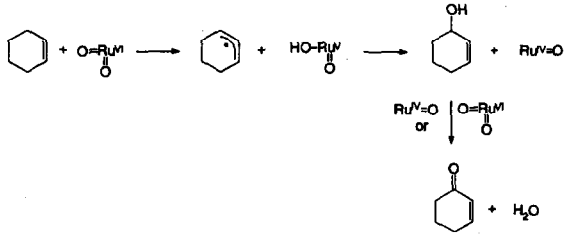


Fig. 9. Ruthenium catalyzed allylic oxidation.

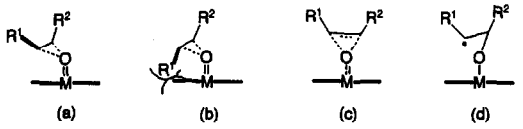


Fig. 10. Side-on approach model for oxygen atom transfer to a *cis* olefin (a) and a *trans* olefin (b) via a concerted mechanism (c) and a stepwise mechanism (d).

suggested by Drago [37,38] to explain the $Ru^{II}(dmp)_2$-catalyzed epoxidation of olefins with dioxygen. In this proposal the putative monooxoruthenium(IV) intermediate preferentially reacts with dioxygen to form the *cis*-dioxoruthenium(VI) complex, which is the active epoxidizing agent.

In short, the involvement of oxoruthenium species as active oxidants in these systems appears to be well established but further mechanistic details are still a matter of debate. To complicate matters even further Griffith and coworkers [45] recently synthesized a dioxoruthenium(VI) complex containing a periodate ligand. This is the first example of the isolation of a ruthenium–oxygen donor complex. The structure depicted in Fig. 8, containing a slight distortion from linearity for the *trans*-dioxoruthenium(VI) moiety, was confirmed by X-ray crystallography.

Interestingly, this complex was a more effective catalyst, for the epoxidation of olefins with $NaIO_4$, than the earlier mentioned $RuCl_3$/bipy [29,30] (see Table 3, Section 6.1 for comparison). Stoichiometrically the complex functioned as a six-electron oxidant, oxidizing 3 equiv. of olefin to produce ruthenium(II) and iodate. From a mechanistic viewpoint it would be of interest to establish, possibly by oxygen labelling studies, which oxygen atom undergoes transfer to the olefin.

In addition to epoxidation and oxidative cleavage another reaction – oxygen atom insertion into a C–H bond – is possible when an oxoruthenium species reacts with olefins containing labile allylic C–H bonds. For example, Kochi and coworkers [46] observed that formation of 2-cyclohexen-1-one (40% yield) by allylic oxidation was the predominant pathway for reaction of the *trans*-dioxoruthenium(VI)complex, $Ru(py)_2(O)_2(O_2CR)_2$, with cyclohexene. The reaction can be envisaged as proceeding via hydrogen atom abstraction as shown in Fig. 9.

In this context it is worth noting that competing allylic oxidation is a disadvantage that is associated with olefin epoxidations involving oxometal mechanisms in general. It is not merely coincidence that most authors use olefin substrates – styrenes, stilbenes, etc. – not containing allylic C–H bonds for their studies of metal-catalyzed epoxidations. Epoxidations involving peroxometal species as the active oxidant, in contrast, do not, generally speaking, suffer from competing attack at allylic C–H bonds.

Oxygen atom transfer to the double bond of the olefin is generally thought [3,13,47,48] to involve a side-on approach of olefin to the putative oxometal species (see Fig. 10). This also accounts for lower enantioselectivities generally observed with *trans*-olefins, both with porphyrin-based complexes and Jacobsen type manganese salen ligands, since the approach of *trans*-olefins is more hindered than for *cis*-olefins.

Two possible mechanisms can be envisaged, a concerted mechanism (c) or stepwise bond formation (d), either through polar or nonpolar intermediates. The appearance of, in many cases, *trans* epoxides, as by-products, in metal catalyzed epoxidations of *cis* olefins is consistent with a pathway via stepwise bond formation.

5. Choice of oxidant

A variety of oxygen donors can, in principle, be used for catalytic oxygen transfer processes

Table 1
Different oxidants and their active oxygen contents

Oxidant	Active oxidant content/wt.%	Waste product
O_2/reductor	50.0	H_2O
H_2O_2	47.0	H_2O
O_3	33.3	O_2
NaOCl	21.6	NaCl
CH_3CO_3H	21.1	CH_3COOH
t-BuOOH	17.8	t-BuOH
$C_5H_{11}NO_2$ [a]	13.6	$C_5H_{11}NO$
NaOBr	13.4	NaBr
$KHSO_5$	10.5	$KHSO_4$
$NaIO_4$	7.5	$NaIO_3$ (NaI)
PhIO	7.3	PhI

[a] *N*-Methylmorpholine-*N*-oxide.

[18,19] (Table 1). In addition to price, other factors which are important from the viewpoint of practical utility are the percentage of active oxygen and the nature of the coproduct. The former has a direct bearing on the productivity of the process (yield per unit reactor volume per unit time) and the latter on the environmental acceptability. On the basis of these criteria it is readily apparent that the most commercially attractive oxygen donor (after dioxygen) is hydrogen peroxide. Generally speaking organic oxidants, such as TBHP or amine oxides, can be more easily recycled (by reaction of the reduced form with hydrogen peroxide) than inorganic ones. With inorganic oxidants environmental considerations are relative: obviously hypochlorite, persulphate and periodate are preferable compared to stoichiometric oxidations with heavy metal oxidants. Ease of recycling may ultimately be more important than price per kg, e.g. NaOBr preferable to NaOCl as NaBr can be reoxidized with H_2O_2. In this context it is worth noting that iodate can be reoxidized electrochemically to periodate [49].

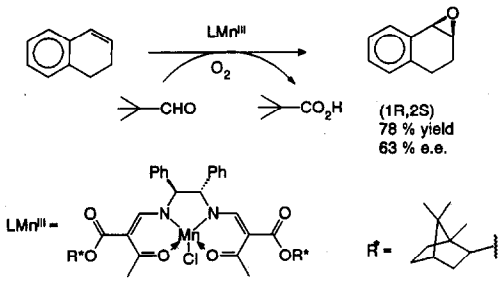
In addition to the above enviro-economic factors the choice of oxidant will, of course, be influenced by the selectivity of the process. In this context each oxidant tends to have its own set of problems, in particular with regard to the competing side reactions, such as catalytic decomposition of the oxidant.

Ruthenium-catalyzed epoxidations have been described with periodate [29,30], iodosylbenzene [43,50–56], pyridine-*N*-oxides [44], hypochlorite [56,57], hydrogen peroxide [58], TBHP [54] and even dioxygen [37–42]. The use of inorganic oxidants, e.g. NaOCl, $NaIO_4$ (and H_2O_2), dictates that the reaction takes place in the presence of water, either in two-phase systems or in polar solvents. Such systems suffer from the inherent disadvantage that polar molecules, particularly water and alcohols, often greatly retard catalytic oxidations by competing with the substrate and/or oxidant for coordination sites on the metal.

Of the organic oxidants used, N-oxides are preferable to iodosylbenzene as they can be readily regenerated by reaction of the amine with H_2O_2. Indeed, the generation of *N*-methylmorpholine-*N*-oxide (NMO) in situ, from *N*-methylmorpholine and H_2O_2, was used in combination with a $Ru(Ph_3P)_3Cl_2$ catalyst for the oxidation of primary alcohols to the corresponding aldehydes [59].

The use of peroxidic reagents, in particular H_2O_2, is plagued with the problem of competing nonproductive decomposition of the oxidant. Ruthenium is an excellent catalyst for the decomposition of H_2O_2 into O_2 and H_2O [60]. This explains the necessity for a 100-*fold excess* of H_2O_2 in the $Ru(bipy)_2Cl_2$-catalyzed epoxidation of octadec-9-enoic acid in *tert*-butanol [58] (see Section 6.1).

The use of a percarboxylic acid, such as peracetic acid, is potentially attractive in the context of enantioselective epoxidations but has the complication of a significant blank reaction in the absence of the catalyst. Recently, Mukaiyama [60–63] and Murahashi [64] have touted the use of a combination of an aldehyde and dioxygen as the oxidant in metal-catalyzed (ep)oxidations. Enantioselective epoxidation (e.e.s up to 77%) was observed [63] with a variety of substituted styrenes using Jacobsen-type manganese(III) Schiff's base complexes in combination with pivalaldehyde and dioxygen and *N*-methylimidazole as a cocatalyst, as depicted in Scheme 10.



Scheme 10.

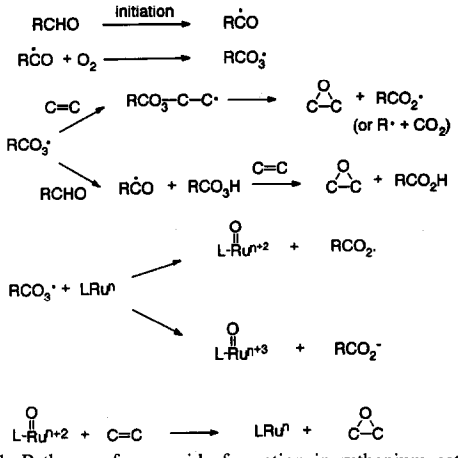


Fig. 11. Pathways for epoxide formation in ruthenium catalyzed oxidations with $RCHO/O_2$.

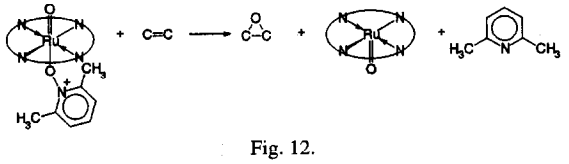


Fig. 12.

The oxidation of *cis*-stilbene with $RCHO/O_2$ in the presence of a ruthenium catalyst afforded a mixture of the *cis* and *trans* epoxides (*cis*/*trans* = 17/83) [64]. A system consisting of $RCHO/O_2$ and RuO_2 as catalyst, on the other hand, was reported [65] to be an effective reagent for the oxidative cleavage of olefins.

Mechanistically these systems are rather complex as several species that are present in the reaction mixture can effect epoxidation of the olefin. In the presence of aldehydes, olefins undergo facile cooxidation, in the presence of metal catalysts, to afford epoxides as major products in many cases [66]. Acylperoxy radicals ($RCO_3^{\cdot}$) are the key intermediates in these processes [67,68] and the epoxide product can be formed either via direct reaction of $RCO_3^{\cdot}$ with the olefin or via initial hydrogen transfer with RCHO to form the peracid, which then epoxidizes the olefin (Fig. 11). Epoxidation with RCO_3H should be stereospecific while with $RCO_3^{\cdot}$ one could expect a mixture of *cis* and *trans* epoxides. The relative contribution of the two routes to epoxide will depend on many factors, e.g. the structure of the olefin and the aldehyde and the aldehyde/olefin molar ratio.

A recent study [69] of the cooxidation of 1-octene or diisobutylene with isobutyraldehyde or pivalaldehyde indicated, in contrast to earlier suggestions [66], that addition of the acylperoxy radical to the double bond is the dominant pathway for epoxide formation. Convincing evidence was also presented in support of a concerted mechanism for the ring closure of the resulting acylperoxyalkyl radical to the epoxide, with simultaneous formation of an alkyl radical and CO_2 [69]. The stereochemistry (*cis*/*trans* ratio) is dependent on the rate of this process and, hence, will be very much influenced by the structure of R in RCHO. Pivalaldehyde is expected to afford an adduct which rapidly undergoes ring closure, as this leads to the formation of the relatively stable *tert*-butyl radical. In short, *cis*/*trans* ratios are not a reliable measure of homolytic vs. heterolytic pathways in these systems.

In the presence of a metal catalyst intermediate acylperoxy radicals or percarboxylic acids can also react with the metal ion to afford oxometal complexes which can act as epoxidizing agents (see Fig. 11). The best evidence for the intermediacy of oxometal species as the active oxidants in these systems is the observation of enantioselectivity, e.g. with chiral manganese Schiff's base complexes [62,63]. Here again the relative contributions of the various pathways will depend on many factors, e.g. the nature of the metal, olefin and aldehyde and their molar ratios, temperature, solvent, etc. Preliminary results with $RCHO/O_2$ in conjunction with ruthenium complexes as catalysts indicate a substantial contribution from (nonselective) radical pathways [70].

A comparison of results obtained in epoxidations of selected olefins with various primary oxi-

Table 2
Comparison of different ruthenium catalyzed epoxidations of *trans*-stilbene, cyclohexene and norbornene

Substrate	Catalyst	Oxidant [a]	Solvent	Conversion (%)	Selectivity (%)	References
trans-stilbene	$RuCl_3$/bipy	$NaIO_4$	CH_2Cl_2/H_2O	100	83	[29]
	$[Ru(O)_2(bipy)IO_3(OH)_3]$	$NaIO_4$	CH_2Cl_2/H_2O	100	99	[45]
	$[Ru(dppp)_2Cl]^+$	PhIO	CH_2Cl_2	16	20	[55,56]
	cis-$[RuO_2(Me_3tacn)(CF_3CO_2)]^+$	TBHP	CH_2Cl_2	42	95	[54](b)
	$[Ru(terpy)(bipy)(OH_2)]^{2+}$	NaOCl	CH_2Cl_2/H_2O	58	11	[57]
cyclohexene	$RuCl_3$/bipy	$NaIO_4$	CH_2Cl_2/H_2O	100	10	[29]
	trans-$[Ru(bipy)_2(OH)(OH_2)]^{2+}$	PhIO	acetone	54	83	[51](a)
	$[Ru(dppp)_2Cl]^+$	PhIO	CH_2Cl_2	3	<1	[55,56]
	cis-$[RuO_2(Me_3tacn)(CF_3CO_2)]^+$	TBHP	CH_2Cl_2	83	86	[54](b)
norbornene	$RuCl_3$/bipy	$NaIO_4$	CH_2Cl_2/H_2O	100	56	[29]
	$[Ru(O)_2(bipy)IO_3(OH)_3]$	$NaIO_4$	CH_2Cl_2/H_2O	100	19	[45]
	trans-$[Ru(bipy)_2(OH)(OH_2)]^{2+}$	PhIO	acetone	26	100	[51](a)
	$[Ru(dppp)_2Cl]^+$	PhIO	CH_2Cl_2	7	58	[55,56]
	cis-$[Ru(dmp)_2(CH_3CN)_2]^{2+}$	O_2 (4 atm)	CH_3CN	40 [b]	94	[37–39]

[a] With iodosylbenzene less than an equimolar amount was used, the conversions in these cases are based on iodosylbenzene consumed. In the case of all other primary oxidants an excess was used.
[b] The reaction was stopped after 40 turnovers.

dants in combination with ruthenium catalysts is shown in Table 2. As noted above each primary oxidant has its own set of tribulations and most of these systems still leave a lot to be desired from the viewpoint of practical utility.

Obviously it is difficult to decide which is the best catalyst and oxidant for a specific olefin on the basis of the literature. $NaIO_4$ seems to be an excellent oxidant for aromatic olefins but not for aliphatic ones. Phosphine ligands have not generally given good results. We note that they were mostly used in combination with iodosylbenzene, which is not the most favourable oxidant. A major problem is that the conditions (solvent, reaction time, reaction temperature, catalyst and oxidant) are not comparable. In order to obtain a better understanding of ruthenium-catalyzed epoxidations it is essential that one catalyst will be tested with a whole range of primary oxidants under a standard set of reaction conditions.

6. The effect of coordinated ligands

Both electronic and steric properties of coordinated ligands can have a profound effect on the activity and selectivity of ruthenium catalysts in (ep)oxidation reactions. Indeed, as noted earlier, modulation of the reactivity of high-valent oxoruthenium species by electron donating ligands appears to be essential for observing epoxidation to any significant degree. We note, however, that Kochi and coworkers showed [71] that, with cyclohexene, *cis*-$[Ru^{VI}(O)_2Cl_3]^-(Ph_3P)_2N^+$ afforded 24% conversion and 17% selectivity to the epoxide. In addition to this primary effect, coordinated ligands can also influence, for example, the formation of *cis* vs. *trans* dioxoruthenium(VI) complexes which may have a direct bearing on competition between epoxidation and oxidative cleavage. The nature of the coordinating ligand may also have an effect on which oxidation state of ruthenium predominates in solution.

Generally speaking, we may assume that two bidentate N, O or P ligands occupy four coordination positions around the ruthenium. The availability of the remaining two coordination positions in an octahedral ruthenium complex will then be influenced by whether the ligand is electroneutral or whether it is anionic. For example, the tetradentate porphyrinato ligand is a dianion and, hence, a ruthenium(II) porphyrin complex

has two axial positions available for disposition of the two oxo ligands in the transformation to a *trans*-dioxoruthenium(VI) complex. In a bis bipyridyl complex, on the other hand, the electroneutrality of this ligand necessitates the coordination of the two extra anionic ligands (e.g. chloride) in analogous complexes. In this case, dissociation of the anionic ligands is a prerequisite for the formation of dioxoruthenium(VI) complex. Hence, one would expect this to be facilitated when the anion is noncoordinating, e.g. PF_6^- or ClO_4^-.

Steric effects of coordinating ligands can play an important role by hindering the formation of less reactive μ-oxo species by dimerization of reactive oxoruthenium compounds. Steric effects of chiral ligands are also of primary importance in the context of enantioselective epoxidations (see later).

6.1. Nitrogen containing ligands

Porphyrins have been widely used as ligands in metal catalyzed (ep)oxidations in general [16,72] and in ruthenium catalyzed epoxidations in particular [73]. Moderate to high enantioselectivities have been observed in asymmetric epoxidations of unfunctionalized olefins with metal complexes of chiral porphyrins [8,74,75]. There are no examples, however, of enantioselective epoxidations with ruthenium porphyrins as catalysts. Iodosylbenzene [43], pyridine-*N*-oxides [44] and dioxygen [41,42,53] have been used as the primary oxidant, in combination with sterically hindered ruthenium porphyrin complexes. As discussed earlier (see Section 4) experimental observations [41,53] are consistent with a *trans*-dioxoruthenium porphyrin complex being the active epoxidizing agent when dioxygen is the primary oxidant (see Fig. 6). *cis*-Olefins were more reactive than *trans*-olefins which was rationalized [53] on the basis of the approach of the olefin to the Ru=O bond being more facile with *cis*-olefins (see earlier).

Hirobe and coworkers [44](b) have presented evidence in favor of a different active oxidant in ruthenium porphyrin-catalyzed epoxidations with 2,6-disubstituted pyridine-*N*-oxides. A possible candidate for the active oxidant is a monooxoruthenium(IV) complex containing a lutidine-*N*-oxide as an axial ligand (e.g. Fig. 12).

The substituents in the 2 and 6 positions are necessary in order to inhibit coordination of the substituted pyridine base to the ruthenium, resulting in loss of activity.

Kochi showed [46](b) that *trans*-$[Ru^{VI}(O)_2(py)_2(O_2CR)]$ ($R=CH_3$ or Ph) afforded 12–48% in the epoxidation of norbornene, styrene, α-methylstyrene, *E*- and *Z*-β-methylstyrene. With olefins containing allylic C–H bonds products resulting from allylic oxidation were also found. The nonstereospecific epoxidation of *Z*-β-methylstyrene was consistent with the stepwise transfer of oxygen (see earlier).

Bipyridyl and related bidentate ligands have been extensively studied in conjunction with ruthenium catalysts [29,30,37–39,45,50–52,57,58,76]. With in situ generated ruthenium bis(bipyridyl) complexes as catalyst and sodium periodate as the primary oxidant, in a two-phase system, *trans*-stilbene, for example, afforded *trans* epoxide in 83% yield [29]. Several other olefins were also oxidized (see Table 3). With PhIO as the primary oxidant low yields were observed for the epoxidation of cyclohexene (9 and 22% yield with bipy and pyridine as ligand, respectively) [52]. An attempt [76] to improve the selectivity of the epoxidation of *trans*-stilbene by attaching a crown-ether moiety, as a built-in phase transfer agent, to bipyridine (see Fig. 13)

Table 3
Epoxidation of olefins with $NaIO_4$ in the presence of $RuCl_3$/bipy or $RuO_2bipyIO_3(OH)_3 \cdot 1.5H_2O$ as catalyst

Olefin	Epoxide yield (%)	
	$RuCl_3$/bipy	$RuO_2bipyIO_3(OH)_3$
cyclooctene	70	83
styrene	24	25
trans-stilbene	83	99
cis-stilbene	45	75
norbornene	56	19

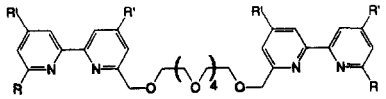


Fig. 13. Bis(bipyridyl) crown ether ligand.

Table 4
Catalytic oxidation of olefins by $[Ru(bpy)(terpy)(OH_2)]^{2+}$/NaOCl at pH 10.5

Olefin	Conversion (%)	Products (%)	
		Epoxide	Benzaldehyde
styrene	60	22	78
trans-stilbene	58	11	71
cis-stilbene	35	trace	99

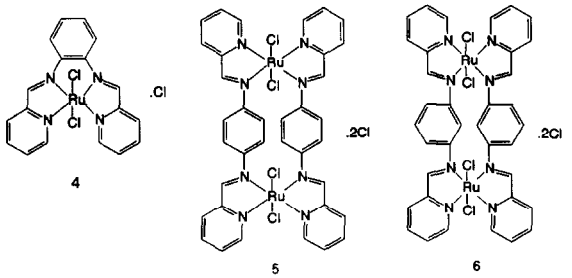


Fig. 14. Different diiminedipyridine ruthenium complexes.

actually afforded lower selectivities (33–52%).

$Ru(bpy)_2Cl_2$ and derivatives were also used in the epoxidation of octadec-9-enoic acid with H_2O_2 as external oxidant [58]. In *tert*-butanol 75% yield was found but a 100-fold excess of oxidant was needed because of ruthenium catalyzed decomposition of H_2O_2. Recently a ruthenium complex containing one bipyridyl as ligand, $[Ru^{VI}O_2(bpy)\{IO_3(OH)_3\}]\cdot 1.5H_2O$, was reported [45] to afford yields for epoxidation, higher than in the earlier discussed $RuCl_3$/bpy/$NaIO_4$ system, [29] in most, but not all, cases. Some of the results of these two systems are compared in Table 3. It should be noted that catalysts are often added as ruthenium(III) compound, e.g. $RuCl_3$ or $Ru(acac)_3$ but in the presence of the ligand it may be reduced in situ to ruthenium(II).

Meyer and coworkers [57] used $[Ru^{IV}(O)(bpy)_2(py)]^{2+}$ and $[Ru^{IV}(O)(bpy)(terpy)]^{2+}$ as stoichiometric oxidants in the epoxidation of styrene, *cis*- and *trans*-stilbene. The latter complex was also applied as catalyst in the same reactions with ClO^- as the primary oxidant. However, in this case the product of oxidative cleavage, benzaldehyde, was predominant (see Table 4).

Similarly, Che and coworkers [51](a) investigated *trans*-$[Ru^{III}(bpy)_2(OH)H_2O)](ClO_4)_2$ and *trans*-$[Ru^{III}(phen)_2(OH)H_2O)](ClO_4)_2$ as catalysts for the epoxidation of cyclohexene (39% yield) and norbornene (26% yield), using iodosylbenzene as the primary oxidant. The dioxo complex *trans*-$[Ru^{VI}O_2(phen)_2)](ClO_4)_2$, isolated by Ce oxidation of the aqua complex, was claimed not to react with double bonds. A Ru(IV)oxo or Ru(V)oxo intermediate was proposed to be responsible for the observed epoxidation. Another *trans*-ruthenium dioxo complex with a macrocyclic ligand containing one pyridine and three aminomethyl moieties was observed to give only oxidative cleavage for styrene and only allylic oxidation for cyclohexene [51](b). When a ruthenium complex was forced in the *cis* conformation by using 6,6′-dichlorobipyridine as ligand, epoxidation afforded, with *cis*-$[Ru^{VI}O_2(6,6'\text{-}Cl_2bpy)_2](ClO_4)_2$ as oxidant, 76% conversion and 58% selectivity in the epoxidation of styrene [51](c).

$[Ru(dmp)_2(CH_3CN)_2](PF_6)_2$ (**3**) was used as catalyst in the epoxidation of norbornene with molecular oxygen as external oxidant [37–39] (see also Section 4.). Turnover numbers of 35 were reached and a catalytic cycle was proposed.

Starting from 2-pyridinecarboxaldehyde and 1,2-, 1,3- or 1,4-phenylenediamine the complexes, containing one or two ruthenium metals, shown in Fig. 14 were synthesized and characterized [50]. *cis*-Cyclooctene was epoxidized in water/dioxane with iodosylbenzene as external oxidant.

The complexes **5** and **6** showed a doubling of the reaction rate compared to complex **4**. Norbornene, *cis*-cyclooctene, styrene, *trans*-4-octene and cyclohexene were also tested with this system (Table 5). The yields with norbornene and *trans*-4-octene were poor.

The same authors showed that the ruthenium(III) complexes depicted in Fig. 15 afforded low yields (up to 20%) with iodosylben-

Table 5
Epoxidation of olefins with different ruthenium diiminedipyridine complexes with iodosylbenzene as external oxidant

Olefin	Catalyst	Yield (%)
cis-cyclooctene	**4**	19
	5	24
	6	32
styrene	**4**	17
	5	23
	6	27
cyclohexene	**4**	40
	5	20
	6	26

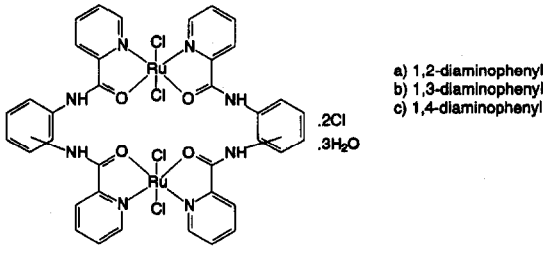


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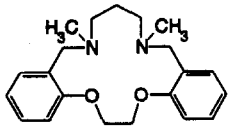
Fig. 15. Dimeric ruthenium complex with a bisamidobipyridyl ligand.

zene as external oxidant in the epoxidation of cyclohexene and *cis*-cyclooctene [53]. The low yields were attributed to the deactivation of the catalyst, probably by disintegration of the ligand, as was indicated by IR spectroscopy.

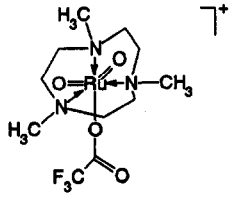
Taqui Khan and coworkers [77–80] have described the use of $[Ru^{III}EDTA]^-$ as catalysts for the oxidation of cyclohexene with molecular oxygen [77](a,b). They claimed that, via a μ-peroxo complex, both the oxygen atoms of dioxygen are utilized for the epoxidation. The complex, mentioned above was converted to $[Ru^{V}(O)EDTA]^-$ by oxidation with iodosylbenzene and tested as a stoichiometrical oxidant with a range of olefins affording yields of epoxide of 35–60% [77](c). With a ruthenium salophen complex, on the other hand, a completely different mechanism was suggested [78]. With ruthenium(III) aqua complexes and dioxygen, cyclohexene, methylcyclohexene and *cis*-cyclooctene afforded the corresponding epoxides in (calculated) yields of 40, 28 and 14%, respectively [79]. The relevance of these results is questionable, however, since e.g. cyclohexene undergoes facile autooxidation by dioxygen even in the absence of any catalyst. Strangely enough, according to the authors, in contrast to the case mentioned above, only one of the two molecular oxygen atoms is transferred to the olefin. Moreover, with virtually the same catalytic system 10 to 20% oxidative cleavage was reported in a later publication [80].

Che, and coworkers reported [54](a) the use of the saturated macrocycle (dddd) (**8**) as ligand. The complex *trans*-$[Ru^{III}(dddd)Cl_2]Cl$ was synthesized and characterized. This complex was converted to *trans*-$[Ru^{III}(dddd)OH(OH_2)](ClO_4)_2$ (**8b**), *trans*-$[Ru^{IV}(dddd)OH(OH_2)](ClO_4)_2$ (**8c**) and *trans*-$[Ru^{VI}(dddd)O_2](ClO_4)_2$ (**8d**). The second of these was characterized by X-ray analysis. With styrene, *cis*- and *trans*-stilbene and complex **8d** as stoichiometric oxidant the major product was benzaldehyde. Cyclohexene afforded cyclohexenone in 93% yield while with cyclooctene and norbornene high yields (75 and 85%, respectively) of the corresponding epoxides were observed. With complex (**8c**) as catalyst and iodosylbenzene, cyclooctene



8a

(1,12-dimethyl-3,4:9,10-dibenzo-1,12-diaza-5,8-dioxacyclopentadecane) (dddd)



9

$[Ru(O)_2(Me_3tacn)CF_3CO_2]^+$

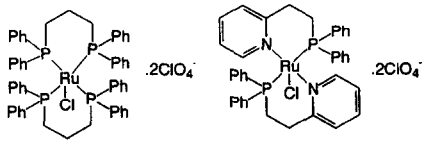
Me_3tacn = N,N',N"-trimethyl-1,4,7-triazacyclononane

Fig. 16.

Table 6
Epoxidation with $[Ru(O)_2(Me_3tacn)(CF_3CO_2)](ClO_4)$ as stoichiometric oxidant and as catalyst with TBHP as the primary oxidant

Substrate	Complex (**9**) (stoichiometric)		Complex (**9**)/TBHP [a] (catalytic)	
	Conversion (%)	Selectivity (%)	Conversion (%)	Selectivity (%)
styrene	79	4	65	71
cis-stilbene	75	51 [b]	83	>99 [c]
trans-stilbene	13	38	42	95
cyclohexene	76	42	83	86
cyclooctene			81	>99
norbornene			87	>99 [d]

[a] Excess TBHP was used.
[b] *cis*/*trans* ratio 8.5/1.
[c] *cis*/*trans* ratio 12.6/1.
[d] *exo*-2,3-epoxynorbornane.



10 11

Fig. 17.

Table 7
Epoxidation of olefins with phosphine containing ligands

Olefin	$[RuCl(dppp)_2]^+$ **10**		$[RuCl(ppy)_2]^+$ **11**	
	Conversion (%)	Selectivity (%)	Conversion (%)	Selectivity (%)
norbornene	7	58	13	46
cyclooctene	4	67	7	55
styrene	7	37	12	34
trans-β-methylstyrene	21	25	32	45
cis-β-methylstyrene	20	20	27	25
trans-stilbene	16	20	15	25
cis-stilbene	20	35	17	38

and norbornene afforded 35 and 50% of the corresponding epoxide, respectively. Styrene gave 30% benzaldehyde as the main product (Fig. 16).

The same authors also reported [54](b) the application of a novel *cis*-dioxoruthenium(VI) complex of *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane (Me_3tacn) (**9**) as an oxidant for olefins. It was used both as a stoichiometric oxidant and as a catalyst with iodosylbenzene and TBHP as the primary oxidant. The yields and selectivities for epoxidation were higher for the catalytic reaction than for the stoichiometric reaction (see Table 6). A markedly different result was observed, for example, with styrene (4 vs. 71% selectivity, respectively). For the aromatic olefins oxidative cleavage to benzaldehyde was the main side reaction. In contrast, for the aliphatic olefins the main byproducts resulted from allylic oxidation. With TBHP turnover numbers of 77 (for norbornene and cyclooctene) were reached.

6.2. *Phosphorus containing ligands*

$Ru^{II}(PPh_3)_3Cl_2$ catalyzes the epoxidation of styrene with dioxygen or TBHP as the primary oxidant, to give the epoxide in 14% and 25% respectively [31]. Bressan and coworkers [55,56] used bidentate P,P (**10**) and P,N (**11**) ligands (Fig. 17) in the epoxidation of several olefins, with iodosylbenzene as the primary oxidant (Table 7).

Olefin conversions and epoxide selectivities were poor to moderate. With both ligands the results (reaction rate, selectivity) were more or less similar. *cis*-Olefins afforded substantial amounts of *trans*-epoxide, consistent with a stepwise mechanism for the epoxidation step. Various aliphatic olefins were also applied but afforded only very low conversions (<5%) and are therefore not mentioned in Table 7.

7. Asymmetric epoxidation

Asymmetric epoxidation constitutes a powerful tool for the synthesis of optically active molecules. The discovery of the titanium/tartrate catalyzed asymmetric epoxidation of allyl alcohols, by Sharpless and Katsuki in 1980[9], represented a benchmark in catalytic asymmetric synthesis. The remarkable generality of the method – high enantioselectivities being obtained with a wide variety of allylic alcohol substrates – overthrew conventional wisdom which held that high enantioselec-

tivity requires narrow substrate specificity. However, in common with the extremely versatile Ru(binap)-catalyzed directed asymmetric hydrogenations, propagated by Noyori and coworkers [81], Sharpless epoxidation requires a directing group in the substrate for high enantioselectivity.

The next major challenge in asymmetric catalysis was the development of versatile catalysts that do not require any directing groups in the substrate. Here again Sharpless demonstrated the feasibility of such a concept with the development of the osmium-catalyzed asymmetric dihydroxylation of olefins which proved to be highly effective with a wide variety of unfunctionalized prochiral olefins [82].

Similarly, practical methods for the asymmetric epoxidation of unfunctionalized olefins have enormous synthetic potential. The most successful approach to this goal has involved a biomimetic strategy, based on chiral oxometal complexes as the active oxidants, analogous to the putative oxoiron(V) intermediates in cytochrome P450-mediated oxidations. The first example of asymmetric catalytic (ep)oxidation with chiral Fe and Mn porphyrin complexes was reported by Groves in 1983 [40]. Subsequently, several groups [8] have reported the use of chiral metal porphyrins as catalysts for the asymmetric epoxidation of unfunctionalized olefins. However, the porphyrin ligand has inherent drawbacks from a practical viewpoint. It is relatively difficult to introduce chirality into the porphyrin structure and it is susceptible to oxidative degradation. Hence, the development of chiral manganese Schiff's base complexes, by Jacobsen in 1990 [12,13], added new impulses to this avenue of research. These complexes proved to be highly competent catalysts for the asymmetric epoxidation of a range of unfunctionalized olefin substrates with NaOCl as the primary oxidant. Notwithstanding the enormous success of the Jacobsen system there is still considerable interest in the development of practical systems that use H_2O_2 and RO_2H as the primary oxidant and/or are applicable to *trans*-olefin substrates, where the Jacobsen method is not effective. We note, however, that Jacobsen

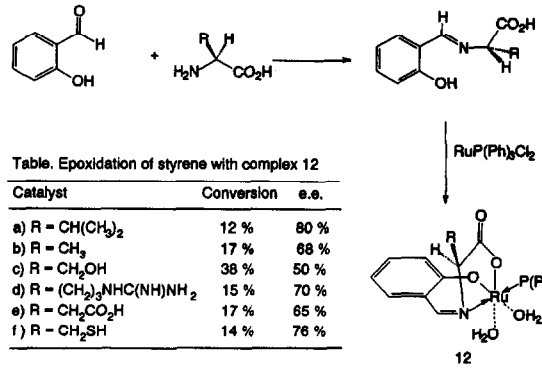


Table. Epoxidation of styrene with complex 12

Catalyst	Conversion	e.e.
a) R = $CH(CH_3)_2$	12 %	80 %
b) R = CH_3	17 %	68 %
c) R = CH_2OH	38 %	50 %
d) R = $(CH_2)_3NHC(NH)NH_2$	15 %	70 %
e) R = CH_2CO_2H	17 %	65 %
f) R = CH_2SH	14 %	76 %

Fig. 18. Synthesis and results with ruthenium Schiff's base complexes.

recently showed [83] that an alternate route to *trans*-epoxides is provided via the direct, nonstereospecific epoxidation of *cis*-olefins.

Two examples of ruthenium-catalyzed asymmetric epoxidation have been described in the literature. Kureshy and coworkers [84] described the catalytic asymmetric epoxidation of styrene using a series of chiral ruthenium(II) complexes of general structure (**12**) in combination with iodosylbenzene as the primary oxidant. The chiral tridentate ligands were synthesized by condensing optically pure amino acids with salicylaldehyde (see Fig. 18). Reaction of the resulting Schiff's base with $Ru(P(Ph)_3)_3Cl_2$ afforded (**12**). The best result (80% e.e.) was obtained with complex (**12a**)

Interesting features of (**12**) are that it contains N,O and P functionalities coordinated to ruthenium and would be expected to generate a *cis*-dioxoruthenium(VI) complex on oxidation. In view of the singularly high e.e.'s claimed with these complexes it would be interesting to carry out further investigations of these systems.

More recently, chiral 2-pyridyl-oxazolines (**13**) were used as the ligand in ruthenium-catalyzed epoxidations with $NaIO_4$ [85]. Analogous ligands have been successfully applied to other catalytic asymmetric syntheses, e.g. rhodium-catalyzed hydrosylilation of ketones [86]. Modest enantioselectivities (8–21%) were observed with *trans*-stilbene and 1-phenylcyclohexene as substrates (see Table 8, Fig. 19).

Table 8
Results of epoxidation with chiral 2-pyridyloxazolines

Olefin	Ligand	Yield (%)	e.e. (%)
trans-stilbene	**13a**	45	14
	13b	50	15
	13c	54	12
	13d	48	10
1-phenylcyclohexene	**13a**	48	21
	13b	44	11
	13c	42	8

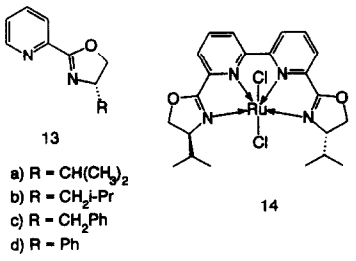


Fig. 19.

Similarly, Nishiyama and coworkers [87] used the chiral ruthenium(II) bis 2-pyridyloxazoline complex (**14**) as a catalyst for epoxidations with iodosylbenzene. However, only low yields of epoxides (28 and 3% from *trans*-β-methylstyrene and *trans*-stilbene, respectively) and no asymmetric induction was observed.

8. Concluding remarks

Ruthenium complexes appear to offer promise as selective epoxidation catalysts. However, there is a definite need for more systematic studies of the nature of the active oxidant involved in the epoxidation step and of the effect of ligand structure and primary oxidant on its reactivity and selectivity. A better understanding of the mechanistic details and the factors influencing epoxidation versus oxidative cleavage and allylic oxidation would provide a basis for further optimalization. It may even lead to the development of effective catalysts for the asymmetric epoxidation of unfunctionalized olefins.

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