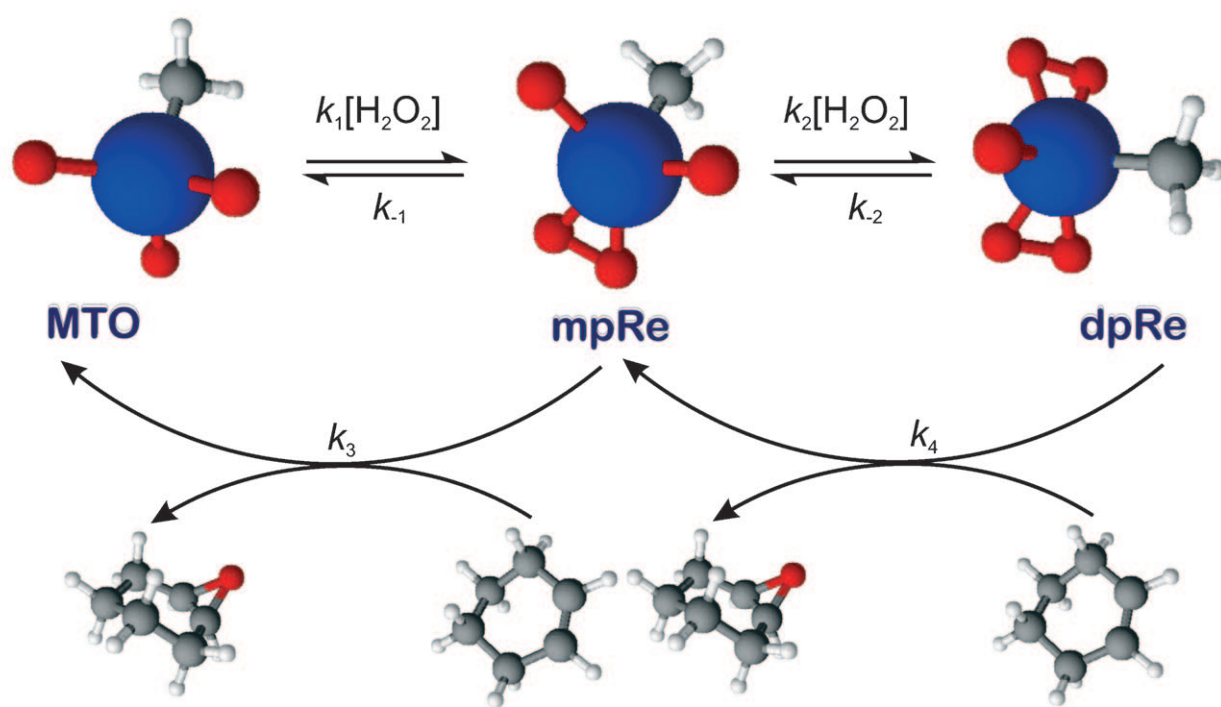


Methyltrioxorhenium Catalysis in Nonconventional Solvents: A Great Catalyst in a Safe Reaction Medium

Marcello Crucianelli,^{*,[a]} Raffaele Saladino,^{*,[b]} and Francesco De Angelis^[a]



The requirement that chemical processes are sustainable, reflected in waste reduction and the use of safe reagents and reaction conditions, is becoming even more stringent as a result of pressure by society and governments to preserve the environment and protect human health. Catalysis offers numerous benefits related to green chemistry, including lowered energetic reaction requirements; catalytic, rather than stoichiometric, amounts of materials; increased selectivity; lowered consumption of processing and separation agents; and, in many cases,

the use of less-toxic compounds. Our research group has for a long time been studying methyltrioxorhenium in the oxyfunctionalization of different substrates, by using H_2O_2 or its urea-hydrogen peroxide complex as the primary oxidant. In this Review paper we aim to provide a full literature account on the catalytic activity and selectivity of methyltrioxorhenium in the oxyfunctionalization reaction, either in nonconventional solvents or under solvent-free conditions, with a particular emphasis on the use of ionic liquids as green reaction media.

1. The “Goal” of Sustainability

The requirement that chemical processes are sustainable, reflected in waste reduction and the use of safe reagents and reaction conditions, is becoming even more stringent as a result of pressure by society and governments to preserve the environment and protect human health. As a consequence chemists, as the main actors in these fields, are expected to strictly control all steps of a chemical process. When going into detail, the careful examination of a reaction's parameters such as its *E* factor^[1] and its atom efficiency,^[2] as well as adherence to the “Twelve Principles of Green Chemistry,”^[3] emerge as issues that must be thoroughly addressed, and these have thus become driving factors in efforts to design and implement sustainable chemical processes. The Twelve Principles of Green Chemistry identify catalysis as one of the most important tools for implementing green chemistry.

Catalysis offers numerous benefits related to green chemistry, including lowered energetic reaction requirements; catalytic, rather than stoichiometric, amounts of materials; increased selectivity (i.e., highest reaction yield/efficiency); lowered consumption of processing and separation agents; and, in many cases, the use of less-toxic compounds. In terms of efficiency and selectivity, transition-metal-catalyzed synthetic oxidation processes that employ environmentally benign oxidants (e.g., H_2O_2 or O_2) are often superior compared to traditional reactions carried out with oxidative reagents used in stoichiometric amounts. During the last decades many catalytically active organometallic derivatives, containing a variety of transition metals, have been developed. This development has been aimed at achieving H_2O_2 -promoted oxidative functionalization of a wide range of substrates, both in homogeneous and heterogeneous phases.

Heterogeneous catalysis, also, complies with the requirements of green chemistry by allowing the easy separation and recovery of a catalyst from the reaction products. In this manner the need for separation through extraction or other physical separations is eliminated. Accordingly, the immobilization of active homogeneous catalysts on a solid, inert support would potentially render these catalysts recyclable, and has been presented as an alternative tool for the design of more-complex heterogeneous systems.^[4a,b]

Organic solvents are generally employed as reaction media in traditional catalytic processes, with the related unavoidable safety, health, and environmental drawbacks that result from

their typical flammability, toxicity, and volatility characteristics. It follows that solvents are key components for making a process “green.” A recent study has suggested that rigorous management of solvents effects the greatest improvement towards a greener organic synthesis.^[4c] In principle, the best solvent is no solvent at all, and where a solvent is to be used, green or less-toxic alternatives are to be considered. Also, such alternative solvents should preferably enable easy catalyst separation and recycling. While a number of reactions can be optimized under solvent-free conditions, many still require an appropriate reaction medium in order to get satisfying conversions of the starting materials. Hence, several alternatives to traditional organic solvents have been designed. As examples of nonconventional solvents, water, supercritical CO_2 (scCO_2), ionic liquids (ILs), and fluororous solvents are subjects of considerable interest.^[5] In general, water is the best choice if a solvent must be used: it is cheap, readily available, nontoxic, nonflammable, and environmentally safe.

ILs are salts formed by an organic cation and an organic or inorganic anion. During the last several years they have received considerable attention as versatile reaction media, owing to the possibility of using them as alternatives to traditional organic solvents.^[6] Their negligible vapor pressures; polar but in general noncoordinating anions; tunable melting points; full miscibility with conventional solvents, including water; and ability to dissolve a wide range of inorganic and organic compounds are highly favorable features that make them attractive alternatives to organic solvents. Accordingly, their use is generally considered to agree well with green chemistry principles. However, a detailed general study of the environmental impacts of their life-cycle phases in comparison with traditional solvents is not available. Such a life-cycle as-

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assessment is essential before any claims of “greenness” can legitimately be made. A study of this type has recently been performed on the ionic liquid [BMIM]BF₄, evaluating its use as a solvent for the manufacture of cyclohexane and in the Diels–Alder reaction.^[7] Another study has also evidenced the relatively high solubility of imidazolium-based ILs in water and the low EC₅₀ values obtained for some of them in a toxicity test, but also their poor biodegradabilities, which make them persistent pollutants with possibly important environmental consequences that should be thoroughly evaluated when scaling up processes based on their use.^[8a] In general ILs show a low solubility towards low-polar compounds, such as ethers or alkanes, and are also insoluble in scCO₂; while the latter can be highly soluble in ILs.^[8b] Most interestingly, when using ILs in the work-up procedure, the catalyst/product separation can be readily carried out by extraction of the product, leaving the catalyst in the ILs for use in successive recycling steps. In most cases,

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Raffaele Saladino was born in Rome (Italy), on August 31, 1964. He was educated at the University La Sapienza (Rome, Italy) where he earned a degree and a Ph.D. in Chemistry. After attending the University of Montréal (Quebec, Canada) as a visiting scientist, he spent most of his career at the University of Tuscia (Viterbo, Italy) where he is Associate Professor of Organic & Bioorganic Chemistry and head of the Agrobiology & Agrochemistry Department. He is founder of the Italian Society of Astrobiology (ISA). He has developed programs on green chemistry (alternative reaction solvents, heterogeneous catalysis, and valorization of fine-chemicals in industrial wastes), environmental and pharmaceutical biotechnology (design, preparation, and application of enzymatic nanobiocatalysts) and medicinal chemistry, including fundamental studies on prebiotic chemistry.



transition-metal catalysts can be dissolved or “immobilized” in ILs, and they appear stable without having to resort to specially designed ligands.

As to fluororous solvents, for example perfluorinated alkanes: these possess unusual physicochemical properties, such as low dielectric constants, high chemical and thermal stabilities, and low toxicities. They usually exhibit a temperature-dependent miscibility with organic solvents, being immiscible at lower temperatures but strongly increasing their solubility with temperature, thereby allowing for homogeneous catalysis at high temperatures and easy catalyst/product separation at ambient conditions.

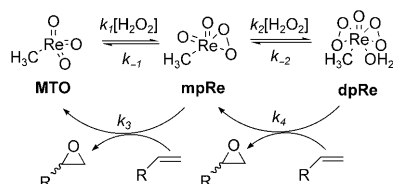
Our research group has for a long time been studying methyltrioxorhenium (MTO) in the oxyfunctionalization of different substrates, by using H₂O₂ or its urea-hydrogen peroxide (UHP) complex as the primary oxidant (see references in the following). In this Review paper we aim to provide a full literature account on the catalytic activity and selectivity of MTO in the oxyfunctionalization reaction, either in nonconventional solvents or under solvent-free conditions, with a particular emphasis on the use of ILs as green reaction media.

2. The Era of Methyltrioxorhenium as Catalyst in Oxidative Reactions

Methyltrioxorhenium(VII) (CH₃ReO₃), first observed by Beattie and Jones in 1979,^[9a] has now become one of the most-used catalysts for the activation of H₂O₂ in oxidation reactions. During the catalytic cycle it rapidly reacts with H₂O₂ (usually 30%) affording two active catalytic species, as monoperoxo and diperoxo η^2 metal complexes (**mpRe** and **dpRe**, respectively; Scheme 1) and/or their adducts with solvent molecules.^[9] As for olefin epoxidation: this is undoubtedly the most thoroughly examined reaction amongst the many applications of this versatile catalyst. The reaction mechanism has been studied in great detail; both from kinetic and theoretical points of view,

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Scheme 1. Formation of monoperoxo (**mpRe**) and diperoxorhenium (**dpRe**) complexes by MTO activation of hydrogen peroxide, and its reaction with olefins.

by means of UV/Vis spectrophotometry and NMR spectroscopy, in the homogeneous and heterogeneous variants of the reaction, and in aqueous as well as organic media (Scheme 1).^[10–12]

The creation of the two active oxygen-transfer complexes **mpRe** and **dpRe** during the catalytic cycle has been well-established, as well as the mechanisms of oxygen transfer itself. In general, however, the most important drawback of the epoxidation reaction is the concomitant ring-opening of the newly formed oxiranyl ring to afford the corresponding diols, as a consequence of the acidic properties of MTO. To overcome this limit, when using aqueous H₂O₂, low-molecular-mass Lewis bases bearing one or more nitrogen atoms in their structures have been used as mediators of the oxidation reaction to avoid ring-opening of the oxiranyl ring and possible concomitant rearrangement of the carbon skeleton of the molecule.^[13]

Another possibility to prevent the epoxide ring-opening, especially in the presence of particularly sensitive molecules, may be found in the use of “anhydrous H₂O₂,” that is, the UHP complex [CO(NH₂)₂·H₂O₂].^[14a] This reagent was first used by Adam and co-workers as the oxidant species for the MTO catalytic system in chloroform,^[14b] and it may be considered as a water-free peroxide source for MTO-catalyzed epoxidations. Usually, when working on olefin epoxidation reactions, the use of UHP as primary oxidant yields the corresponding epoxide product, whereas the use of aqueous H₂O₂ quantitatively converts the olefin into the corresponding 1,2-diol. This has been attributed to the production of urea during the consumption of UHP, which modulates the pH of the solution and thereby prevents any acid-catalyzed ring opening.

Concerning the toxicity of MTO: to the best of our knowledge no reports targeted at its rigorous evaluation have appeared so far. In any event, the rapid conversion of MTO to the corresponding soluble perhenate salts, especially occurring in alkaline media (see section 4), may be regarded as one valid reason to consider it a scarcely toxic compound.

3. MTO-catalyzed oxidations in ILs

Some reports describe an interesting acceleration effect for MTO-catalyzed oxidation reactions in ILs compared to molecular solvents. For example, the palladium-catalyzed Suzuki cross-coupling reaction in [BMIM]BF₄ has been described to proceed 90–200 times faster than in a mixture of toluene, water, and ethanol;^[15] rate enhancements have also been observed in biphasic Trost–Tsuji couplings when a biphasic mixture of [BMIM]Cl/methylcyclohexane is used instead of butyronitrile/

water.^[16] Even the neutral ionic liquid 1-methyl-3-pentylimidazolium bromide [PMIM]Br, promoted a one-pot, three-component condensation of an amine, carbon disulfide, and an activated alkene/dichloromethane/epoxide to produce the corresponding dithiocarbamates in high yields and at a faster rate than in other reaction media.^[17]

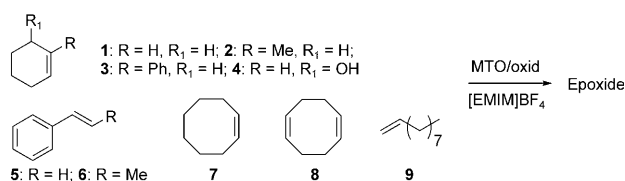
The availability of kinetic and thermodynamic data on reactions carried out in ionic liquids is a primary requirement for the evaluation of their economic viability when used as alternative reaction media, especially where industrial applications are concerned. The kinetics and thermodynamics of the reaction of MTO with hydrogen peroxide in ILs have been thoroughly studied.^[18] The rate constant for the formation in [BMIM]NO₃ of the **dpRe** complex with H₂O₂ (Scheme 1) from the **mpRe** complex is $0.053 \pm 0.002 \text{ M}^{-1} \text{ s}^{-1}$. The equilibrium constants for the binding of two peroxide units have been determined in [EMIM]BF₄ to be $K_1 = 110 \pm 28$ and $K_2 = 160 \pm 36$. From the literature data,^[18] it appears that the majority of the equilibrium constants of MTO with H₂O₂ in IL solutions fall between values obtained in water and acetonitrile. The experimental evidence that K_2 is larger than K_1 for all cases indicates cooperativity in peroxide binding. Also, as expected, there is no appreciable difference in equilibrium constants for a particular IL when UHP is used instead of aqueous H₂O₂. Analogous rate constants and equilibrium constants have been obtained in other water-miscible dialkylimidazolium and alkylpyridinium ionic liquids. In general, the values of the rate constants proved to be highly dependent on the concentration of water in the solvent. These results indicate that the ILs behave like organic solvents or aqueous solutions of high salt concentrations.

In addition, the kinetics of the oxygen-atom transfer from the peroxo complex of MTO (Scheme 1) to alkenes in ILs have been investigated by means of UV/Vis and NMR spectroscopy.^[19] Noncatalytic conversions of alkenes to epoxides were monitored by UV/Vis measurements at 360 nm, a wavelength at which **mpRe** and **dpRe** complexes both absorb. ²H NMR experiments performed with [D₃]dpRe under non-steady-state conditions confirmed the speciation of the catalytic system in ILs, and asserted the validity of the UV/Vis kinetics. Based on kinetic simulations and their agreement with experimental data, the fast step was assigned to the reaction of olefin with **dpRe** complex (k_4 , Scheme 1) and the slow step to the reaction of olefin with **mpRe** complex (k_3 , Scheme 1). In general, while the latter is more reactive towards alkenes in CH₃CN/H₂O 1:1, the opposite occurs when the reaction is performed in ILs. For example, in a series of ILs [EMIM]BF₄, [BMIM]BF₄, [BMIM]NO₃, and [BUPY]BF₄, the value of k_4 is 4.5 times k_3 . Finally, the rate constants k_3 and k_4 were unaffected by the nature of the ionic liquid cation; conversely, a discernable kinetic effect was observed with coordinating anions such as nitrate.^[19]

3.1. Examples of catalytic oxidations in ILs

The first example of MTO-catalyzed epoxidation carried out in ILs was reported in 2000, by Abu-Omar and Owens.^[20] In this work, several different olefinic substrates **1–9** were oxidized at

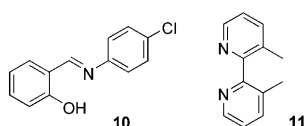
room temperature (RT) to the corresponding epoxides, with yields ranging from fair (in the case of 1-decene, **9**) to excellent (Scheme 2). The advantages shown by this oxidation system compared to others comprising conventional solvents are sig-



Scheme 2. Reagents and conditions: 0.5 mol substrate, 1.0 mol of UHP, 2% MTO, RT, 8 h.

nificant: (1) UHP and MTO are completely soluble in [EMIM]BF₄, giving a homogeneous reaction solution; (2) the oxidation solution is practically waterfree, thus allowing conversion of the substrate into the epoxide without formation of diols; (3) left-over reactants, if any, and products are easily separated from the oxidation solution by extraction with an immiscible solvent; (4) most of the epoxidation rates are at least comparable, if not higher than those reported in previously published data.

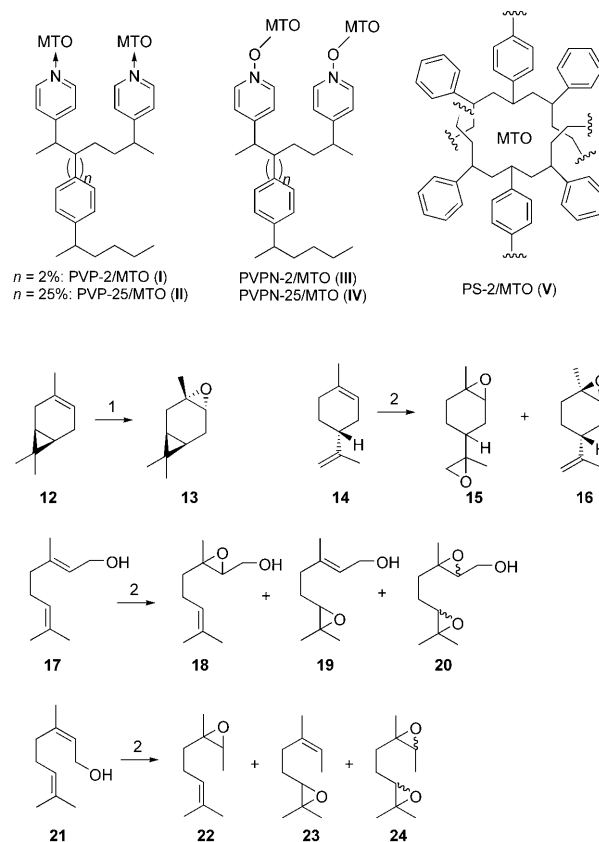
Recently, the H₂O₂-promoted epoxidation of cyclooctene in four different water-equilibrated ILs, [BMIM]NTf₂, [BMIM]PF₆, [BMIM]BF₄, and [C₈MIM]PF₆, was reported, with Schiff- and Lewis-base adducts of MTO and ligands **10** and **11** (1:1 ratio with MTO, formed in situ), respectively, acting as active catalytic species.^[21] The main aim of this work was to provide further insight into the applicability of ILs for replacing conventional



solvents such as dichloromethane on a laboratory scale. In all cases the MTO/**10** system led to higher cyclooctene epoxidation reaction yields than MTO/**11**. Both catalytic systems showed the highest activity when [BMIM]PF₆ was used as the solvent. Interestingly, with all tested ILs the MTO adducts formed cyclooctene oxide in higher yields than with pure MTO. This is not surprising because ring-opening reactions are suppressed with the ligated system while with MTO alone the parasitic diol formation occurs. The use of ILs was meaningful in this reaction because in all cases higher yields were obtained compared to the solvent-free systems, working at room temperature.

An efficient catalytic epoxidation of monoterpenes by homogeneous and heterogeneous MTO-based catalytic systems, in [BMIM]PF₆ and [BMIM]BF₄, was recently published.^[22a] In this work, MTO, poly(4-vinylpyridine) 2% or 25% (cross-linked with divinylbenzene)/MTO (PVP-2/MTO **I** or PVP-25/MTO **II**, respectively) and polystyrene/MTO (PS-2/MTO **V**) systems acted as efficient and selective catalysts for the conversion of monoter-

penes such as 1(*S*)-(+)-3-carene **12**, 1(*R*)-(+)-limonene **14**, geraniol **17**, and nerol **21** to their corresponding epoxides, using UHP as the oxygen atom donor (Scheme 3).



Scheme 3. Reagents and conditions: (1) 5% w/w of catalyst (loading factor 1.0 mmol g⁻¹ with catalysts **I–III**), [BMIM]PF₆ or [BMIM]BF₄, UHP, RT; (2) 5% w/w of catalyst (loading factor 1.0 mmol g⁻¹ with catalysts **I–III**), [BMIM]BF₄, UHP, RT.

The oxidation of allylic monoterpenes **17** and **21** proceeded selectively at the more electron-rich 6,7-double bond, irrespective to the type of catalyst used, in accordance with the electrophilic character of the oxidant, indicating that the electron density of the double bond is a useful tool to predict selectivity of the oxidation (Scheme 3). Polymer-supported MTO catalysts (**I–II**, **V**) showed reactivity and facial selectivity similar to that of simple MTO in the oxidation of the cyclic monoterpenes **12** and **14** (Scheme 3), thus suggesting the absence of kinetic barriers to the diffusion of substrate towards the active heterogeneous rhenium species. Interestingly, heterogeneous catalysts were stable systems for at least four recycling experiments (Table 1). As a general trend, the use of ILs enhanced the reaction rates and improved the regioselectivity of epoxidation as compared to similar oxidations previously performed in molecular solvents.

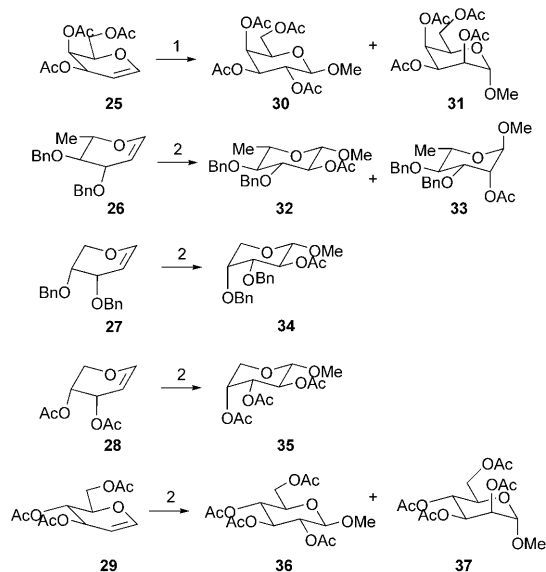
Two stable and widely used ILs, [BMIM][BF₄] and [BMIM][PF₆], were found to behave as appropriate reaction media for the MTO-catalyzed domino epoxidation/methanolysis of a series of diversified glycals **25–29** to the corresponding methyl glyco-

Table 1. Stability of polymer-supported MTO catalysts **II** and **V** in the oxidation of **12** (Scheme 3).

Catalyst ^[a]	Conversion [%] ^[b]			
	Run 1	Run 2	Run 3	Run 4
II	> 98 (> 98)	> 98 (> 98)	> 98 (89)	> 98 (91)
V	87 (85)	87 (83)	84 (82)	86 (86)

[a] Catalyst: PVP-25/MTO (**II**), PS-2/MTO (**V**). [b] Isolated yields of **13** are given in parentheses; reaction time: 2 h.

sides **30–37** (Scheme 4), with UHP or H₂O₂ as primary oxidants, under homogeneous and heterogeneous conditions.^[23] The oxidation of glycals represents a challenging target because of

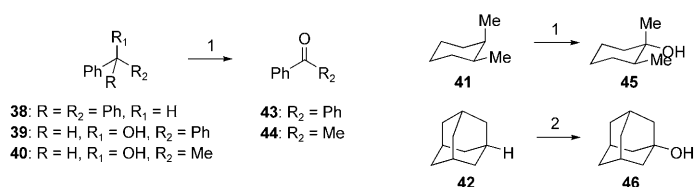


Scheme 4. Reagents and conditions: (1) a) MTO (10% w/w) or **I–IV** (loading factor 1.0 mmol/g), H₂O₂ or UHP (3–5 equiv), IL/MeOH (20:1), 2 days; b) Ac₂O, pyridine. (2) a) MTO (10% w/w) or **I–IV** (loading factor 1.0 mmol g^{−1}), UHP (3–5 equiv), [BMIM]BF₄/MeOH (20:1), 2–4 days; b) Ac₂O, pyridine.

the sensitive nature of the intermediate epoxide. It is therefore essential to perform this reaction in anhydrous and nonnucleophilic solvents. The facial diastereoselectivity of the oxidation, from satisfactory to excellent, is mainly related to the substrate, while the use of UHP as the primary oxidant gave a much higher stereoselectivity than aqueous H₂O₂. Both ILs turned out to work well, with [BMIM]BF₄ being generally preferable in terms of diastereoselection. Homogeneous MTO and heterogenized MTO-based catalysts (**I–II**, **IV–V**) afforded the corresponding methyl glycosides efficiently, with excellent chemoselectivity and isolated yields; PVP-25/MTO **II** being the most efficient one. The stability of heterogeneous MTO catalysts in ILs was evaluated by repeating the oxidation of 3,4-dibenzyl-D-arabinal **27** with catalysts **II** and **V** in [BMIM]BF₄ and UHP, in successive transformations. In comparison with MTO alone, it is worth noting that while the activity of MTO was not retained in [BMIM]BF₄ after work-up of the reaction mixture, re-

cycled **II** and **V** showed acceptable efficiency in the oxidation even after four runs, affording the methylglycoside **34** as the main isolated product in good yields. However, a general decrease of the reactivity was observed (more pronounced in the case of **V**), probably due to a partial leaching of the catalyst in the organic solvent used for the product extraction.

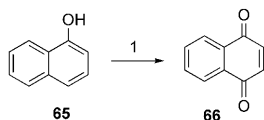
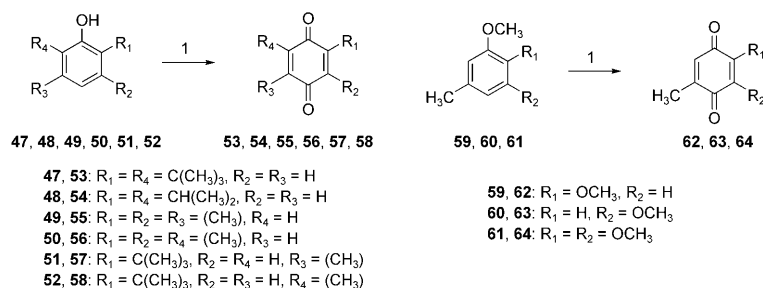
The advances in developing environmentally friendly and selective oxidations of hydrocarbons to the corresponding oxygenated derivatives is an important and challenging area in industrial and commodity chemistry, as most of the existing processes are performed in molecular solvents, make use of toxic oxidants (often in stoichiometric amounts), and eventually produce waste. In this field many alternative processes employing nonconventional, and less toxic, solvents and oxidants have been studied in recent years. An interesting example of oxygen C–H insertion at representative hydrocarbons by reaction of H₂O₂, promoted by MTO and heterogeneous polymer-supported MTO catalysts **I–V** in ILs such as [BMIM]PF₆ and [EMIM]Tf₂N has been published.^[24] Triphenylmethane **38**, benzhydrol **39**, 1-phenylethanol **40**, cis-1,2-dimethylcyclohexane **41**, and adamantane **42** were selectively oxidized to their corresponding ketones **43–44** and alcohols **45–46** (Scheme 5).



Scheme 5. Reagents and conditions: (1) catalysts **I–V** (100 mg, loading factor 1.0 mmol g^{−1}), ILs (1.0 mL mmol^{−1}), H₂O₂ (4–6 equiv), 25–45 °C, 24–48 h. (2) catalysts **I–V** (100 mg, loading factor 1.0 mmol g^{−1}), ILs (1.0 mL mmol^{−1}), H₂O₂ (4–6 equiv), 60 °C, 48 h.

Interestingly, the efficiency and selectivity of catalysts **I–V** showed to be sensitive to the nature of the polymeric support, with poly(4-vinylpyridine) and polystyrene affording the best performances. In most cases the activity of catalysts **I–V** in ionic liquids was higher than that observed in molecular solvents.^[25] Moreover, in the oxidation of adamantane **42**, catalysts **I**, **II**, and **V** were more reactive and selective than parent MTO. While MTO was not entirely retained in the ionic liquids during extraction of the reaction mixtures with diethyl ether, catalyst **V** was easily recycled and reused for successive transformations with similar selectivity and reactivity. In a similar manner, a variety of primary and secondary alcohols were oxidized to the corresponding aldehydes and ketones, in good yields, by using homogeneous MTO and sodium bromide as the catalytic system for the activation of H₂O₂, in [BMIM]BF₄.^[26]

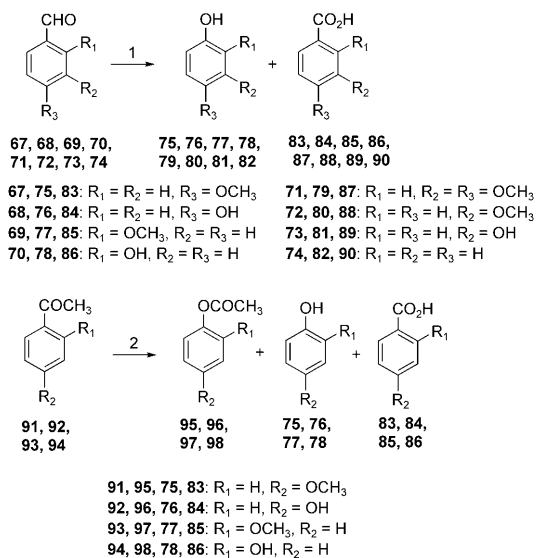
The same neutral ionic liquid [BMIM]BF₄ was used in a study describing the efficient catalytic procedure for the selective conversion, under homogeneous conditions, of the alkylated phenols **47–52** and methoxytoluenes derivatives **59–61** to the corresponding 1,4-benzoquinones **53–58** and **62–64**, in the presence of the MTO/H₂O₂ system (Scheme 6).^[27] All of the products were obtained in very good conversions (> 98%) and



Scheme 6. Reagents and conditions: (1) MTO (5% w/w), H_2O_2 (6–15 equiv), [BMIM] BF_4 (1.0 mL mmol $^{-1}$), 25–60 °C, 6–24 h.

yields (ranging from 70% to quantitative), in 6–24 h. α -Naphthol **65** was efficiently converted into 1,4-naphthoquinone **66** in good yields (> 98%).

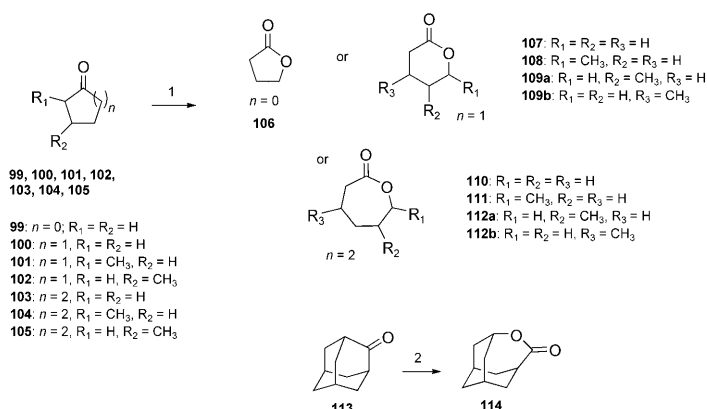
The selective oxidation of variously substituted aromatic aldehydes and ketones to the corresponding phenols is a stimulating research field, as witnessed by the interest in diphenols such as hydroquinone, catechols in general, and their methyl ethers as chemicals with high added-value. In this field a new efficient application of the MTO/ H_2O_2 catalytic system in ILs as [BMIM] BF_4 and [BMIM] PF_6 was published a few years ago (Scheme 7).^[28] In this work, the formyl group of the benzaldehyde derivatives **67–74** and the acetyl moiety of the hydroxylated acetophenones **91–94** is either oxidized to a carboxyl group or converted into a hydroxy function. The oxidation of 4-methoxybenzaldehyde **67**, chosen as model substrate for the initial investigation, showed to be faster, even if less selective, at 50 °C as compared to 25 °C, affording, besides 4-methoxy-



Scheme 7. Reagents and conditions: (1) MTO (2% w/w), H_2O_2 (2.0–10.0 equiv), ILs (1.0 mL mmol $^{-1}$), 50 °C, 2–24 h. (2) MTO (2% w/w), H_2O_2 (3.0–8.0 equiv), ILs (1.0 mL mmol $^{-1}$), 80 °C, 3–5 h.

phenol **75**, small amounts of hydroquinone **76** and 4-methoxybenzoic acid **83** (Scheme 7). The nature of the ionic liquid anion did not affect either the reactivity or selectivity of the oxidation reaction. Good results were obtained with activated benzaldehydes such as **68–71**. The corresponding phenols **76–79** were obtained in good yields. Nevertheless, benzaldehydes with *meta*-substituted electron-donating groups **72, 73**, and the unsubstituted benzaldehyde **74** failed to oxidize to the phenol derivatives **80, 81**, and **82**, respectively: in these cases the only observed products were the corresponding benzoic acids **88–90**.

Since its discovery, the astonishing ability of MTO to selectively catalyze a large variety of oxyfunctionalization reactions of many different organic compounds has been well recognized. Concerning the selective oxidation of ketones and of their nitrogen-containing derivatives such as aldimines, two interesting examples of MTO-promoted catalytic oxidations in ILs were recently published. In the first one, an efficient Baeyer–Villiger oxidation of cyclic ketones (**99–105**) to the corresponding lactones by means of the MTO/ H_2O_2 catalytic system, in [BMIM] BF_4 , was described (Scheme 8).^[29] This reaction appears to be an important

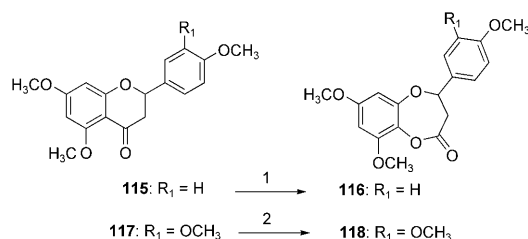


Scheme 8. Reagents and conditions: (1) MTO (2% w/w), H_2O_2 (50% aq. solution, 2.0–6.0 equiv), ILs (1.0 mL mmol $^{-1}$), 25–60 °C, 1–48 h. (2) MTO (2% w/w), H_2O_2 (50% aq. solution, 4.0 equiv), ILs (1.0 mL mmol $^{-1}$), 60 °C, 12 h.

contribution to the industrial applications of the Baeyer–Villiger reaction, because lactones are synthetic key intermediates in the agrochemical, chemical, and pharmaceutical industries. As expected, for the simplest ketones the highest reactivity was exhibited by the ring-strained cyclobutanone **99** which, after only 1 h, was quantitatively converted into γ -butyrolactone **106**, easily isolated from the reaction mixture. Cyclopentanones **100–102** were also transformed, in good yields, into the corresponding lactones **107–109**, while cyclohexanones **103–105** were less reactive. Adamantanone **113**, conversely, reacted easily giving the lactone derivative **114**, with quantitative conversion and reaction yields.

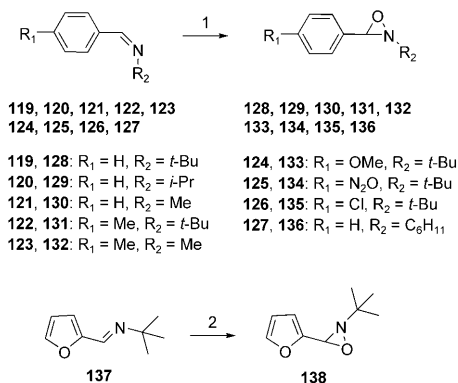
The same catalytic oxidation procedure was used for the methylated flavanones naringenin **115** and hesperetin **117**

(Scheme 9).^[30] In this case the homogeneous catalytic system MTO/H₂O₂, in [BMIM]BF₄, was more efficient than the previously studied system based on MTO heterogenized on poly(4-vinylpyridine) polymers, used in *tert*-butanol, with H₂O₂. Indeed, in this latter application lactonization proceeded under more drastic conditions.



Scheme 9. Reagents and conditions: (1) MTO (2% w/w), H₂O₂ (50% aq. solution, 2.0 equiv), ILs (1.0 mL mmol⁻¹), 25–40 °C, 2 h.

In the second case, related to the oxyfunctionalization of the imine derivatives of aldehydes and ketones, a recent publication dealt with the oxygenation of a series of aldimines **119**–**127** and **137** to the corresponding oxaziridines **128**–**136** and **138**. The reaction was catalyzed by various rhenium-based catalysts, including MTO immobilized in [BMIM]BF₄, with solid peroxides such as UHP, sodium percarbonate (SPC), and sodium perborate (SPB) as oxidants (Scheme 10).^[31] It is worth mentioning that aldimines oxygenation is an important research topic, because the formed oxaziridines find wide application in synthetic organic chemistry as nitrogen- and oxygen-transfer reagents.

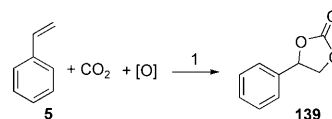


Scheme 10. Reagents and conditions: (1) MTO (1.0 mol%), oxidant (UHP or SPC or SPB; 2.0 equiv), [BMIM][BF₄] (0.15 mL mmol⁻¹), 50 °C, 0.75–3.5 h (with UHP oxidant) or 1.5–6.5 h (with SPC or SPB oxidants).

Among the various rhenium-based catalysts studied (i.e., MTO, HReO₄, Re₂O₇), MTO was found to be the most efficient, selectively affording the corresponding oxaziridines (with yields ranging from 80 to 98%, irrespective of the nature of used oxidant), without any evidence for the formation of nitrones and any other side-products. Generally aromatic aldimines with electron-withdrawing groups on the phenyl ring, such as

125–**126**, were less reactive. Also oxidation of furfurylidine-*tert*-butylamine **137** was found to be slow, giving a comparatively lower yield (80%) of the corresponding oxaziridine **138** (Scheme 10). The following advantages for this catalytic protocol can be underlined: (1) MTO and UHP are both completely soluble in [BMIM]BF₄, thus providing a homogeneous, more efficient oxidation system; (2) the use of solid peroxides offers nearly water-free reaction environments, selectively driving the reactions towards the formation of oxaziridines without ring-opening side effects; (3) the recovery and reusability of MTO immobilized in [BMIM]BF₄, for three successive runs, is very attractive from a sustainability point of view.

A further interesting application of catalytic MTO-promoted oxidation processes, in ILs was recently published in the field of chemical fixation of CO₂, through the one-pot preparation of styrene carbonate **139** starting from styrene **5** and CO₂, by using the complex catalytic system MTO/UHP/Zn[EMIM]₂Br₄/[BMIM][BF₄] (Scheme 11).^[32] The synthesis of five-member ring cyclic carbonates using CO₂ as raw material represents one of the most attractive routes for the chemical fixation of CO₂, owing to the large market of cyclic carbonates as solvents, intermediates, fuel additives, and building block for polymer synthesis.



Scheme 11. Reagents and conditions: (1) for the epoxidation: MTO (2% w/w), UHP (1.1 equiv), [BMIM][BF₄] (0.5 g mmol⁻¹), 30 °C, 2 h; for the CO₂ coupling: Zn[EMIM]₂Br₄/styrene (1:50), CO₂ (3 MPa), 110 °C, 2 h.

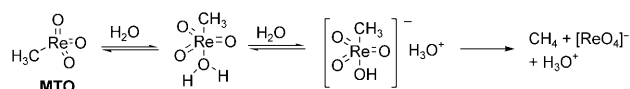
The one-pot procedure applied in this study was based on a multistep protocol. It differs from the single-step method in that it treats the whole process as two separate reactions, that is, epoxidation and CO₂ coupling reaction, thus producing a fair increase of the formation yield of styrene carbonate **139**, as compared to previously published methods,^[32] of up to 83%. This result was based on the use of two catalytic species for each reaction step, namely MTO for styrene epoxidation and Zn[EMIM]₂Br₄ for CO₂ addition to styrene oxide.

A few years ago another paper was published, describing the use of MTO as co-catalyst in the osmium-catalyzed dihydroxylation by H₂O₂, in a mixture of acetone/H₂O/[BMIM]PF₆, of a variety of aromatic and aliphatic olefins such as cyclohexene **1**, styrene **5**, and *trans*-β-methylstyrene **6**, to give the corresponding 1,2-diols in good to excellent yields.^[33] MTO operates as the electron-transfer mediator and hydrogen peroxide activator. Electron transfer from the co-catalyst to osmium is facilitated by the presence of catalytic amounts of *N*-methylmorpholine (NMM), as an additional electron-transfer mediator. It was demonstrated, however, that in some cases the direct electron transfer from MTO to osmium, to oxidize OsO₃ to OsO₄, is also efficient without any NMM present. Interestingly, immobilization and recycling of the catalytic system was dem-

onstrated by extraction of the product and then reuse of the catalytic system with moderate or even without any loss of activity, for three successive runs.

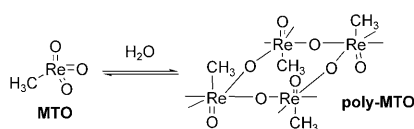
4. MTO in Water and Water-Mixed Solvents

MTO is water-soluble and stable toward protic acids. In aqueous solutions it shows weak acid properties ($pK_3 = 7.5$).^[34] Dilute solutions of MTO (e.g., concentration of MTO in the range $1.0 \cdot 10^{-4}$ – $3.0 \cdot 10^{-4}$ M) are stable for days, with minimal decomposition ($< 5\%$), generating CH_4 and perrhenate anion ReO_4^- as the only recovered products. The reaction proceeds by a fast deprotonation equilibrium of the $[\text{MTO}(\text{H}_2\text{O})]$ complex, to the corresponding $[\text{MTO}(\text{OH})]^-$ ($k_1 = 2.76 \cdot 10^3 \text{ M}^{-1} \text{ s}^{-1}$) (Scheme 12), followed by the Re–C and O–H bond cleavage, in the rate-limiting step.^[35] Irrespective to the experimental conditions (CH_4 pressure, pH, temperature, reaction time), MTO decomposition in water is not a reversible reaction.



Scheme 12. The behavior of MTO in water solution, under dilute conditions.

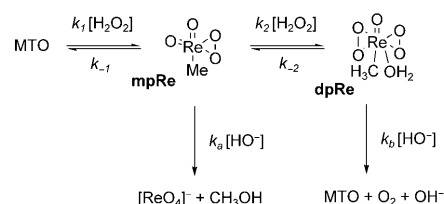
When more-concentrated MTO aqueous solutions ($2.4 \cdot 10^{-2}$ M) are heated at 323.2 K, a polymerization–precipitation process takes place with formation of a gold-colored poly-MTO compound of elemental composition $\text{C}_{0.92}\text{H}_{3.3}\text{ReO}_{3.0}$, which is characterized by a graphite-like consistency (Scheme 13).^[36] PolyMTO is an electrical conductor (specific resistance: $6 \cdot 10^{-3} \Omega \text{ cm}$), and shows weak paramagnetism.



Scheme 13. Schematic representation for the formation of polyMTO.

The rate of formation of polyMTO is independent of pH, while the polymerization–precipitation process is reversible in freshly prepared systems. In alkaline solutions MTO is quickly hydrolyzed to CH_4 and ReO_4^- , via formation of a hydroxide ion adduct.^[37] On the other hand, the stability of MTO increases in acidic aqueous solutions, in the presence of Brønsted acids such as H_2SO_4 , HClO_4 , HNO_3 , and HBF_4 . The reaction of MTO with H_2O_2 in H_2O , at 25°C under controlled pH (0.1 M HClO_4), yields the reactive monoperoxorhenium complex $[\text{CH}_3\text{Re}(\text{O})_2(\eta^2\text{-O}_2)]$, **mpRe**, Scheme 1] and the diperoxorhenium complex $[\text{CH}_3\text{Re}(\text{O})(\eta^2\text{-O}_2)_2]$, **dpRe**, Scheme 1], with of equilibrium constant values of $k_1 = 7.7 \text{ L mol}^{-1}$ and $k_2 = 145 \text{ L mol}^{-1}$, respectively,^[38] similar to those observed for conventional organic solvents.^[9c] The formation of **dpRe** complex appears favored. In the presence of a $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (1:1) mixture, used to increase

the substrate solubility, values of $k_1 = 13.0 \text{ L mol}^{-1}$ and $k_2 = 136 \text{ L mol}^{-1}$ were determined. The activation of H_2O_2 upon coordination with Re^{VII} in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (1:1) is remarkable, and a high value of the ratio between catalyzed and uncatalyzed oxidation is usually observed, as it is the case of the oxidation of phosphines ($k_{\text{cat}}/k_{\text{uncat}} = 0.2 \times 10^6$; see below). The decomposition of peroxorhenium intermediates occurs in a few hours, depending on the peroxide concentration and the pH of the solution. In this latter case, the decomposition of the **mpRe** complex affords methanol and perrhenate, while **dpRe** yields molecular oxygen, also regenerating MTO (Scheme 14).^[39]



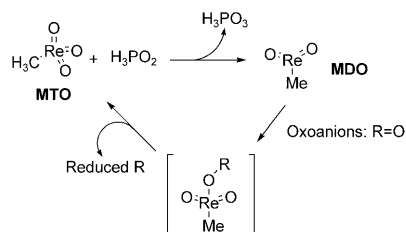
Scheme 14. The behavior of MTO in the presence of H_2O_2 , in water solution.

In accordance with the general reaction pathway observed for MTO alone, the rate of decomposition of the complex **mpRe** increases by increasing the basicity of the reaction medium, mainly due to attack of either the hydroxide or HO_2^- anions. Thus, neutral or acidic aqueous solutions are the optimized experimental conditions to be used for the application of MTO in H_2O .

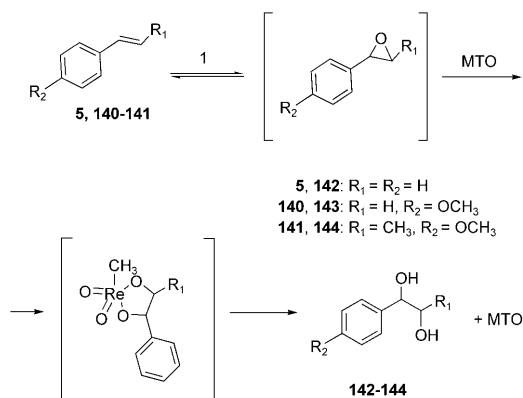
4.1. Examples of catalytic oxidations in water and water-mixed solvents

Examples of the use of MTO for the oxidation of a large panel of organic derivatives in water or in water-mixed solvents have been reported in the literature. The oxidation of bromide by H_2O_2 in aqueous solution, which is very slow, is strongly accelerated by MTO with formation of BrO^-/HOBr as the first reaction product. The subsequent disproportionation of this intermediate yields bromine or oxygen, depending on the specific experimental conditions. Bromine can further act as oxidant.^[40] In a similar context, MTO catalyzed the oxidation of H_3PO_2 to H_3PO_3 in H_2O in the presence of different oxoanions (ClO_4^- , ClO^- , BrO_4^- , IO_4^- , and others) as primary oxidants.^[41] In this reaction, methyldioxorhenium (MDO) is formed as the first intermediate along the oxygen-atom transfer process (Scheme 15). Upon standing, MDO reacts further with the oxoanions to yield the reduced species and MTO, thus closing the catalytic cycle.

As we have already seen, 1,2-diols can be directly synthesized from the parent olefins by oxidation with MTO and H_2O_2 , in aqueous solution. In particular, Espenson and co-workers reported the synthesis of the aromatic 1,2-diols **142–144** by oxidation of styrene **5**, 4-methoxystyrene **140**, and *trans*-4-propenylanisole **141**, with the MTO/ H_2O_2 system in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1) in the presence of 0.1 M HClO_4 .^[11] Mechanistically, the reaction proceeds by the initial formation of the corresponding epoxide, which is then followed by two competitive pathways: the

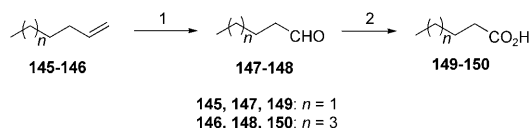
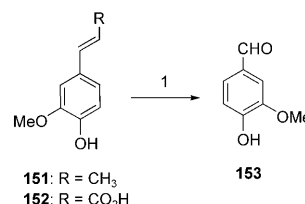
Scheme 15. MTO-catalyzed oxidation of H_3PO_2 .

epoxide ring-opening to the expected diol or, to some extent, the overall C–C double-bond cleavage to aldehydes and carboxylic acids formation. As revealed by ^1H NMR experiments in CD_3CN , in the absence of perchloric acid, a rhenium–diol chelate complex is formed along the reaction pathway (Scheme 16). It is interesting to note that the rate of oxidation

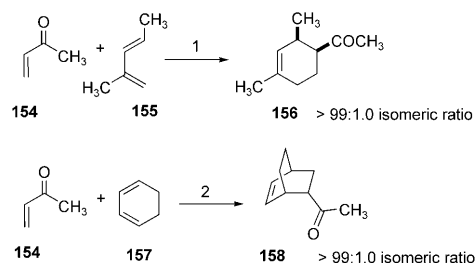
Scheme 16. Reagents and conditions: (1) MTO/ H_2O_2 , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), 0.1 M HClO_4 .

of compounds **140** and **141** increases with the amount of water in solution, consistent with the higher values of k_s (solubility constant) for the formation of peroxorhenium complexes in H_2O .^[42] As a general observation, the rate constant is higher with the presence of electron-donating groups, while steric factors only have marginal effects.

The selective and efficient cleavage of the C–C double bond catalyzed by MTO, in a two-phase olefin/aqueous H_2O_2 system, has been reported by Herrmann and co-workers.^[43] In the case of the aliphatic olefins 1-hexene **145** and 1-octene **146**, oxidation to the corresponding aldehydes **147–148** was performed in methyl-*tert*-butyl ether (MTBE), in the presence of HBF_4 or HClO_4 to further increase the lifetime of the catalyst. A large excess of H_2O_2 as well as a stoichiometric amount of the Brønsted acid were required to obtain the carboxylic acid derivatives **149–150** (Scheme 17). A different behavior was observed in the case of some styrene derivatives of natural origin, currently available from renewable resources, such as isoeugenol **151** and *trans*-ferulic acid **152**.^[43,44] In these cases the corresponding vanillic aldehyde **153** was formed, by using a three-time excess of H_2O_2 in *tert*-butanol (*t*BuOH) without the use of the Brønsted acids (Scheme 18).

Scheme 17. Reagents and conditions: (1) MTO/ H_2O_2 , MTBE/ H_2O , HBF_4 , or HClO_4 . (2) MTO/ H_2O_2 (excess), MTBE/ H_2O , HBF_4 , or HClO_4 (stoichiometric).Scheme 18. Reagents and conditions: (1) MTO/ H_2O_2 (3.0 equiv), *t*BuOH/ H_2O .

Most importantly, the Diels–Alder (DA) reaction between dienes and dienophiles allows the synthesis of cyclic derivatives with a very high diastereoselectivity control. It can be performed in H_2O at room temperature, in the presence of different metal ions which function as catalysts.^[45] MTO is an effective and efficient catalyst for this reaction in water, when the dienophile is an α,β -unsaturated ketone or aldehyde. For example, the DA reaction between *trans*-2-methyl-1,3-pentadiene **155** and the methylvinylketone **154** in H_2O , using a catalytic amount of MTO (1.0 mol%), afforded the cycloaddition product **156** in 90% yield and 99.0:1.0 isomeric ratio (Scheme 19). Similar results were obtained with the reaction

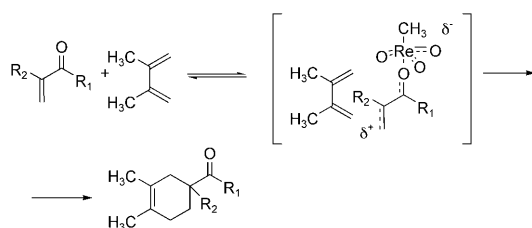
Scheme 19. Reagents and conditions: (1) MTO (1.0 mol%), H_2O , RT, 2.5 h.

between the same ketone **154** and cyclohexadiene **157** to give the cycloadduct **158**, in 91% yield.^[46] It is interesting to note that the DA reaction performed in H_2O is faster than that in conventional organic solvents (e.g., CHCl_3 , CH_3CN , THF, benzene, and acetone) or in water-mixed solvents [e.g., $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1) or acetone/ H_2O (1:1)], under similar experimental conditions.

It was observed that the substrates are not decomposed by MTO, and that the end products do not inhibit the catalyst activity. Concerning the reaction mechanism, the authors suggested that the catalytic activity of MTO lies in its ability to reversibly bind the dienophile at the oxygen atom, thus lowering the energy of the highest occupied molecular orbital (HOMO)

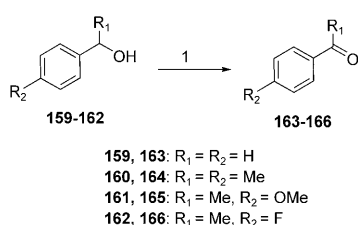
and lowest unoccupied molecular orbital (LUMO) in relation to the starting materials (Scheme 20).

Oxygen atom insertion into the sigma C–H bond is one of the most useful transformations in organic synthesis. Espenson



Scheme 20. Mechanism of the MTO catalyzed Diels–Alder reaction

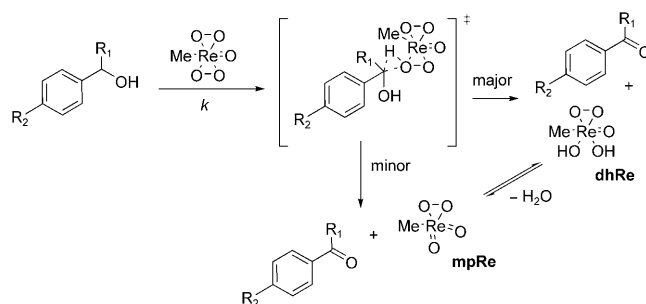
and co-workers reported on an efficient procedure for the oxidation of both primary and secondary alcohols with MTO and H_2O_2 in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), in the presence of HClO_4 (0.1 M aqueous solution).^[47] The authors also reported a detailed investigation of the value of the second-order rate constant k_4 , carried out by the initial rate method, to determine the kinetics of the initial oxygen atom transfer from the diperoxorhenium complex (**dpRe**) to the organic substrate. To this end they studied a large range of benzyl alcohol derivatives, carrying substituents with different electronic properties. In the case of the benzyl alcohol **159** itself, as well as with substituents at the *para*-position such as in 4-methyl- α -methyl benzyl alcohol **160**, 4-methoxy- α -methyl benzyl alcohol **161**, and 4-fluoro- α -methyl benzyl alcohol **162**, the values of k_4 ranged from $2.3 \cdot 10^{-4} \text{ L mol}^{-1} \text{ s}^{-1}$ to $10.2 \cdot 10^{-4} \text{ L mol}^{-1} \text{ s}^{-1}$, and the corresponding ketones **163–166** were isolated in fair to good yield (50–91%; Scheme 21). The structure–activity relationship study



Scheme 21. Reagents and conditions: (1) MTO (1.0 mol %)/ H_2O_2 , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), or H_2O , 0.1 M HClO_4

showed that electron-donating substituents increase the reaction rate, while electron-donating groups would operate in the opposite way. These observations agree with a mechanistic pattern where the rhenium peroxo-oxygen inserts as an electrophile into the C–H bond of the substrate.

In particular, as shown in Scheme 22, the reaction requires the initial interaction between the peroxorhenium oxygen with both the carbon and hydrogen atoms of the C–H bond, to yield a butterfly-like transition state that further evolves to the ketone. Dihydroxorhenium (**dhRe**) or monoperoxorhenium (**mpRe**) are also produced as by-products. The formation of di-

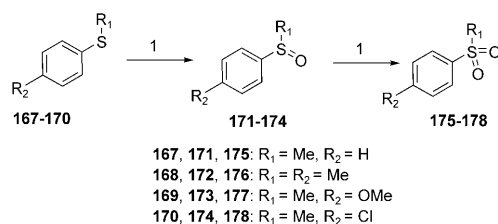


Scheme 22. Mechanism of MTO-catalyzed alcohols oxidation

hydroxorhenium intermediate was evaluated as the major operative pathway by means of experiments on ^{18}O -labeled substrates. **dhRe** is then quickly transformed to the **mpRe** complex by loss of a water molecule (Scheme 22).

Oxidations of benzyl alcohol derivatives were also performed under solvent-free conditions (see Chapter 6 for a complete description of solvent-free catalytic oxidations), using neat substrate and excess of H_2O_2 (30% water solution), at 40°C for 24 h.^[47] Under these experimental conditions most of the ketones were formed with yields higher than 80%, and also most of the oxidation reactions were complete in only 8 h. When HBr was added as a co-catalyst, ketones were isolated in yields higher than 90%, probably due to the already observed oxidation of Br^- to BrO^- , and successive formation of Br_2 as a strong oxidant. It follows that the presence of HBr also requires a large excess of H_2O_2 , to compensate for its depletion due to Br^- oxidation.

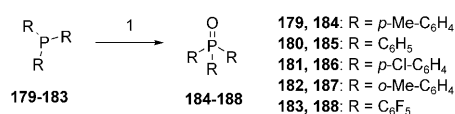
The oxidation of sulfides to sulfoxides, and then to sulfones is an organic transformation of relevant importance in different industrial processes, including the production of fine chemicals, commodities, and biologically active substances. Aryl thioethers such as **167–170** are easily oxidized to the corresponding sulfoxides **171–174** by the MTO/ H_2O_2 system in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), at 25°C and pH 1.0 (HClO_4 0.1 M). The sulfoxides are further converted to the sulfones **175–178** in the presence of excess H_2O_2 (Scheme 23).^[48] The rate constants for the transformation into sulfoxides were evaluated by the use of the initial rate method, and were found to be in the range between $k = 4.0 \cdot 10^{-1} \text{ L mol}^{-1} \text{ s}^{-1}$ (in the case of heterocyclic methylmercaptobenzimidazole, not shown) and $k = 8.5 \cdot 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$ (in the case of 2-methyl-4-methoxyphenylmethylsulfide, not shown), depending on the nature of the substrate. During oxidation, the nucleophilic sulfur atom attacks the peroxo group of the



Scheme 23. Reagents and conditions: (1) MTO (1.0 mol %)/ H_2O_2 , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), 0.1 M HClO_4

activated peroxorhenium complex. A structure–activity relationship study showed that the rate of the reaction increases by increasing the electron-donating ability of the substituent at the *para*-position of the aromatic ring. Electron-withdrawing substituents, such as chlorine and protonated amine groups, result in a decrease of the reaction rate. Moreover, when the aromatic moiety is replaced by an alkyl group, the reaction rate becomes almost ten times faster because of its electron-donating property. These results were correlated with the Hammett linear free-energy relationship, showing a negative slope ($\rho = -0.98$) which is in accordance with the proposed mechanism.

In a similar manner, tertiary symmetrically substituted phosphines such as **179–183** are oxidized to the corresponding oxides **184–188** by the MTO/H₂O₂ system in CH₃CN/H₂O (1:1), at 25 °C and pH 1.0 (HClO₄ 0.1 M) (Scheme 24).^[42b] The oxida-



Scheme 24. Reagents and conditions: (1) MTO (1.0 mol %)/H₂O₂, CH₃CN/H₂O (1:1), 0.1 M HClO₄

tion is very efficient, as shown by the high values of the rate constants observed during the oxygen atom transfer from the monoperoxorhenium (**mpRe**) complex to the substrate, ranging from $k = 1.9 \cdot 10^5 \text{ L mol}^{-1} \text{ s}^{-1}$ to $k = 3.9 \cdot 10^5 \text{ L mol}^{-1} \text{ s}^{-1}$.

The catalyst remained stable during the oxidation reaction, and a high turnover number (TON) was observed. On a preparatory scale, high yields were also detected (e.g., tris-pentafluorophenyl phosphine oxide **188** was isolated in 97% yield). The structure–reactivity correlation analysis devised by the Hammett procedure suggested that all the studied phosphines reacted through the same mechanistic pathway. In particular, the nucleophilic phosphorous atom adds onto the electrophilic peroxorhenium complex, and the oxygen atom transfer occurs through a concerted mechanism, forming an activated complex (Figure 1).

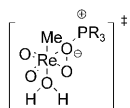


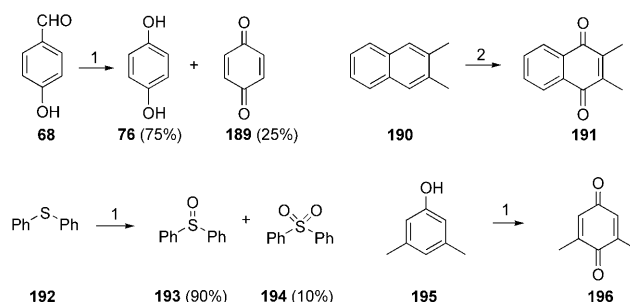
Figure 1. Structure of the transition state in the major pathway accounting for the oxidations of phosphines **179–183**.

result because other catalytic systems, such as those based on ruthenium, show different selectivities.^[49] Steric factors did not significantly affect the oxidation rates.

5. MTO-Catalyzed Oxidations in Different Media

Dimethyl carbonate (DMC), a chemical reagent produced through a green catalytic process by Enichem (Italy), is a well-known reagent used in organic synthesis as a benign substi-

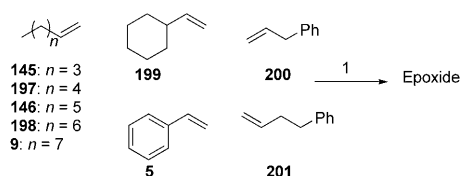
tute for hazardous and toxic reagents such as dimethyl sulfate, methyl iodide, and phosgene. Its low toxicity, the absence of irritating or mutagenic effects, and its high biodegradability qualify DMC as an environmentally friendly chemical with interesting solvating properties, potentially able to also be used as a reaction solvent. Although DMC has found many diverse industrial applications, for example in the fields of natural leather coating, metal cleaning, and also as an extraction solvent replacing toluene in the pharmaceutical industry, its use as a reaction medium has so far not been extensively exploited. A recent publication described the applicability of the hydrogen peroxide/MTO catalytic system using DMC as solvent for the oxidation of a wide variety of organic compounds.^[50] MTO and its diperoxo complex (**dpRe**, Scheme 1) showed to be soluble in DMC, being stable for days at room temperature, as evaluated by spectrophotometric analysis. A series of organic substrates having different functional groups such as styrene **5** (Scheme 2), benzhydrol **39** (Scheme 5), 2-adamantanone **113** (Scheme 8), *p*-hydroxybenzaldehyde **68**, 2,3-dimethylnaphthalene **190**, diphenyl sulfide **192**, and 3,5-dimethylphenol **195** (Scheme 25), along with different alkyl-substituted phenols **47–52** (Scheme 6), 1-naphthol **65**, and methoxytoluene derivatives **59–61** (Scheme 6) were oxidized, under catalytic conditions, also comparing reactivities in DMC with those previously reported for molecular solvents and ILs.^[27–29]



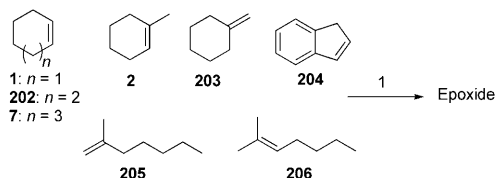
Scheme 25. Reagents and conditions: (1) MTO (1.0–2.0 %, w/w), H₂O₂ (1–3 equiv), DMC (2.0 mL mmol⁻¹), 50–60 °C, 2.5–7 h. (2) MTO (5.0 %, w/w), H₂O₂ (10 equiv), DMC (2.0 mL mmol⁻¹), 60 °C, 20 h.

Generally, oxidations afford high substrate conversions and yields. Products were obtained after shorter reaction times than in traditional solvents, and similar to those observed in ILs. By using DMC as solvent, in most cases a lower amount of catalyst was needed with respect to traditional solvents or ILs.

Since about 10 years ago, many studies dealing with epoxidation reactions have shown that the activity of hydrogen peroxide is markedly increased when reactions are performed in fluorinated alcohols as solvents, such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). The first example of the use of the MTO/pyrazole system in TFE, for the selective and efficient H₂O₂-promoted epoxidation of both terminal (**5**, **9**, **145–146**, **197–201**) and internal (**1**, **2**, **7**, **202–206**) alkenes, was described in 1999 (Schemes 26 and 27, respectively).^[51] In comparison to reactions performed in CH₂Cl₂, the amount of catalyst was reduced from 0.5 to 0.1 mol %, even if



Scheme 26. Reagents and conditions: (1) 10 mmol alkene, MTO (0.1 mol%), 0.5 mmol pyrazole, 20 mmol 60% H_2O_2 , 5 mL TFE, RT.



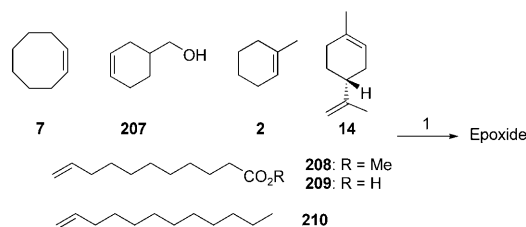
Scheme 27. Reagents and conditions: (1) MTO (0.1 mol%), 1 mmol pyrazole, 20 mmol 60% H_2O_2 , 5 mL TFE, 5 °C. The alkene (10 mmol) was added dropwise over 20–30 min.

the use of 60% aqueous solution of H_2O_2 (2.0 equiv) was needed. The higher rates observed in TFE, at room temperature, in comparison to those observed in dichloromethane, was in agreement with earlier observations by Sharpless and co-workers, who found that the highest rates during olefin epoxidations occur by using polar, noncoordinating solvents.^[52] Indeed, despite its alcoholic nature, TFE is a noncoordinating solvent because of the strong electron-withdrawing effect of the trifluoromethyl group. The trifluoromethyl group also prevents oxidation of the alcohol moiety, thus allowing this primary alcohol to be used as a solvent in the oxidation reactions.

As to the terminal alkenes, with the exception of styrene **5**, in most cases a complete conversion was observed within 24 h at RT; the corresponding epoxide being formed with high selectivity. In the case of styrene **5**, its very sensitive epoxide was partly converted into phenylethane-1,2-diol and benzaldehyde (not shown). In the case of the internal alkenes the reaction was performed at a lower temperature (5 °C) also to avoid catalyst decomposition. Under these conditions, selectively (with the exception of indene **157**) quantitative yields of the corresponding epoxides were obtained within 0.5–1.5 h. In general, epoxidation at both terminal and internal double bonds shows high TONs. One disadvantage, however, of this catalytic system may be found in the high polarity of the reaction medium (TFE): very apolar alkenes (C_{12} or higher alkenes and stilbenes) do not dissolve in the reaction medium and are therefore not oxidized. In the other cases, as those shown in Schemes 26 and 27, the alkenes do not dissolve completely as the reaction mixture is prepared but during the reaction course the solution becomes clear because of the formation of the more polar and soluble epoxides.

To achieve milder experimental conditions, an improvement was realized by substituting TFE with HFIP as the reaction medium. HFIP is a more efficient hydrogen-bond donor (hydrogen-bond donor acidity $\alpha = 1.96$) than TFE ($\alpha = 1.51$), and also a better dissociative solvent (ionizing power $Y = 3.61$, vs. $Y =$

1.80 for TFE). By combining the powerful catalytic activity of MTO with HFIP as a strong H_2O_2 activator, a quantitative conversion of cyclic and terminal olefins was obtained, working only with 30% H_2O_2 and 0.1 mol% of catalyst, at 0 °C or RT (Scheme 28).^[53]



Scheme 28. Reagents and conditions: (1) 4 mmol alkene, 0.1 mol% MTO, 10 mol% pyrazole, 2.0 equiv 30% H_2O_2 , 2 mL HFIP, 0 °C–RT, 1–24 h.

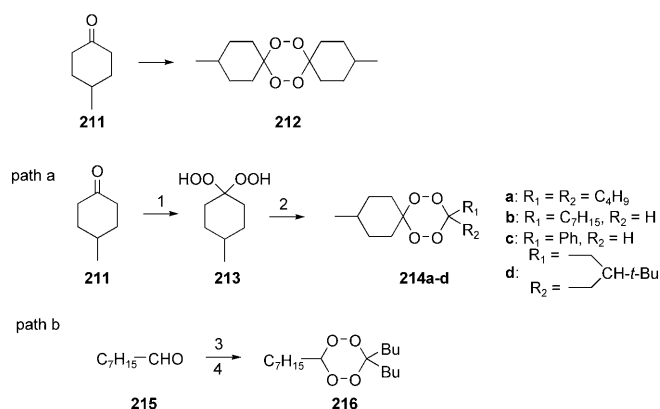
The stability of HFIP and the MTO/ H_2O_2 oxidative system was also evaluated in the presence of pyrazole to modulate the acidity of the catalyst and increase its stability. MTO (1 mg) was dissolved in 2 mL of solvent, 1 mL of 30% H_2O_2 was added, and the solution was stirred at room temperature. The yellow color of the solution indicated the presence of the catalyst active form. In TFE, over 1 h, the solution became colorless, thus indicating catalyst decomposition. Conversely, in HFIP the catalyst decomposed only after 6 h.

Cyclic alkenes [cyclooctene **7**, (3-cyclohexenyl)methanol **207**] are fully reactive, and oxiranes are formed quantitatively within 1 h at 0 °C. However, with cyclic trisubstituted alkenes such as 1-methylcyclohexene **2** and limonene **14**, the catalyst decomposes (as indicated by disappearance of the yellow color) while epoxidation is not complete (Scheme 28). Better results were observed by changing the ligand from pyrazole to 2,2'-bipyridine, affording quantitative conversion to the corresponding oxiranes, in 1 hour at 0 °C. Epoxidation of limonene occurred only at the cyclic double bond and diastereoisomers were formed in a 1.3:1 ratio.

Terminal long-chain alkenes showed to be less reactive. Indeed, as an example, the methyl ester of 10-undecenoic acid **208** was quantitatively converted into the corresponding epoxide with 0.1 mol% of MTO and 10 mol% of pyrazole at RT, in 1 day. The presence of the free acid functionality, as in the fatty acid **209**, is also compatible with this epoxidation method, the epoxide being obtained with quantitative conversion, at RT within 6 h. Long-chain terminal olefins, such as 1-dodecene **210**, are known to be usually difficult to epoxidize because of their low reactivity and their very poor solubility in polar solvents. Indeed, a low reactivity was also observed in HFIP as the solvent. The use of a mixture of two fluoruous solvents, a protic (HFIP) and an aprotic (trifluoromethylbenzene) solvent, allowed epoxidation of 1-dodecene **210** by improving both reactivity and solubility: after 24 h at RT an 88% yield of formation of the relevant epoxide was observed (Scheme 28).

A few years ago a further interesting application of an H_2O_2 /MTO/fluorous alcohol system was published, for the one-pot synthesis of nonsymmetric tetraoxanes **214a–d** starting from

simple ketones and aldehydes (Scheme 29).^[54a] Several types of synthetic cyclic peroxides were found to possess good antimalarial activities, because of the presence in the structure of the pharmacophoric endoperoxide functional group. They are re-



Scheme 29. Reagents and conditions: (1) MTO (0.1 mol%), 30% H₂O₂ (2.0 equiv), TFE (0.5 M), 2 h, RT; (2) 2.0 equiv of R₁R₂CO, 1.0 equiv of HBF₄, 1 h, RT; (3) MTO (0.1 mol%), 30% H₂O₂ (2.0 equiv), HFIP, 1 hour, RT; (4) 2.0 equiv of 5-nonanone, 1.0 equiv of HBF₄, 1 h, RT.

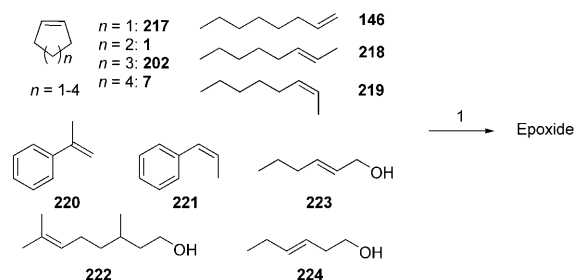
garded as synthetic analogs of artemisinin, a well-known antimalarial compound. Among them, the dispiro-1,2,4,5-tetraoxane **212** (7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane) exhibits a remarkable activity. In general, however, the synthetic efforts are directed to the preparation of nonsymmetric tetraoxanes, because they would offer more opportunities for selective incorporation of various functional groups on the tetraoxane scaffold, possibly in a one-pot route, thus avoiding isolation of the unstable and explosive *gem*-dihydroperoxide intermediate. In their paper,^[54a] the authors showed that a clean preparation of mixed tetraoxanes could be obtained by using the H₂O₂/MTO/TFE oxidative system. First, conversion of the more-reactive carbonyl compound, such as **211**, to the *gem*-dihydroperoxide **213** (without isolation) was carried out, with a stoichiometric amount of H₂O₂ in the presence of MTO, then acid-catalyzed coupling of the other carbonyl compound followed to form, selectively, the required tetraoxane (Scheme 29).

Starting from ketone **211**, in fact, this method allowed the preparation of mixed tetraoxane **214a** in a 64% overall yield as the major reaction product, accompanied by a small amount of the symmetric tetraoxane **212** (**214a**:**212** = 15:1). When the more oxidizable 4-*tert*butylcyclohexanone was used as the second carbonyl compound, the reaction was less selective, as demonstrated by the presence in the product mixture of both symmetric tetraoxanes, even if in small quantities, besides the required mixed tetraoxane **214d**. Nevertheless **214d** was obtained in 45% yield after crystallization. Aliphatic as well as aromatic aldehydes were also used for the cyclization, as reported in Scheme 29, path a, while the mixed tetraoxane **216** was also prepared starting from the base carbonyl unit of the aldehyde **215**, which reacted with an aliphatic ketone (Scheme 29, path b). It can be concluded that the use of fluororous alcohols as solvents has some advantages: the use of an

excess of H_2O_2 is no longer required, the amount of MTO is kept low (0.1 mol%) while, finally, the cyclization step is highly selective, because the formation of trimeric cyclic peroxides (hexaoxonanes) is completely avoided; the required tetraoxanes being the only reaction products.

6. MTO-Catalyzed Oxidations Under "Solvent-Free" Conditions

Synthetic procedures based on organic-solvent-free conditions are highly desirable methods for both health and environmental safety reasons. The epoxidation of olefins with the MTO/ H_2O_2 system is usually performed in CH_2Cl_2 , in which the catalytically active peroxorhenium species shows a high reactivity (for a Review on the epoxidation of olefins in conventional solvents see [9e]). As already pointed out, to avoid the formation of diols as side-products different heterocyclic amines, including pyridine,^[55] pyrazole,^[56] and 3-methyl pyrazole,^[57] can be used as additives, in order to neutralize the acidic properties of MTO as well as to tune the selectivity of the oxidation reaction.^[58] Recently, Yamazaki reported the efficient organic-solvent-free epoxidation of olefins with H_2O_2 , catalyzed by MTO and heterocyclic amines (Scheme 30).^[59]

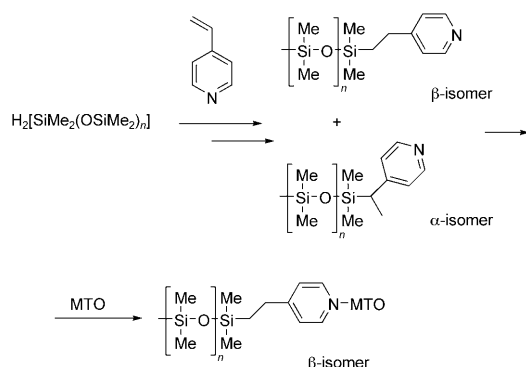


Scheme 30. Reagents and conditions: (1) substrate (20 mmol), H₂O₂ (35 % aq. solution, 40 mmol), MTO (0.1–0.5 mol %), 3-methylpyrazole (2 mmol).

As a general procedure, olefins have been oxidized with a catalytic amount of MTO (0.1–0.5 mol%) in the presence of amines (10 mol.%) and an excess of H₂O₂ (35% aqueous solution), either at room temperature or at 10 °C, depending on the nature of the substrate. Among the tested amines, 3-methylpyrazole was the most efficient additive, probably because of its low basicity (pK_a = 3.3) which prevents, in part, MTO decomposition, associated with its high solubilizing and phase-transfer properties.^[60] The rate of epoxidation of a selected panel of cyclic olefins such as cyclohexene **1**, cyclopentene **217**, and cycloheptene **202**, as well as that of the aliphatic terminal olefin 1-octene **146**, and the internal olefins *trans*- and *cis*-2-octene **218** and **219** (Scheme 30), under the previously described experimental conditions, was generally lower than in CH₂Cl₂, chosen as a reference. This was probably due to the low solubility of peroxorhenium complexes (**mpRe** and **dpRe**, Scheme 1) in those olefins. On the other hand epoxidation of styrene **5**, conjugated aromatic olefins **6**, **220–221**, and alkenols **222–224**, performed at 10 °C, was faster in organic-sol-

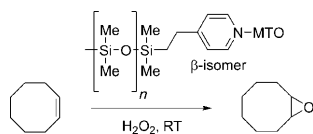
vent-free conditions than in CH_2Cl_2 , suggesting that the peroxorhenium complexes are well dissolved by the olefins themselves (Scheme 30). The procedure was applied on a preparative scale (20 g of substrate) too, for the oxidation of citronellol **222**, affording citronellol oxide in 76% yield and >96% purity (by GC).

Organic-solvent-free epoxidations have also been performed by immobilization of MTO on polymers that are liquid at room temperature. These systems are able to significantly increase the TON of the catalytic system, as a result of superior catalyst stability. For example, Montilla and co-workers reported the preparation of novel complexes between MTO and functionalized poly(dimethylsiloxane) (PDMS)/pyridine ligands (PDMSpy) and their extensive use for the epoxidation of olefins under organic-solvent-free conditions.^[61] The poly(dimethylsiloxane) (PDMS)-functionalized polymer was obtained as a mixture of α - and β -isomers (in a ratio of 1:2), by reaction of the hydride-terminated PDMS $\text{H}_2[\text{SiMe}_2(\text{OSiMe}_2)_n]$ with 4-vinylpyridine, under hydrosilylation conditions catalyzed by the Karstedt catalyst.^[62] After treatment of freshly prepared PDMSpy with MTO, the complex PDMSpy/MTO was isolated in high yield and selectivity as the only β -isomer, in accordance with the isomeric resolution previously reported by the authors during the synthesis of PDMS/palladium complexes (Scheme 31).^[63] The iso-



Scheme 31. Synthesis of the pyridine-functionalized poly(dimethylsiloxane).

meric resolution is probably due to the different solubilities of the complexes in the reaction medium. When the PDMSpy/MTO complex was used in the epoxidation of *cis*-cyclooctene **7** with H_2O_2 (30% aqueous solution) under organic-solvent-free conditions, a high substrate conversion and complete selectivity in the epoxide formation was observed (Scheme 32). Notably, the PDMSpy/MTO complex was stable and entirely compatible with the use of aqueous H_2O_2 , in contrast to previously

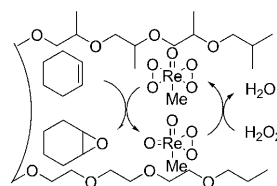


Scheme 32. Reagents and conditions: MTO (0.025 mmol), β -isomer (see Scheme 28) (0.1 mmol), 30% H_2O_2 (3.0 equiv), **7** (3.65 mmol), 18 h.

described data on the catalytic activity of MTO entrapped into pre-formed PDMS membranes.^[64]

Other olefins, such as 1-octene **146**, *trans*-2- and *trans*-4-octenes **218** and **225**, cyclohexene **1**, and styrene **5**, as well as allylic alcohol and ethyl acrylate were oxidized in a similar manner to afford the corresponding epoxides in acceptable to high yields. To further evaluate the potential of this procedure in industrial applications, different epoxidations were also performed in the presence of very low (0.005%) catalyst loadings (corresponding to a maximum achievable TON of 20000). In this latter case, the PDMSpy/MTO complex showed a reactivity higher than a simple MTO/pyridine mixture, MTO/4-tridecylpyridine, or MTO/3-methylpyrazole, probably due to a specific stabilizing effect of PDMS. Moreover, density functional theory (DFT) calculations showed that in the PDMSpy/MTO complex, the polymer chains are in the proximity of the oxo ligands, thus originating novel $\text{C}-\text{H}\cdots\text{O}$ interactions (ca. $2.2 \text{ kcal mol}^{-1}$) able to tune the reactivity and selectivity of the catalyst.^[65]

An analogous strategy developed by Neumann and co-workers is based on the use of some silica-tethered polyethers, both as anchorage site for MTO and organic reaction medium, in solvent-free MTO/ H_2O_2 catalyzed epoxidation of olefins.^[66] In this case, reaction systems with tuneable physical and chemical properties were designed by tethering different amounts of hydrophobic poly(propylene oxide) (PPO) on the surface of silica particles, with the aim to increase the substrate solubility and that of poly(ethylene oxide) (PEO), required to dissolve the aqueous oxidant and to stabilize MTO. These novel catalysts were used for the oxidation of a large number of cyclic and acyclic olefins, under organic-solvent-free conditions, to give the corresponding epoxides in high substrate conversions and product yields (see Scheme 33 for a selected example of cyclohexene oxidation). Irrespective of the experimental conditions, balanced amounts of PEO (10%) and PPO (10%), and catalytic MTO (0.02 mol%) yielded the best results in terms of selectivity towards epoxide formation. Moreover, even after five runs the catalyst retained its activity.



Scheme 33. Schematic drawing of cyclohexene oxidation by MTO supported on silica-tethered polyether/ H_2O_2 systems.

7. Conclusions

The concept that catalysis is a powerful tool to promote and optimize the sustainability of chemical processes, with the aim of improving the environment, health, and quality of life, is widely shared by the scientific community. Many recently published examples, with the main goal of modifying and improving some already known oxidative catalytic processes by using safer reagents and greener reaction conditions, go exactly in

this direction. Within this context, this Review documents papers that have been published in the field of catalytic and selective oxyfunctionalizations of many different substrates, working with one of the most valuable and studied oxidative catalysts: methyltrioxorhenium. In particular, we have focused our attention on examples based on the use of either nonconventional (e.g., ILs or fluorous solvents) or aqueous solvents, as reaction media, as well as on those working under solvent-free conditions. In most of them, MTO showed to be more active and selective than in traditional solvents, always being able to activate hydrogen peroxide or UHP as primary oxidants. Because MTO-catalyzed oxidations are well studied in literature, this Review may provide further insight into new alternatives to traditional solvents in laboratory-scale reactions.

8. Symbols and Abbreviations

EMIM *N,N'*-ethylmethylimidazolium

BMIM *N,N'*-butylmethylimidazolium

PMIM *N,N'*-methylpentylimidazolium

BUPY *N*-butylpyridinium

C₈MIM *N,N'*-octylmethylimidazolium

Tf₂N bis-triflic amide

Keywords: catalysis • ionic liquids • oxidation • rhenium • sustainable chemistry

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