STUDIES ON TRANSITION METAL-CATALYSED OXIDATIONS WITH HYDROGEN PEROXIDE AS TERMINAL OXIDANT

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Part of this work have been published:

1. *Hydrocarbon oxidations with hydrogen peroxide catalyzed by a soluble polymer-bound Manganese(IV) complex with 1,4,7-triazacyclononane.* Galina V. Nizova, Carsten Bolm, Simona Ceccarelli, Chiara Pavan, Georgiy B. Shul'pin, *Adv. Synt. Cat*. **2002**, *344*, 899.

2. *Iron-catalyzed Oxidation of Cycloalkanes and Alkylarenes with H_2O_2.* Chiara Pavan, Julien Legros, Carsten Bolm, *Adv. Synt. Cat.* **2005**, *347*, 703.

I would like to thank Prof. Dr. C. Bolm for giving me the opportunity to work in his group, for the stimulating research topic and for the exceptional working conditions.
I am very grateful to Prof. Dr. D. Enders for his kind assumption of the co-reference.

The art of losing isn't hard to master;
so many things seem filled with the intent
to be lost that their loss is no disaster.

Lose something every day. Accept the fluster
of lost door keys, the hour badly spent.
The art of losing isn't hard to master.

Then practice losing farther, losing farther:
places, and names, and where it was you meant
to travel. None of these will bring disaster.

I lost my mother's watch. And look! my last, or
next-to-last, of three loved houses went.
The art of losing isn't hard to master.

I lost two cities, lovely ones. And, vaster,
some realms I owned, two rivers, a continent.
I miss them, but it wasn't a disaster.

--Even losing you (the joking voice, a gesture
I love) I shan't have lied. It's evident
the art of losing's not too hard to master
though it may look like (Write it!) like disaster.

One Art *by Elisabeth Bishop*

To my family and friends

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1. Introduction

1.1 Oxidation Reactions: A Challenge

Oxidation and reduction reactions constitute a wide part of chemistry and it is difficult to imagine a synthesis, either in the laboratory or in nature, which does not include an oxidative/reductive step. Although a rigorous definition for oxidation contemplates either the loss of an electron or an increase in oxidation number, many reactions related to the conversion of a functional group, such as for example hydroxylation, epoxidation, dihydroxylation, aziridination, hydroxyamination and halogenation, are classified as oxidation reactions.

An important quest in this field is the search for safe and clean industrially applicable processes. Some oxidation reactions are centuries old and the optimum conditions still involve the use of strong oxidants, which contribute to global pollution with their toxic emissions and by-products. The search for friendly oxidation methods is, therefore, not only challenging, but also imperative for sustainable development.

Oxygen is the preferred oxidant in many biological systems and several studies have been devoted to its application on both academic and industrial scale.[1] A major disadvantage usually associated with the use of molecular oxygen is the need, in most of the cases, for an excess of co-reductant in the reaction cycle. It is needed to promote insertion of one oxygen atom into the substrate and to reduce the second oxygen atom to water. A second disadvantage is the risk of explosion, which still represents a serious safety issue for the industrial application of O_2-mediated processes. In the last few decades, hydrogen peroxide has emerged as a viable alternative to molecular oxygen.[2] This oxidant does not require the use of a co-reductant and in the presence of non-toxic, inexpensive metals, such as iron, affects homogeneous liquid phase oxidations, producing water as the sole by-product. This "green" combination represents a highly desirable solution to the environmental issue.

A second, but not less important, aspect to be considered in oxidation chemistry is the need for selective oxidation systems. The most environmentally friendly process would not be

[1] R. A. Sheldon, in: *Catalytic Oxidation – Principles and Applications*, (Ed. R. A. van Santen), World Scientific, Singapore, **1995**.

[2] a) *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*, (Ed. G. Strukul), Kluwer Academic, Dordrecht, **1992**; b) C. W. Jones, *Applications of Hydrogen Peroxide and Derivatives*, Royal Society of Chemistry, Cambridge, **1999**.

industrially interesting if it would not be also selective. Separation procedures and the formation of large quantity of by-products would imply higher post-production costs and more complex plants.

Oxidation is often the key step in the total synthesis of optically active compounds and**,** in many approaches, is performed by biological systems, such as isolated enzymes and whole cells. Consequently, chemo- and stereo-selective oxidation systems, which could mimic enzymatic active sites, are highly desirable as powerful tools towards the production of drugs.

Following these guidelines, we chose hydrogen peroxide as terminal oxidant and investigated three oxidation reactions:

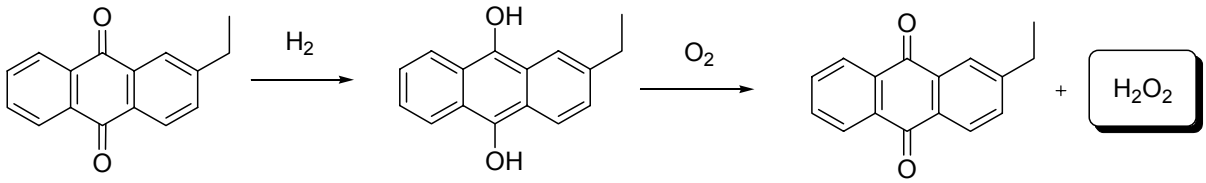
- Fe-catalysed oxidation of unreactive substrates
- Fe-catalysed oxidative cleavage of double bonds
- Fe- and Mn-TACN catalysed stereoselective oxidation of saturated and unsaturated hydrocarbons.

1.2 Hydrogen Peroxide: Production and Uses

Hydrogen peroxide was discovered in 1818 by L.-J. Thénard,[3] who treated barium peroxide (BaO_2) with sulphuric acid and obtained a relatively dilute (*ca*. 3%) solution of hydrogen peroxide. The first industrial production of H_2O_2 on the basis of this reaction[4] originates in 1873 from the German companies Schering (Berlin) and Merck (Darmstadt), and the company Bariumoxyd GmbH in Bad Honningen practiced this process until 1966. The industrial application of the electrochemical process[5] based on the electrolysis of sulphuric acid began in 1908 and was followed in 1910 by a similar process depending on the production of potassium persulphate. These processes led to the manufacture of more pure and stable solutions containing up to 30% by weight of hydrogen peroxide. The electrochemical process was further improved by direct hydrolysis and distillation of the electrolysed solution of ammonium sulphate in sulphuric acid and this method, called "Weißenstein process", was used up to the mid-sixties, before the present-day antraquinone process went on stream. The latter reaction was developed and patented by Pfleiderer[6]

[3] L. J. Thénard, *Ann. Chim. Phys.* **1818**, *8*, 306.
[4] A. von Schrotter, *Ber.* **1874**, *7*, 980.
[5] W. S. Wood, *Hydrogen Peroxide*, The Royal Institute of Chemistry, London, **1954**.
[6] G. Pfleiderer, *Ger. Pat.* 629234 **1934**; I. G. Farbenindustrie, *B.P.* 449360 **1934**.

(BASF), on the basis of the work of Manchot,[7] during World-War II[8] and the first large scale manufacturing unit started the production in USA in 1953. In this industrial process, basically a simple hydrogen-plus-oxygen reaction, alkyl antraquinones, such as 2-ethylantraquinone, or quinones could be used and hydrogen peroxide could be readily extracted with water (Scheme **1**). The antraquinone process is used at the moment in most of the technical hydrogen peroxide plants worldwide and allows the production of ultra pure and highly concentrated solutions of H_2O_2 under economically beneficial conditions.



2-ethylantraquinone (**1**) 2-ethylantrahydroquinone (**2**)

Scheme 1. Antraquinone process by Pfleiderer.[6]

Although several patents covering other methods have been published, none of them represents an alternative to date to the established antraquinone process.

The properties and reactivity of hydrogen peroxide make it an excellent candidate for improving the environmental acceptability of a wide range of chemical processes. Besides the fact that its constituents are oxygen and water, H_2O_2 has got a number of desirable features, such as purity, stability, oxidation efficiency and versatility that make it suitable for a range of applications within a number of industries. Hydrogen peroxide is used in the textile and paper industries for bleaching in direct competition to chlorine oxidants. Moreover, peroxides reagents are good disinfectants in a large number of applications, including the treatment of municipal effluents leading directly to cleaner beaches and inland waterways. In chemical synthesis, hydrogen peroxide is the starting material for preparing most of the peroxy compounds used industrially and it is employed as source of free radicals to initiate, for example, polymerisations. There is a large potential for the use of H_2O_2 and its derivatives in the treatment of a range of industrial effluents. In the chemical processing industry, H_2O_2 chemistry offers environmentally improvements in both less attractive oxidants and opening up cleaner routes to desired products. Until some years ago, hydrogen

[7] W. Manchot, *Liebigs Ann. Chem.* **1901**, *314*, 177.
[8] O. von Schinckh, *Chem. Ing. Tech.* **1960**, *32*, 462.

peroxide could be economically used as an oxidising agent only in situations where the kind of oxidised compound required or the reaction desired cannot be readily produced by less expensive oxidation methods. Consequently, products formed by oxidation with hydrogen peroxide were generally of two types: a) where the value of the product is relatively high; b) where one or two oxygen atoms, i.e., where the quantity of peroxide consumed is small relative to the quantity of the product formed. Increasing effluent treatment costs and environmentally based legislation are lately altering the balance in favour of hydrogen peroxide in many traditional industrial processes, as exemplified by the replacement of chlorine reagents in the synthesis of rubber accelerators and glycidyl compounds[9] and the substitution of metal oxides in the production of carbonyl compounds and carboxylic acids.[10] Moreover, H_2O_2 can often provide a clean method of rendering hazardous effluents, such as sulphur, phenols, cyanide and organic phosphate, environmentally more acceptable. These few examples well demonstrated the large, and not yet completely explored, potentialities of hydrogen peroxide and explained the great interest of industries, as well as universities, for new H_2O_2-based processes.

[9] K. Dear, in: *Organic Peroxygen Chemistry*, (Ed. W. A. Herrmann), Springer-Verlag: Berlin Heidelberg, **1993**.
[10] a) B. M. Trost, Y. Masuyama, *Tetrahedron Lett.* **1984**, *25*, 173; b) S. E. Jacobson, D. A. Muccigrosso, F. Maro, *J. Org. Chem.* **1979**, *44*, 921.

2. Fe-Catalysed CH Activation of Hydrocarbons

2.1 Introduction

Functionalisation of alkanes and cycloalkanes is rare and challenging.[11] Alkanes have neither lone pairs nor low-lying empty orbitals, only the C-H and C-C σ- and σ*- levels. It is therefore relatively hard to attack either the former with an oxidising agent or the latter with a reducing agent or base. This means that vigorous conditions and reactive reagents must often be used. It will almost always be the case that the product of an alkane functionalisation reaction is more reactive than the starting material and therefore reacts faster with the functionalising reagent. As a consequence, over-oxidation can be a severe problem and many of the oxidation reactions have to be run to low or very low conversion in order to obtain a satisfactory selectivity. This aspect can be tolerable for substrates such as methane, but becomes a problem with more valuable starting materials.

A second important selectivity issue arises when there are different types of C-H bonds in the molecule. Since tertiary radicals and carbonium ions are more stable than their secondary or primary analogues, many oxidation processes display the expected selectivity pattern: tertiary > secondary > primary.

There are three general classes of mechanisms often encountered in alkane reactions: a) radical,[11] b) electrophilic,[11] and c) carbenoid.[12] Among these, the first and second have been recognised to be involved in the oxygenation of unreactive substrates.

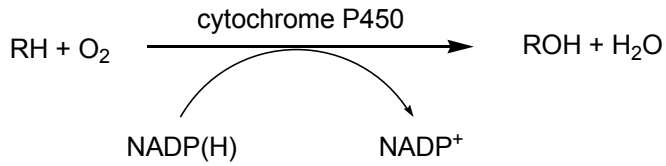
2.1.1 Alkane Oxidation

2.1.1.1 Biological Systems

Alkane oxidation is catalysed in nature by a variety of enzymes, but those, which have attracted most attention, are the cytochrome P450-depending systems.[13] The cytochrome P450 enzymes include a large family of heme-containing monooxygenases with a cysteine in the active site that acts as axial ligand to the iron. They are used by all forms of life to

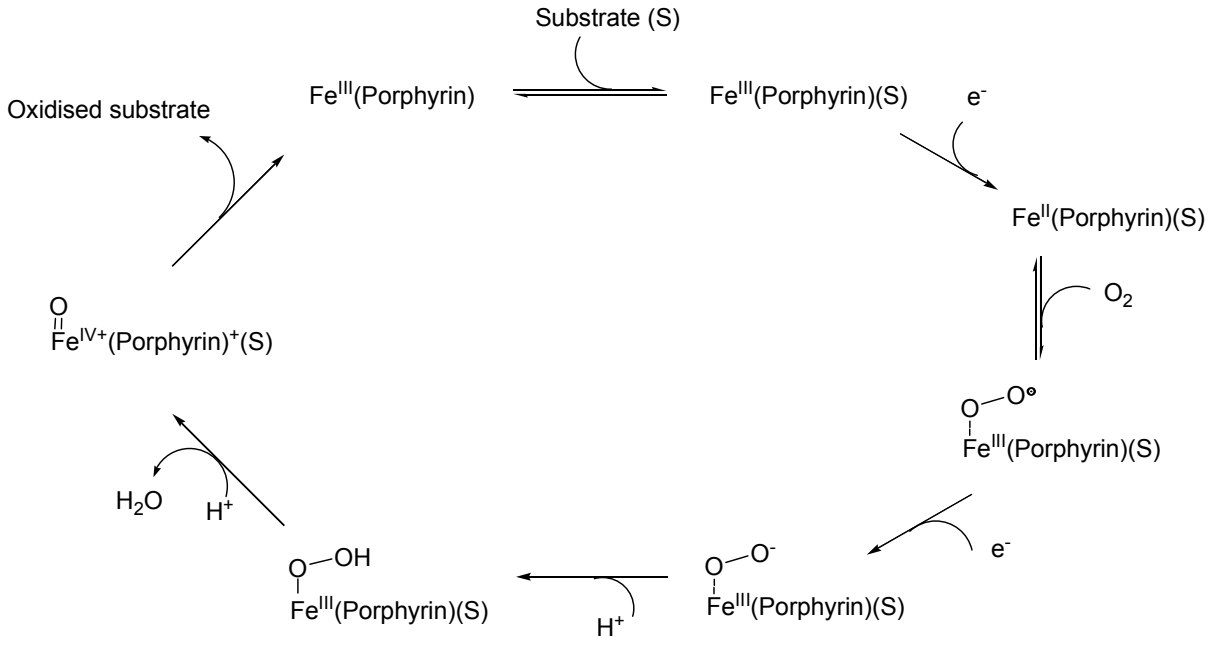
[11] A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879.
[12] See for example: M. P. Doyle, M. A. McKervey, T. Ye, in: Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides, Wiley: New York, **1998**.
[13] a) R. Sato, T. Omura, *Cytochrome P-450*, Academic Press: New York, **1978**; b) I. G. Denisor, T. M. Makris, S. G. Sligar, I. Schlichting, *Chem. Rev.* **2005**, *105*, 2253.

transform O_2 into a more suitable form for oxidation reactions, i.e. they catalyse the transfer of one oxygen atom to many different substrates while the second oxygen atom is reduced to H_2O by two electrons provided by NADPH (Scheme **2**).



Scheme 2. Oxidation of alkanes by cytochrome P450.

Among the various types of possible transformations catalysed by this class of enzymes, hydroxylation, epoxidation, alcohol oxidation and heteroatom oxidation are those most commonly observed. The mechanism of action of cytochrome P450 enzymes has been studied intensively and, although some steps are still unclear or controversial, the commonly accepted cycle is depicted in Scheme **3**.



Scheme 3. Simplified P450 catalytic cycle.

The substrate bound to the six-coordinated low-spin ferric Fe(III)(Porphyrin) resting form of the enzyme displaces a water ligand and induces the transition to the high-spin ferric form. This species is then reduced to the ferrous state Fe(II)(Porphyrin)(S) by an external reductant

and is able to bind dioxygen to generate a ferric superoxide complex. A second electron is then accepted to form a ferric peroxo species, which is rapidly protonated to give the ferric hydroperoxo intermediate [Fe(III)(Porphyrin)(S)]OOH, a species with reactivity analogous to H_2O_2. The ferric hydroperoxo species is heterolytically cleaved after the incorporation of a second proton, to give an oxoferryl porphyrin cation radical species that finally dissociates into oxidised substrate and the initial low-spin ferric resting form.

Metalloenzymes, an important class of monooxygenases containing non-heme diiron centres, have been intensively investigated in the past decade in order to characterise their structures and elucidate their functions.[14] The oxo-bridged diiron centre has been recognised as one of the most frequently utilised structures by living organisms for oxygen activation and substrate oxidation[15] and shows the potential to catalyse hydroxylation reactions.

A similar active centre, a hydroxo-bridged diiron centre (non-heme centre), has been found in the hydrolase component of the methane monooxygenase (MMO)[15b,c] which catalyses a remarkable reaction, the oxidation of methane to methanol by molecular oxygen, but it is also able to oxidise a great variety of alkanes, alkenes and aromatic compounds.[16]

2.1.1.2 Chemical Systems

Non-Iron Metal Oxidants

The oxidation of saturated hydrocarbons by inorganic oxidants, such as transition metals complexes and oxides, sometimes requires quite vigorous conditions and suffers from a lack of selectivity, since the initial products of these reactions are usually susceptible to further oxidation under mild conditions. For example, oxidation of simple alkanes by chromium(VI), manganese(VII), ruthenium(IV) and vanadium(V) derivatives has been long known.

The most versatile reagents for alkane oxidation are permanganate ions and their use is recommended except when solubility becomes the limiting factor. In this case it is better to use chromium(IV) compounds since they are soluble in a number of non-aqueous solvents, even though it has been found difficult to avoid further oxidation of the initial products.

[14] D. M. Kurtz, Jr., *J. Biol. Inorg. Chem.* **1997**, *2*, 159.
[15] a) B. J. Wallar, J. D. Lipscomb, *Chem. Rev.* **1996**, *96*, 2625; b) M. P. Woodland, H. Dalton, *J. Biol. Chem.* **1984**, *259*, 53; c) A. C. Rosenzweig, C. A. Frederick, S. J. Lippard, P. Nordlund, *Nature* **1993**, *366*, 537.
[16] J. Green, H. Dalton, *J. Biol. Chem*. **1989**, *264*, 17698.

Iron-Containing Systems

Iron is a widespread, inexpensive and non-toxic metal used to catalyse a wide variety of organic transformations.[17] It is involved in many oxidative biological systems. Iron compounds are used as initiators and catalysts in the oxidation of various organic substrates, mostly with hydrogen peroxide. Iron complexes, containing various ligands, play a very important role in living cells as well as in biomimetic oxidations.[18]

The classical Fenton reagent,[19] H_2O_2/Fe^{2+}, hydroxylates alkanes by producing hydroxyl radicals in solution.[20] This reagent is relatively unselective and atom-uneconomical since much of the hydrogen peroxide is wasted through catalytic decomposition to oxygen and water. Ferryl radicals, FeO^{2+}, have been invoked as intermediates by analogy with P450 chemistry, but conclusive evidence is still lacking.

A decisive contribution to the understanding of the properties and reactivity of the monooxygenase active sites came from the design and characterisation of structurally defined models. It was however only recently that some of them were shown to mimic enzyme activities and catalyse various oxidation reactions.[21]

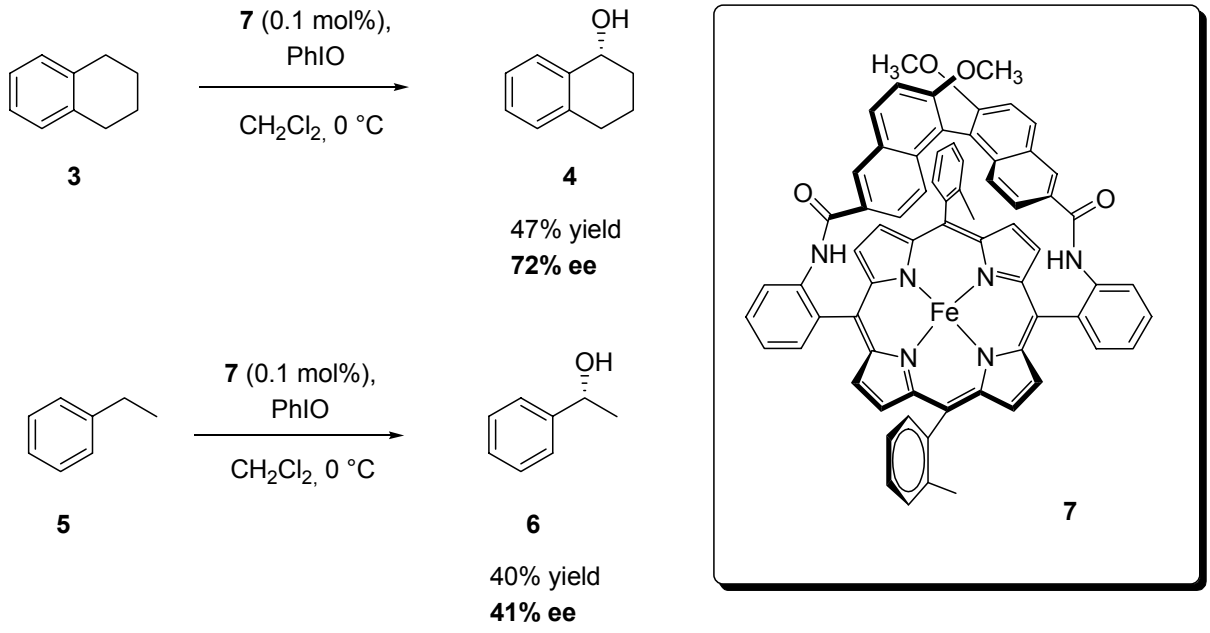
Porphyrins complexes of iron(III) as well as manganese(III), chromium(III) and ruthenium (III) are the most physiologically relevant models for cytochrome P450 enzymes. It is known that high-valent oxometalloporphyrin complexes play an important role in a variety of reactions catalysed by cytochrome P450,[22] chloroperoxidase[23] and nitric oxide synthase (NOS),[24] and heme iron-oxo intermediates have been identified during the oxygen reduction cycle of cytochrome oxidase.[25] Porphyrins have been investigated extensively as ligands to stabilise metals with respect to the undesirable decomposition pathway and, in combination

[17] C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217.
[18] Reviews and books: a) A. E. Shilov, G. B. Shul'pin, *Activation and Catalytic Reactions of saturated hydrocarbons in the Presence of Metal Complexes*, Kluwer Academic Publishers, Dordrecht, Boston, London, **2000**, 466; b) M.-H. Baik, M. Newcomb, R. A. Friesner, S. J. Lippard, *Chem. Rev.* **2003**, *103*, 2385.
[19] H. S. H. Fenton, *J. Chem. Soc.* **1984**, *65*, 899.
[20] C. Walling, *Acc. Chem. Res.* **1975**, *8*, 125.
[21] See for review and examples: a) M. Costas, M. P. Mehn, M. P. Jensen, L. Que, Jr., *Chem. Rev.* **2004**, *104*, 939; b) J. Kaizer, E. J. Klinker, N. Y. Oh, J.-U. Rohde, W. J. Song, A. Stubna, J. Kim, E. Münck, W. Nam, L. Que, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 472; c) C. Nguyen, R. J. Guajardo, P. K. Mascharak, *Inorg. Chem.* **1996**, *35*, 6273.
[22] a) J. T. Groves, Y.-Z. Han, in: *Cytochrome P-450, Structure, Mechanism, and Biochemistry*, (Eds. P. R. Ortiz de Montellano), Plenum Press, New York, **1995**; b) *Selective Hydrocarbon Activation: Principle and Progress*, (Eds. J. A. Davies et al.), VCH, New York, **1994**.
[23] Y.-C. Fann, N. C. Gerber, P. A. Osmulski, L. P. Hager, S. G. Sligar, B. M. Hoffmann, *J. Am. Chem. Soc.* **1994**, *116*, 5989.
[24] a) M. A. Marletta, *J. Biol. Chem.* **1993**, *268*, 12231; b) K. Mc Millan, D. S. Bredt, D. J. Hirsch, S. H. Snyder, J. E. Clark, B. S. S. Masters, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 1141.
[25] See for example: T. Ogura, S. Hirota, D. A. Proshlyakov, K. Shinzawa-Itoh, S. Yoshikawa, T. Kitagawa, *J. Am. Chem. Soc.* **1996**, *118*, 5443.

with mainly iron or manganese, they are considered one of the most important catalyst types for CH oxidation and epoxidation.

Among others, Groves and co-workers devoted several studies to the chemistry of Fe-porphyrins.[26] They used [Fe(TPP)Cl] (TPP = tetraphenylporphyrin) as catalyst for oxidations of alkanes and iodosobenzene as oxidant, a reagent also effective in the enzymatic site, where it obviates the demand for O_2 and a reducing agent.[27] The conversions obtained were rather low and [Mn(TPP)Cl] proved to be a more active catalyst for alkane oxidation, giving a conversion of up to 70% for cyclohexane.[28]

Some years later, Groves and co-workers reported the asymmetric hydroxylation of arylalkanes catalysed by a chiral Fe-porphyrin with reasonably good enantioselectivity (Scheme **4**).[29]



Scheme 4. Asymmetric hydroxylation of alkanes catalysed by chiral Fe-porphyrin **7**.[29]

[26] a) J. T. Groves, T. E. Nemo, *J. Am. Chem. Soc.* **1983**, *105*, 5787; b) J. T. Groves, T. E. Nemo, *J. Am. Chem. Soc.* **1983**, *105*, 6243.

[27] Other oxidants proved to be less suitable. See for example: a) I. Artaud, K. Ben-Aziza, D. Mansuy, *J. Org. Chem.* **1993**, *58*, 3373; b) T. Higichi, K. Shimada, N. Murayama, M. Hirobe, *J. Am. Chem. Soc.* **1993**, *115*, 7551.

[28] J. T. Groves, W. J. Kruper, R. Haushalter, *J. Am. Chem. Soc.* **1983**, *102*, 6375.

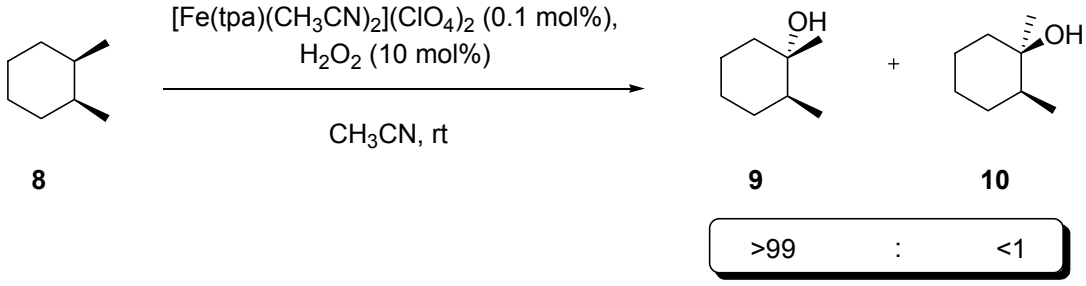
[29] J. T. Groves, P. Viski, *J. Am. Chem. Soc.* **1989**, *111*, 8537; b) J. T. Groves, P. Viski, *J. Org. Chem.* **1990**, *55*, 3628. For example on chiral Ru-porphyrins, see also: R. Zhang, W.-Y. Yu, T.-S. Lai, C.-M. Che, *Chem. Commun.* **1999**, 1791.

Besides the problematic accessibility of the ligands, the major disadvantage of these systems is the rapid oxidation of the catalyst itself, although this can be limited by introducing chloro substituents at the *ortho* positions of the porphyrin moiety.[30]

Several oxidation systems containing iron ions have been described as mimics for non-heme mono- and dioxygenases. Although mononuclear iron derivatives have been reported as models for methane monooxygenase and other proteins,[31] binuclear iron complexes have been more widely investigated and are commonly employed as MMO active-site models.[32]

In the course of developing functional models for non-heme iron oxygenases, Que and co-workers discovered a family of non-heme iron catalysts, represented by $[Fe(II)(tpa)(CH_3CN)_2]^{2+}$ (tpa = tris(2-pyridylmethyl)amine, **11**,

Figure **1**), that are capable of stereospecific hydrocarbon oxidations using H_2O_2 as oxidant.[33] The oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane afforded tertiary alcohol products with >99% retention of stereochemistry and, furthermore, the system allowed oxygen insertion into olefins, affording only epoxide products with complete retention of stereochemistry.



Scheme 5. Hydroxylation of *cis*-1,2,-dimethylcyclohexane (**8**) by Que and co-workers.[33]

Non-heme diiron complexes, involving pyridine-based ligands (Figure **1**) and alkylhydroperoxides, have arisen as a brand new class of catalysts for oxidation in organic solvents and have been intensively studied by various groups.[32]

[30] P. S. Traylor, D. Dolphin, T. G. Traylor, *J. Chem. Soc., Chem. Commun.* **1984**, 279.
[31] For example: a) A. L. Nivorozhkin, J. -J. Girerd, *Angew. Chem. Int. Ed.* **1996**, *35*, 609; *Angew. Chem.* **1996**, *108*, 665; b) M. M. Abu-Omar, A. Loaiza, N. Hontzeas, *Chem. Rev.* **2005**, *105*, 2227.
[32] a) M. Fontecave, S. Menage, C. Duboc-Toia, *Coord. Chem. Rev.* **1998**, *178-180*, 1555; b) S. V. Kryatov, E. V. Rybak-Akimova, S. Schindler, *Chem. Rev.* **2005**, *105*, 2175.
[33] a) C. Kim, K. Chen, J. Kim, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 5964; b) K. Chen, L. Que, Jr., *J. Am. Chem. Soc.* **2001**, *123*, 6327.

Among the active systems reported so far, the $Fe_2(tpa)_2$/ROOH studied by Que and co-workers,[34] the Fe_2O(tmima)/ROOH investigated by Fish and co-workers[35] and more recently the Fe_2(hexpy)/*m*-CPBA[36] proposed by Kodera and co-workers are the most efficient. The major drawback of these systems is the relative instability of the catalysts, which are slowly inactivated during the reaction.[37] Moreover, until recently, hydrogen peroxide as oxidant gave poor results, because of the strong ability of non-heme iron complexes to catalyse the dismutation of H_2O_2.

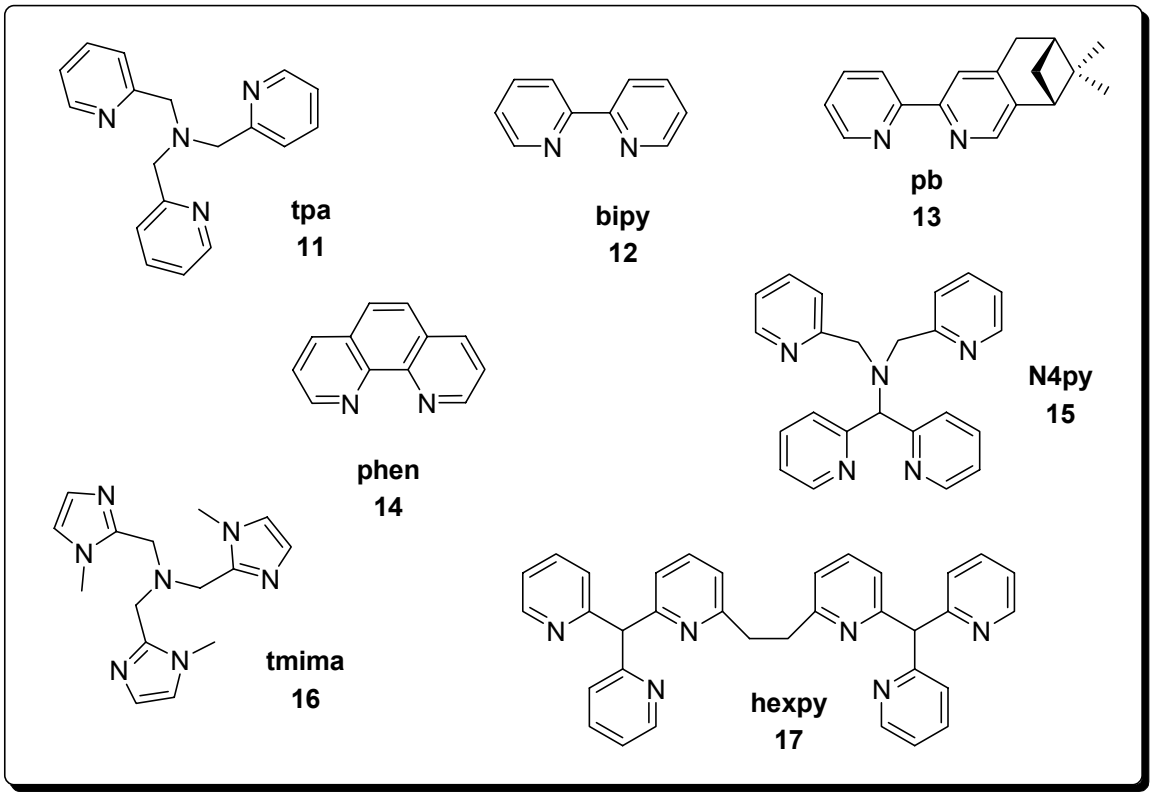


Figure 1. Some ligands forming non-heme mono- and binuclear iron complexes.

The very first complexes with significant, even though limited, catalytic activities for H_2O_2-dependent oxidation of alkanes were the bipyridine- and phenanthroline-based iron

[34] See for example: a) R. A. Leising, J. Kim, M. A. Perez, L. Que, Jr, *J. Am. Chem. Soc.* **1993**, *115*, 9524; b) J. Kim, C. Kim, R. G. Harrison, E. C. Wilkinson, L. Que, Jr, *J. Mol. Catal.* **1997**, *117*, 83; c) A. Bassan, M. R. A. Blomberg, Per E. M. Siegbahn, L. Que, Jr, *Angew. Chem. Int. Ed.* **2005**, *44*, 2939; *Angew. Chem.* **2005**, *117*, 2999.

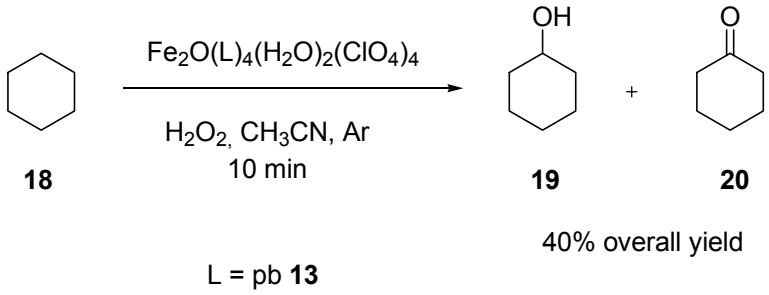
[35] a) R. H. Fish, M. S. Konings, K. J. Oberhausen, R. H. Fong, W. M. Yu, G. Christou, J. B. Vincent, D. K. Coggin, R. M. Buchanan, *Inorg. Chem.* **1991**, *30*, 3002; b) R. M. Buchanan, S. Chen, J. F. Richardson, M. Bressan, L. Forti, A. Morvillo, R. H. Fish, *Inorg. Chem.* **1994**, *33*, 3208.

[36] M. Kodera, H. Shimakoshi, K. Kano, *J. Chem. Soc., Chem. Commun.* **1996**, 1737.

[37] J.-M. Vincent, S. Menage, C. Lambeaux, M. Fontecave, *Tetrahedron Lett.* **1994**, *35*, 6287.

complexes reported by Fontecave and co-workers.[38] Large turnover numbers could be obtained but rather low yields based on the oxidant (about 10% for cyclohexane). Later on, the same research group described the synthesis of chiral bipyridine **13**, and its application as a ligand in the Fe-catalysed oxidation of alkanes and sulfides (Scheme **6**).[39]

The moderate enantiomeric excess (40%) obtained in the case of *p*-bromophenylmethylsulfide provided the first direct evidence that oxidation reactions catalysed by non-heme iron do not proceed exclusively through radical chain autooxidation. Under certain conditions, metal-based pathways may be involved, thus allowing some control of the stereoselectivity of the reactions. Similar conclusions were proposed earlier by Groves and Van der Puy,[40] and more recently by Que and co-workers.[41]



Scheme 6. Oxidation of cyclohexane with Fontecave's system.

Shul'pin and co-workers[42] devoted several studies to the CH activation of unreactive substates and described various systems involving, among the others, hydrogen peroxide and oxygen as oxidising agents and several transition metals complexes as catalysts. For example, they recently reported the use of 2,2'-bipyridine **12** as co-catalyst in the $FeCl_3$-catalysed oxidation of alkanes with hydrogen peroxide in acetonitrile solution at 60 °C.[43] The presence of the additive dramatically accelerated the oxidative process and TONs up to 400 after 1 hour were obtained. The authors supposed that bipy **12** facilitates proton abstraction from a

[38] S. Menage, J.-M. Vincent, C. Lambeaux, M. Fontecave, *J. Chem. Soc., Dalton Trans.* **1994**, 2081.
[39] C. Duboc-Toia, S. Menage, C. Lambeaux, M. Fontecave, *Tetrahedron Lett.* **1997**, *38*, 3727.
[40] J. T. Groves, M. Van der Puy, *J. Am. Chem. Soc.* **1976**, *98*, 5290.
[41] a) J. Kim, R. G. Harrison, C. Kim, L. Que, Jr, *J. Am. Chem. Soc.* **1996**, *118*, 4373; b) C. Kim, K. Chen, J. Kim, L. Que, Jr, *J. Am. Chem. Soc.* **1997**, *119*, 5964.
[42] See for reviews and examples: a) G. B. Shul'pin, in: *Transition Metals for Organic Synthesis*, vol. 2 (Eds. M. Beller, C. Bolm), Wiley-VCH, Weinheim/New York, **2004**, 215; b) G. B. Shul'pin, *C. R. Chim.* **2003**, *6*, 163; c) A. E. Shilov, G. B. Shul'pin, *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*, Chapter X, Kluwer Academic, Dordrecht/Boston/London, **2000**; see also Chapter 4.1.3.2 and references therein.
[43] G. B. Shul'pin, C. C. Golfeto, G. Süss-Fink, L. S. Shul'pina, D. Mandelli, *Tetrahedron Lett.* **2005**, *46*, 4563.

H_2O_2 molecule coordinates to the iron ion and the hydroxyl radicals then attack the alkane to give, as major product, the corresponding alkyl hydroperoxide.

Barton and co-workers[44] developed a family of systems for the oxidation and functionalisation of hydrocarbons that do not require a ligand. The Gif systems[45] (from Gif-sur-Yvette, France, where they were first invented) consist of transition metal complexes, mainly of iron, and a co-reductant, which uses air or oxygen as oxidant (Table **1**). The reaction is carried out in the presence of an organic acid and a nitrogenous base, such as pyridine, which is essential. All Gif systems share an unusual selectivity for secondary CH bonds, which are more readily attacked than either primary or tertiary CH bonds. The ratio of secondary to tertiary selectivity is *ca*. 1:1, which is much higher than expected for radical or oxometal oxidations.[46] The major products of the reaction are ketones, which appear to be formed directly, and the presence of easily oxidisable compounds, such as sulfides, does not suppress alkane oxidation. Despite the numerous works devoted to Gif systems, their mechanism of action is not yet completely clear.

Table 1. Gif systems: an overview.

System	Catalyst	Electron source	Oxidant
Gif^{III}	Fe(II)	Fe (metal)	O_2
Gif^{IV}	Fe(II)	Zn (metal)	O_2
GO (Gif-Orsay)	Fe(II)	cathode	O_2
$GoAgg^{I}$	Fe(II)	-	K_2O/Ar
$GoAgg^{II}$	Fe(III)	-	H_2O_2
$GoAgg^{III}$	Fe(III)/picolinic acid	-	H_2O_2
GoChAgg	Cu(II)	-	H_2O_2
Cu^0/O_2	Cu(I) ?	Cu(0)	O_2

Related to the oxidation by Gif-type systems is the protocol that uses $Fe(pic)_2/H_2O_2$ (or *t*-BuOOH) in pyridine-acetic acid for the oxidation of organic substrates developed by Sawyer, Sobkowiak and co-workers.[47] It has been proposed to mediate "oxygenated Fenton" chemistry and the major products formed from cycloalkanes are ketones. Although the

[44] D. H. R. Barton, M. J. Gastiger, W. B. Motherwell, *J. Chem. Soc., Chem. Commun.* **1983**, 41.
[45] Reviews: a) D. H. R. Barton, *Chem. Soc. Rev.* **1996**, *31*, 10313; b) D. H. R. Barton, *Tetrahedron* **1998**, *54*, 5805; c) P. Stavropoulos, R. Çelenligil-Çetin, A. E. Tapper, *Acc. Chem. Res.* **2001**, *34*, 745.
[46] D. H. R. Barton, A. K. Gokturk, J. W. Morzycki, W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1* **1985**, 583.
[47] D. T. Sawyer, A. Sobkowiak, T. Matsushita, *Acc. Chem. Res.* **1996**, *29*, 409.

presumed active oxidants are differently formulated, Gif and Sawyer systems have been interpreted to perform oxygenation via pathways that, with a few exceptions, do not involve oxygen- or carbon-centered radicals.

2.2 Goal of the Study

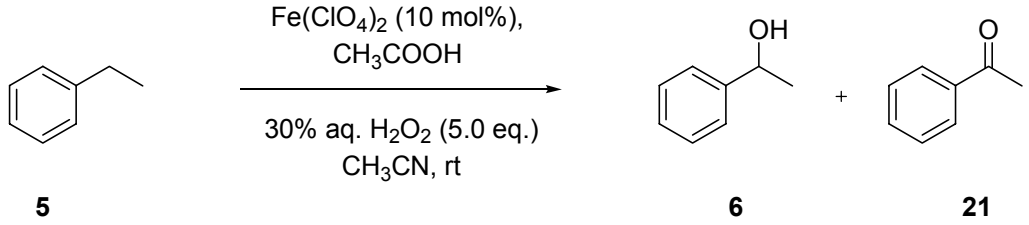
Inspired by the works of Barton,[45] Fish[35] and Sobkowiak[47] on Fe-mediated oxidation of alkanes and by the studies of Shul'pin[42] on transition metals-catalysed CH activation of saturated hydrocarbons, we aimed to develop a mild and efficient method for a truly iron-catalysed oxidation of unreactive substrate employing hydrogen peroxide as terminal oxidant.

2.3 Results and Discussion

The efficient oxidation of saturated hydrocarbons under mild, safe and clean conditions still represents a paramount reaction in organic chemistry. During the last decades several reports have presented iron-induced activation of hydrogen peroxide for the catalytic and selective oxygenation of hydrocarbon substrates. Although scientifically valuable and fundamental, they have been more focused on elucidating mechanistic and kinetic details rather than on using the catalysts for synthetic purpose. In this contest, the development of a simple and green method for iron-catalysed oxidation of poorly reactive substrates was undertaken.

2.3.1 Preliminary Results and Catalyst Optimisation

At the outset, the reaction conditions involved ethylbenzene as test substrate, a catalytic amount of iron(II) perchlorate hexahydrate and an excess of 30% aqueous hydrogen peroxide in acetonitrile at room temperature. No particular precaution was taken over an inert atmosphere (Equation **1**).



Equation 1.

The substrate was easily converted (65%) in 5 hours and phenylethanol and acetophenone were detected as major products. Upon addition of hydrogen peroxide, gas evolution, coming from the decomposition of the oxidant in water and oxygen, was noticed, accompanied by increasing temperature. The latter aspect is undesired when perchlorates and oxidants are involved. The reaction was repeated at 0 °C, but after 5 hours only 33% of the substrate was converted. Warming the reaction to room temperature only slightly increased the conversion and, after 24 hours, 44% of the substrate was transformed. Still concerned by the safety issue, an alternative source of iron was searched for. Various iron complexes, all easily available in bulk at reasonable, or even low, prices were screened and the results are reported in Table **2**.

Table 2. Fe-catalysed oxidation of ethylbenzene **5** with various iron salts.

Entry	Catalyst	Conversion[a][%]	Selectivity[a,b][%]	Ketone: Alcohol[a]	TON
1	$FeCl_3$	–	–	–	–
2	$Fe(OAc)_2$	–	–	–	–
3	$Fe(acac)_2$	–	–	–	–
4	$FeSO_4$	–	–	–	–
5	FeC_2O_4	–	–	–	–
6	$FeBr_2$	20	15	88:12	0.3
7	$FeCl_2$ $4H_2O$	60	15	90:10	0.9
8	$Fe(NO_3)_3 \cdot 9H_2O$	63	50	83:17	3.2
9	$Fe(BF_4)_2$	60	59	89:11	3.5
10	$Fe(ClO_4)_2 \cdot 6H_2O$	65	64	90:10	4.2

Reaction conditions: ethylbenzene (1 mmol), iron salt (0.1 mmol), aq. H_2O_2 (30%, 5 mmol; added within 4 h) in CH_3CN (5 mL) at rt for 5 h. [a] Determined by GC/MS and GC analysis using nitrobenzene as internal standard; [b] Selectivity = [(mmol acetophenone + mmol 1-phenyethanol)/mmol substrate converted].

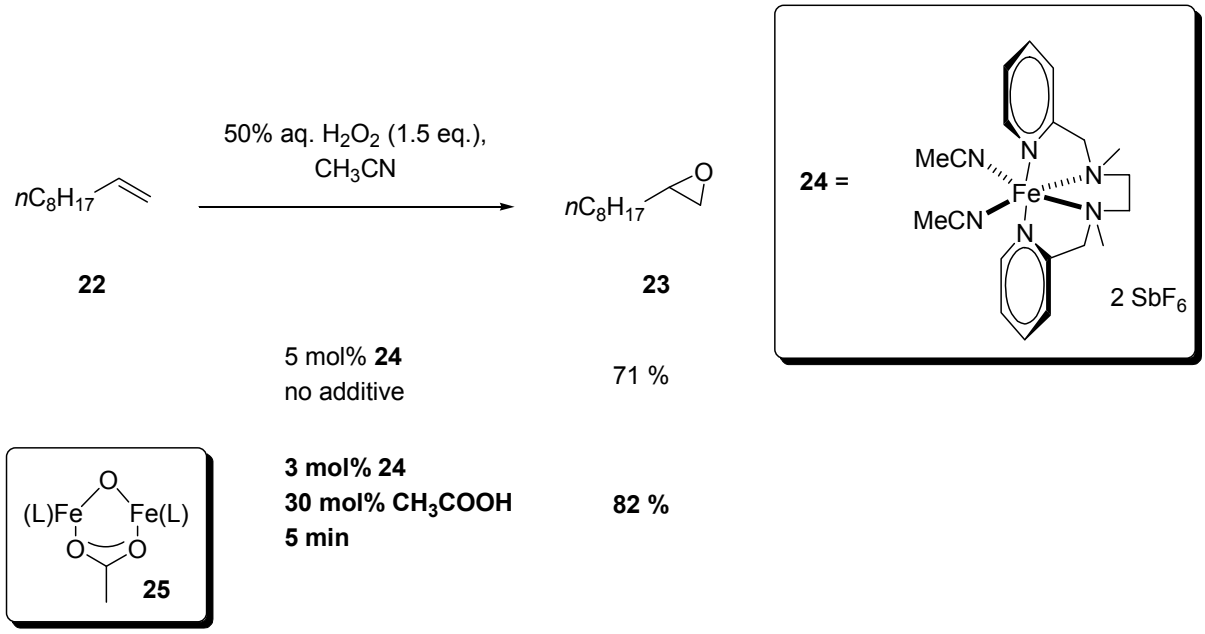
The selectivity of the oxidation of the benzylic position is reported as overall amount of acetophenone and 1-phenylethanol over the converted substrate.

Iron(II) acetate, iron(II) acetylacetonate, iron(III) chloride, iron(II) oxalate, iron(II) sulfate (Table **2**, entries 3-7) showed poor initial solubility in acetonitrile and, upon addition of the oxidant, led to rapid decomposition of hydrogen peroxide, resulting in no conversion of the starting material. Iron(II) bromide (Table **2**, entry 1), though forming a clear orange reaction mixture, did not give a conversion greater than 20%. Conversion using iron(II) chloride seemed promising (60%), but its selectivity toward benzylic oxidation was inadequate (15%, Table **2**, entry 2). Finally, iron(III) nitrate, iron(II) tetrafluoroborate and iron(II) perchlorate (Table **2**, entries 8-10) converted more than 60% of ethylbenzene into oxidised products and no significant decomposition of hydrogen peroxide through evolution of oxygen was observed. Moreover, the latter iron salts showed a pronounced selectivity for oxidation of the benzylic position (≥50%), with acetophenone being the major product. Longer reaction time (24 hours), while slightly improving the overall conversion, had negative effect on the

selectivity towards benzylic oxidation and other products, derived from the oxidation of the benzene ring, were detected.

2.3.2 Optimisation of the Additive

Many homogeneous oxidation systems are greatly enhanced by the addition of molecules with coordinating capability, favourably changing catalytic efficiencies, selectivities and reactivities.[48] These additives are often tertiary heterocyclic amines or carboxylates. For example, the effect of pyridine or its substituted derivatives on Gif systems is well known. In their absence no functionalisation of saturated hydrocarbons was observed anymore.[49] In the field of iron-catalysed oxidations, carboxylic acids proved to be particularly effective,[50] as shown by Jacobsen in the epoxidation of terminal aliphatic alkenes catalysed by the iron complex **24** (Scheme **7**).[50a]



Scheme 7. Enhanced epoxidation of terminal olefins by Jacobsen[50a]

The addition of acetic acid to the system permitted the reduction of the catalyst loading, with no change in selectivity for the epoxide formation, and shortened the reaction time by up to 5

[48] For a list of additives used in metal-catalysed epoxidation with hydrogen peroxide, see: a) B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, *103*, 2458; for a general review on additive effects in catalysis, see: b) E. M. Vogl, H. Gröger, M. Shibasaki, *Angew. Chem. Int. Ed.* **1999**, *38*, 1570; *Angew. Chem.* **1999**, *111*, 1672.
[49] D. H. R. Barton, T. Li, *Tetrahedron Lett.* **1998**, *54*, 1735 and references therein.
[50] a) M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194; b) J. Legros, C. Bolm, *Angew. Chem. Int. Ed.* **2004**, *43*, 4225; *Angew. Chem.* **2004**, *116*, 4321.

minutes. The dinuclear complex **25** formed *in situ* has been suggested as a possible intermediate.

In the system described here, simple carboxylic acids (20 mol%) were added to the reaction medium prior to addition of the oxidant. In Table **3** and Graph **1** the impact of this reaction modification for the most active iron salts is shown.

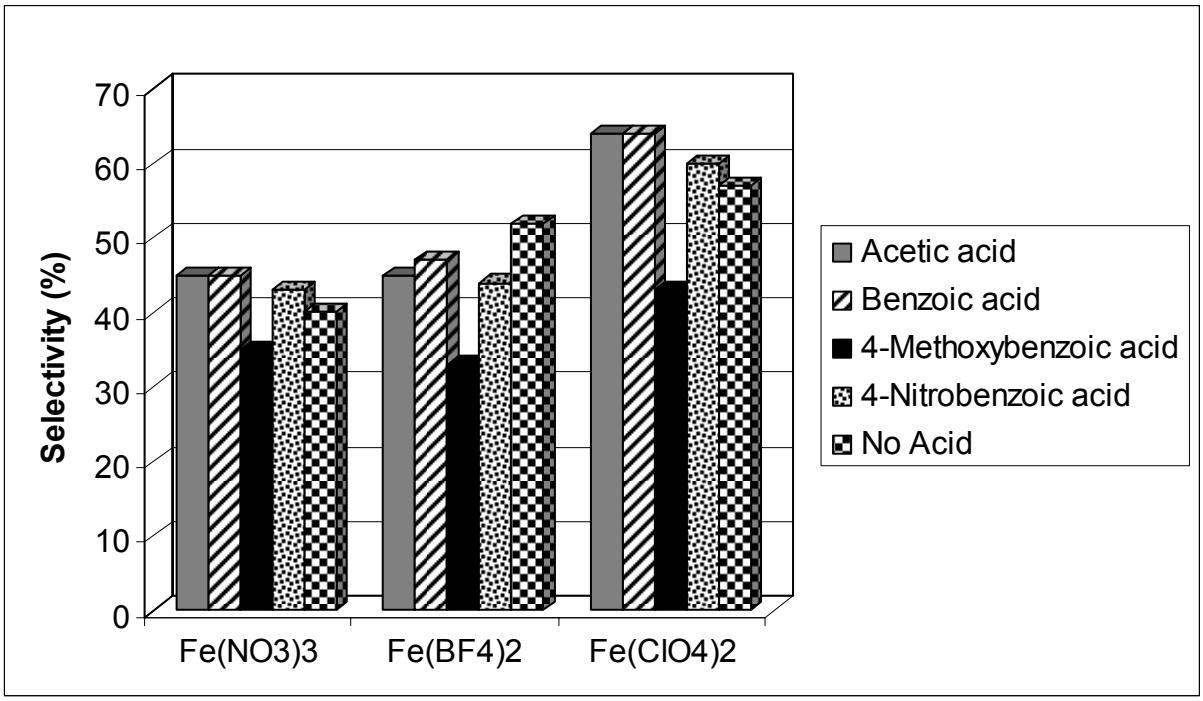
Table 3. Fe-catalysed oxidation of ethylbenzene **5** with different carboxylic acids as additive.

Entry	Catalyst	Carboxylic acid	Selectivity (%)[a,b]
1	$Fe(NO_3)_3 \cdot 9H_2O$	Acetic acid	45
2		Benzoic acid	45
3		4-Methoxybenzoic acid	35
4		4-Nitrobenzoic acid	43
5	$Fe(BF_4)_2$	Acetic acid	45
6		Benzoic acid	47
7		4-Methoxybenzoic acid	33
8		4-Nitrobenzoic acid	44
9	$Fe(ClO_4)_2 \cdot 6H_2O$	Acetic acid	64
10		Benzoic acid	64
11		4-Methoxybenzoic acid	43
12		4-Nitrobenzoic acid	60

Reaction conditions: ethylbenzene (1 mmol), iron complex (0.1 mmol), carboxylic acid (0.2 mmol), aq. H_2O_2 (30%, 5 mmol; added within 4 h) in CH_3CN (5 mL) at rt for 5 h. [a] Conversion as in Table 1 (60-65%); [b] GC/MS and GC analysis using nitrobenzene as internal standard. [c] Selectivity = [(mmol acetophenone + mmol 1-phenyethanol)/mmol substrate converted].

The reaction became very well behaved and the undesiderable exothermicity was no longer present. Moreover, without any decrease in conversion (>60%), the only detected benzylic oxidation product was acetophenone. This increased selectivity could be ascribed to a more rapid transformation of the intermediate alcohol into the ketone or to a different oxidation mechanism involved. Acetic acid, benzoic acid and 4-nitrobenzoic acid (Graph **1**, grey, striped and pointed bars) proved to be the most effective additives for increasing the selectivity towards ketone formation, in combination with iron(II) perchlorate and iron(III) nitrate (>60% with $Fe(ClO_4)_2$). 4-Methoxybenzoic acid, on the other hand, showed a

detrimental effect (only 43% with $Fe(ClO_4)_2$). Surprisingly, the $Fe(BF_4)_2$-catalysed system exhibited better selectivity in the absence of an additive.



Graph 1. Additive effect on the selectivity of the oxidation of ethylbenzene to acetophenone.

A closer look at the pK_a values of the chosen carboxylic acids reveals that the additive effect did not correlate with the strength of the acid and did not seem to be a simple consequence of a change in acidity of the reaction medium. Stronger 4-nitrobenzoic acid (pK_a=3.4) showed comparable results to acetic acid (pK_a=4.8) and benzoic acid (pK_a=4.2), while the weaker 4-methoxybenzoic acid (pK_a=4.5) compromised the oxidation reaction. Moreover, the addition of trifluoroacetic acid (pK_a=0.5) completely inhibited the reaction. The observed differences in selectivity and reactivity could then derived from the binding properties of each carboxylic acid. The *in situ* formation of species stabilised by carboxylate bridges, such as those proposed by Jacobsen, is also well known for simple iron salts. Barton and co-workers, for example, isolated a trinuclear organoiron carboxylate cluster formed by treating iron powder with acetic acid under oxygen in aqueous pyridine.[51] The lack of activity demonstrated by the system in the presence of trifluoroacetic acid and the absence of correlation between the strength of the carboxylic acid and the additive effect also indicated that a peracid

[51] D. H. R. Barton, J. Boivin, M. Gastiger, J. Morzycki, R. S. Hay-Motherwell, W. B. Motherwell, N. Ozbalik, K. M. Schwartzentruber, *J. Chem. Soc., Perkin Trans. I* **1986**, 947.

intermediate couldn't be considered the real oxidative species. Indeed, trifluoroperoxyacetic acid formed *in situ* from CF_3COOH and hydrogen peroxide has been reported to give trifluoroacetates from alkanes.[52] Moreover, peracids, such as 4-nitroperoxybenzoic acid, are known to react with alkanes to give hydroxylated products[53] and an electrophilic mechanism has been proposed for them, since reaction rate increases with increasing acidity of the peracid. Gif reagents have been represented by Fe(III)/H_2O_2 or Fe(III)/*t*-BuOOH combinations, frequently assisted by the presence of 2-picolinic acid (pK_a=1.01) to enhance the rate of catalytic oxygenations.[54] Addition of this acid to our system suppressed the conversion of ethylbenzene into acetophenone or 1-phenylethanol, implying that here a different mechanism is probably involved.

After the optimisation of the catalyst and of the additive, the system consisting of $Fe(ClO_4)_2$, aqueous hydrogen peroxide and acetic acid, or benzoic acid, as additive proved to be the most effective for the efficient and selective conversion of ethylbenzene into acetophenone.

2.3.3 Optimisation of the Catalyst Loading

Next, the optimisation of the catalyst loading was undertaken. The results obtained with decreasing amounts of iron(II) perchlorate are reported in Table **4**.

Table 4. Oxidation of ethylbenzene **5** with different iron(II)perchlorate concentrations

Entry	Catalyst loading (mol%)	Conversion (%)[a]	Selectivity[a,b]
1	10	65	64
2	5	30	63
3	1	< 5	-

Reaction conditions: ethylbenzene (1 mmol), iron perchlorate (mol%), carboxylic acid (0.2 mmol), aq. H_2O_2 (30%, 5 mmol; added within 4 h) in CH_3CN (5 mL) at rt for 5 h. [a] Conversion determined by GC analysis using nitrobenzene as internal standard; [b] Selectivity = [(mmol acetophenone + mmol 1-phenyethanol)/mmol substrate converted].

[52] a) N. C. Deno, D. G. Pohl, *J. Am. Chem. Soc.* **1974**, *96*, 6680; b) N. C. Deno, L. A. Messer, *J. Chem. Soc., Chem. Commun.* **1976**, 1051.
[53] a) W. Müller, H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 407; *Angew. Chem.* **1979**, *91*, 438; b) G. A. Hamilton, J. R. Giacin, T. M. Hellmann, M. E. Snook, J. W. Weller, *Ann. N. Y. Acad. Sci.* **1973**, *212*, 4.
[54] S. Kiani, A. Tapper, R. J. Staples, P. Stavropoulos, *J. Am. Chem. Soc.* **2000**, *122*, 7503.

Lowering the catalyst loading from 10 to 5 mol% had a clear negative effect on the conversion (30%, Table **4**, entry 2), although the selectivity remained unchanged (Table **4**, entry 2).

2.3.4 Optimisation of the Solvent System

As suggested by previous reports,[40,55] acetonitrile was initially chosen as solvent. Solvents other than acetonitrile were also examined and the results obtained are reported in Table **5**. When the reaction was performed in ethyl acetate, dichloromethane or methanol, decomposition of the oxidant occured and no oxidation of the substrate was observed (Table **5**, entries 1-3).

Table 5. Fe-catalysed oxidation of ethylbenzene in different solvents

Entry	Solvent system	Conversion[a]
1	Dichloromethane	-
2	Ethyl acetate	< 5%
3	Methanol	-
4	Benzotrifluoride	-
5	Benzotrifluoride/Acetonitrile (10 mol%)	-
6	Benzotrifluoride/Acetonitrile (20 mol%)	-
7	Benzotrifluoride/Acetonitrile (50 mol%)	-

Reaction conditions: ethylbenzene (1 mmol), iron complex (0.1 mmol), carboxylic acid (0.2 mmol), aq. H_2O_2 (30%, 5 mmol; added within 4 h) in the solvent system (5 mL) at rt for 5 h. [a] Conversion determined by GC analysis using nitrobenzene as internal standard.

Benzotrifluoride (BTF), or trifluorotoluene, is a clear, free-flowing liquid with a boiling point of 102 °C. It is a robust compound with a relatively low toxicity and price.[56] It has been employed as solvent in various oxidative procedures, such as Swern oxidation, Dess-Martin oxidation and Se-catalysed oxidation with hydrogen peroxide.[57] Unfortunately, benzotrifluoride was an inapplicable solvent for the $Fe(ClO_4)_2/CH_3COOH/H_2O_2$ system.

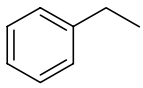
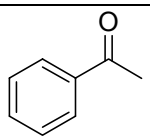
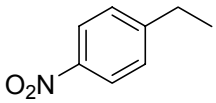
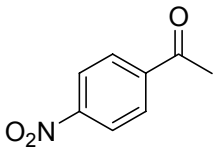
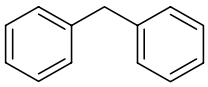
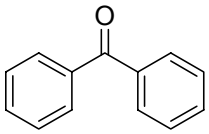
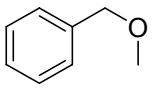
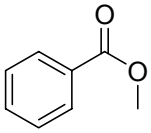
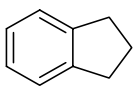
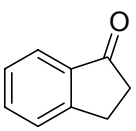
[55] a) R. H. Fish, M. S. Konings, K. J. Oberhausen, R. H. Fong, W. M. Yu, G. Christou, J. B. Vincent, D. K. Coggin, R. M. Buchanan, *Inorg. Chem.* **1991**, *30*, 3002; b) D. H. R. Barton, F. Launay, *Tetrahedron* **1998**, *54*, 12699.
[56] M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood: New York, **1992**.
[57] A. Ogawa, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 450.

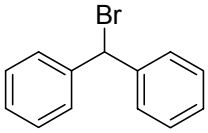
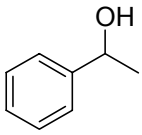
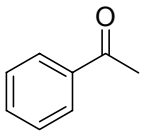
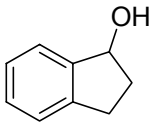
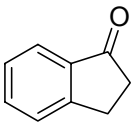
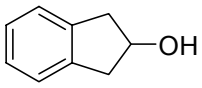
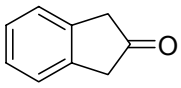
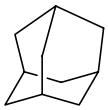
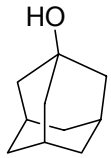
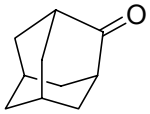
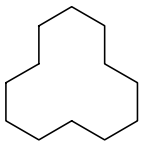
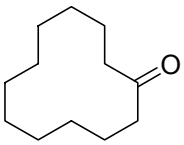
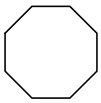
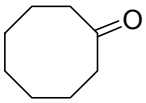
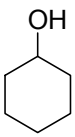
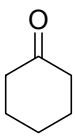
Iron(II) perchlorate is poorly soluble in this medium and, upon addition of hydrogen peroxide, it reacted violently with the oxidant. Catalytic amounts of acetonitrile partially stabilise the two-phase system, but no conversion of ethylbenzene was observed in any case (Table **5**, entries 4-7).

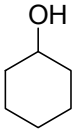
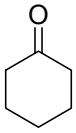
2.3.5 Substrate Scope

Having established the optimal conditions for the oxidation of ethylbenzene, our attention was focused on the substrate scope. Various alkylarenes, cycloalkanes and alcohols were considered and the results obtained are reported in Table **6**.

Table 6. Iron-catalysed oxidation of saturated hydrocarbons.

Entry	Substrate	Major Product	Yield (%)	Conv.[a] (%)	Selectivity[a,b] (%)
1	 **5**	 **21**	50	67	75
2	 **26**	 **27**	48[a]	65	74
3	 **28**	 **29**	35[a]	48	73
4	 **30**	 **31**	22	n.d.	n.d.
5	 **32**	 **33**	46	80	58

6	 **34**	–	–	–	–
7	 **6**	 **21**	92[a]	100	92
8	 **35**	 **36**	57[a]	100	57
9	 **37**	 **38**	15[a]	57	26
10	 **39**	 **40**	10[a]	24	40
		 **41**	13[a]		52
11	 **42**	 **43**	5[a]	10	50
12	 **44**	 **45**	44[a]	55	80
13	 **19**	 **20**	17[a]	20	85

14	 **18**	 **19**	20[c]	n.d.	n.d.
		 **20**	20[c]	n.d.	n.d.

Reaction conditions: substrate (1 mmol), $Fe(ClO_4)_2$ (0.1 mmol), acetic acid (0.2 mmol), aq. H_2O_2 (30%, 5 mmol; added within 4 h) in CH_3CN (5 mL) at rt for 5 h. [a] GC/MS and GC analysis using nitrobenzene as internal standard; [b] Selectivity = [(mmol acetophenone + mmol 1-phenyethanol)/mmol substrate converted]; [c] Determined by ^{1}H-NMR analysis using benzene as internal standard.

The oxidation of ethylbenzene (**5**) was scaled up to 3 mmol and acetophenone was isolated in 50% yield (Table **6**, entry 1), confirming this protocol as suitable for preparative procedures. 4-Nitroethylbenzene (**26**) was smoothly converted into corresponding ketone **27** with selectivity and conversion comparable to those observed for ethylbenzene (Table **6**, entry 2). Diphenylmethane (**28**) gave benzophenone (**29**) with a rather remarkable selectivity (73%, Table **6**, entry 3) although the conversion was only moderate (48%). Indane (**32**) gave 1-indanone (**33**) as major product, which was isolated in 46% yield (Table **6**, entry 5) and benzoic acid methyl ester (**31**) was obtained from benzylmethylether **30** in 22% yield (Table **6**, entry 4). In light of these last results, the introduction of a substituent in β-position seems to deactivate the benzylic position, this effect being more remarkable in the case of electron-withdrawing groups, such as methoxy group.

Bromodiphenylmethane **34** was chosen as substrate in an attempt to stop the oxidation at the alcohol stage, but, under optimised conditions, no benzylic oxidation products were detected by NMR analysis (Table **6**, entry 6).

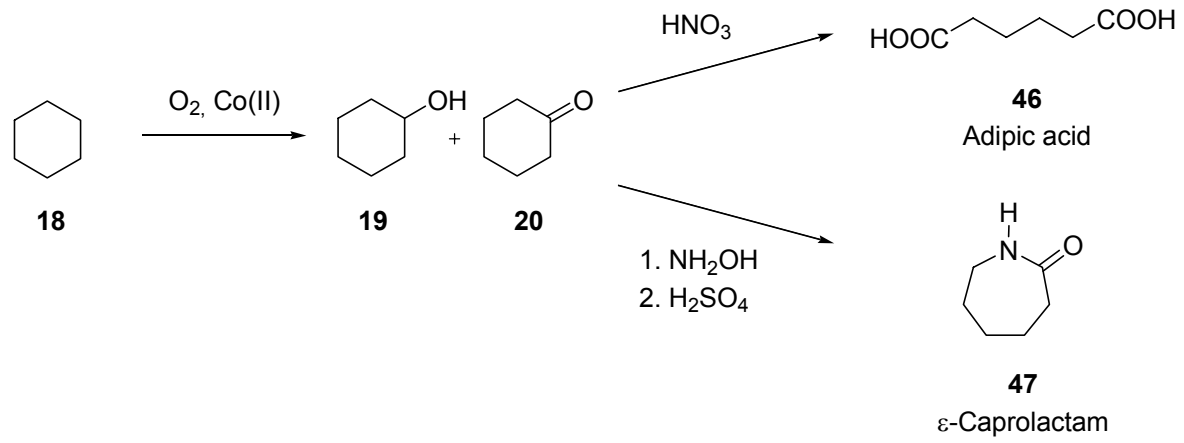
Benzylic alcohol, such as 1-phenylethanol (**6**) and 1-indanol (**35**) were completely converted in five hours, giving as major products the corresponding ketones in 92% and 57% yield, respectively. Non-benzylic alcohols, such as 2-indanol (**37**) and cyclohexanol (**19**), demonstrated a lower reactivity, although the selectivity for cyclohexanone was rather remarkable (80%, Table **6**, entry 13). Recently, a solvent-free $FeBr_3$-catalysed oxidation of alcohols by hydrogen peroxide has been described.[58] The reaction occurred at room

[58] S. E. Martin, A. Garrone, *Tetrahedron Lett.* **2003**, *44*, 549.

temperature and smoothly transformed non-primary alcohols into the corresponding ketones with yield up to 91%.

More challenging oxidations of fully saturated cycloalkanes were also attempted. Cyclododecane (**42**) was dissolved in a 1:1 solvent mixture of CH_3CN/CH_2Cl_2 and although only 10% of starting material was converted, the corresponding ketone **43** was formed with good selectivity (50%, Table **6**, entry 11). Adamantane (**39**) gave adamant-1-ol and adamant-2-one as major products with 40% and 52% selectivity, respectively, and adamant-2-ol as minor product. The prominence of 2-one formation over 2-ol (2-one/2-ol ≈ 10) is probably due to overoxidation of secondary alcohol to the corresponding ketone. Cyclooctane (**44**) was smoothly oxidised, giving a ratio of ketone to alcohols of 8.8 with cyclooctanone (**45**) as the major product (44% yield, Table **6**, entry 12). Other compounds were detected by GC/MS analysis and their masses suggest the formation of diketones.

Finally, the less reactive cyclohexane (**18**) was smoothly converted to give an equimolar mixture of cyclohexanol (**19**) and cyclohexanone (**20**) with overall yield of 40%. The oxidation of cyclohexane under mild conditions is of great industrial interest for the production of adipic acid **46** and ε-caprolactam **47** and various attempts have been made to substitute the low-yielding, not benign classical process (Scheme **8**). Hydrogen peroxide would be the preferred oxidant, but, unfortunately, the numerous systems reported so far still give low conversions and turnovers, thus making its industrial use difficult. In this contest, the results obtained in the oxidation of cyclohexane with hydrogen peroxide are comparable to the best ones reported so far.



Scheme 8. Synthesis of adipic acid and ε-caprolactam from cyclohexane.

On the basis of the product profiles and reaction efficiencies, it is then possible to make some observations about the features of this system and to compare them with those belonging to other reported protocols. For example, the overall selectivity for the activation of tertiary versus secondary positions on a per hydrogen basis (3°/2°) for substrate such as adamantane is an important parameter to evaluate which oxysiding species are involved in the reaction. In Table **7** are reported the 3°/2° values for some known systems.

Table 7. Radical and not-radical systems: overview on 3°/2° selectivity.

Entry	System	3°/2°
1	$HO^{\bullet}$-mediated oxidation of alkanes[59]	≈2-2.5
2	Fe_2O-$(HB(pz)_3)_2(OAc)_2/Zn/O_2$ in CH_2Cl_2/CH_3COOH (400/1)[60]	2.2
3	Gif-type[61]	2.65
4	sMMO (soluble methane monooxygenase)[62]	3
5	$Fe_2O(AcO)_2Cl_2$(2,2'-bipy)$_2/H_2O_2$ in CH_3CN[63]	3.5
6	**$Fe(ClO_4)_2/H_2O_2/CH_3COOH$ in CH_3CN**	**3.67**
7	$Fe(PA)_2/H_2O_2$ (1:16) in pyridine/CH_3COOH (2:1)[64]	4.0
8	$[FeCl_2(tpa)](ClO_4)$/*t*-BuOOH in CH_3CN/C_6H_6 (1:1)[65]	9.5
9	*t*-$BuO^{\bullet}$/Pyridine[66]	10
10	Fe_2O(2,2'-bipy)$_4(H_2O)_2(ClO_4)_4$/*t*-BuOOH in CH_3CN[67]	10
11	P450/PhIO biomimetic (porphyrin-containing)[26]	11-48

Abbreviations used: $HB(pz)_3$ = hydrotris(pyrazolyl)borate; bipy = bipyridine; PA = picolinate; tpa = tris(2-pyridylmethyl)amine.

[59] G. A. Russell, in: *The Chemistry of alkanes and cycloalkanes*, (Eds. S. Patai, Z. Rappoport), Wiley, New York, **1992**, 966.
[60] See for example: N. Kitajima, M. Ito, H. Fukui, Y. Moro-oka, *J. Chem. Soc., Chem. Commun.* **1991**, 102.
[61] B. Singh, J. R. Long, F. Fabrizi de Biani, D. Gatteschi, P. Stavropoulos, *J. Am. Chem. Soc.* **1997**, *119*, 7030.
[62] J. Green, H. Dalton, *J. Biol. Chem.* **1989**, *264*, 17698.
[63] J. B. Vincent, J. C. Huffman, G. Christou, Q. Li, M. A. Nanny, D. N. Hendrickson, R. H. Fong, R. H. Fish, *J. Am. Chem. Soc.* **1988**, *110*, 6898.
[64] C. Sheu, S. A. Richert, P. Cofré, B. Ross Jr., A. Sobkowiak, L. Zhang, D. T. Sawyer, J. R. Kanofsky, *J. Am. Chem. Soc.* **1990**, *112*, 1936.
[65] T. Kojima, R. A. Leising, S. Yan, L. Que Jr., *J. Am. Chem. Soc.* **1993**, *115*, 11328.
[66] D. H. R. Barton, B. Hu, D. K. Taylor, R. U. Rojas Wahl, *J. Chem. Soc., Perkin Trans. 2* **1996**, 1031.
[67] S. Ménage, J. M. Vincent, C. Lambeaux, G. Chottard, A. Grand, M. Fontecave, *Inorg. Chem.* **1993**, *32*, 4766.

Indiscriminate hydroxyl radicals-mediated oxidation of hydrocarbons showed scarce selectivity with a ratio of *ca*. 2 (Table **7**, entry 1). As expected, P450-biomimetic systems (Table **7**, entry 11) presented high values (11-48, depending on the substitution on the porphyrin moiety), thus indicating the involvement of high valent iron-oxo species.[26] Surprisingly, low value (3, Table **7**, entry 3)[62] has been reported for adamantane oxidation by soluble methane monooxygenase (sMMO) isolated from *Methylococcus capsulatus*. On the other side, non-heme mono- and binuclear iron complexes (Table **7**, entries 8 and 10) biomimics of methane monooxygenase, as well as *tert*-butoxy radical in pyridine[66] (Table **7**, entry 19), displayed high values (up to 10), indicating that free $HO^{\bullet}$ are not involved. Interestingly, the average value for Gif-type oxidations[61] is only slightly above that proposed for hydroxyl radicals reactions (Table **7**, entry 3). For the $Fe(ClO_4)_2/H_2O_2/CH_3COOH$ system here reported a value of 3.67 was found (Table **7**, entry 6). It can be argued that the enhanced preference for the activation of the secondary positions of adamantane by comparison to typical radical reactions, although compatible with the action of the most indiscriminate radicals, suggested partial interference of a more selective active oxidant. Moreover, the calculated value is close to those reported by Fish[63] and by Sawyer[64] (Table **7**, entries 5 and 7). In the $Fe_2O(AcO)_2Cl_2(2,2'\text{-bipy})_2/H_2O_2$ system, the authors, considering also the ratio alcohol/ketone obtained for the cyclohexane oxidation (≈ 1), invoked the intermediacy of an alkyl hydroperoxide in the formation of both alcohol and ketone during the alkane functionalisation process. Sawyer and co-workers, on the other hand, although reporting a similar 3°/2° value, obtained cyclohexanone as major product using iron(II)bis(picolinato) as catalyst and proposed as initial step in the catalytic reaction cycle the formation of an HOOH adduct, namely $[(PA)_2FeOFe(PA)_2(HOOH)]$. The latter rapidly forms, with another HOOH, the activated complex, which then transforms methylenic carbons to ketones. This suggestion was also supported from the lower reactivity of cyclohexanol, indicating that the alcohol **19** is not an intermediate for the oxidation of cyclohexane.

The iron(II)-catalysed system here described showed features comparable with those reported for these last two systems: a) 3°/2° value of 3.67; b) ratio cyclohexanol/cyclohexanone *ca*. 1; c) low reactivity of cyclohexanol. This could indicate the co-existence of different pathways in the oxidation of the substrate (i.e. formation of alkyl hydroperoxides and of Fe(OOH) species as intermediates) or could suggest the involvement of a different mechanism.

2.3.6 *In situ* IR Studies

The ReactIR instrument offers the unique possibility to follow *in situ* the consumption and the formation of, respectively, substrates and products during the course of the reaction, thus helping to understand some mechanicistic aspects. Since carbonyl compounds give strong IR-absorption, reactions involving those substances are supposed to be easily followed and, therefore, some experiments on the oxidation of ethylbenzene to acetophenone under the conditions previously described were undertaken.

Changes of the spectrum resulting from interactions between the molecules of the sample and those of the solvent are to be considered, especially in presence of polar substances. Such phenomena may be attributed to dipole interactions, chelate formation (hydrogen-bridge bonds), π-complexes or other types of complexes. Stronger interactions between the sample and solvent may also cause shifting of the band maxima of the dissolved compounds by a few wavenumbers. For this reason, standard solutions (reaction concentration) of all the components of the system (substrate, possible products, catalyst and additive) were prepared and the corresponding spectra were recorded. The reaction was then performed on a 6 mmol scale (30 mL solution), in order to ensure the complete immersion of the IR probe in the reaction mixture. The measurement was started upon the addition of hydrogen peroxide (1 eq.) and in Figure **2** is shown the reaction profile of the first forty minutes, with scansion every minute.

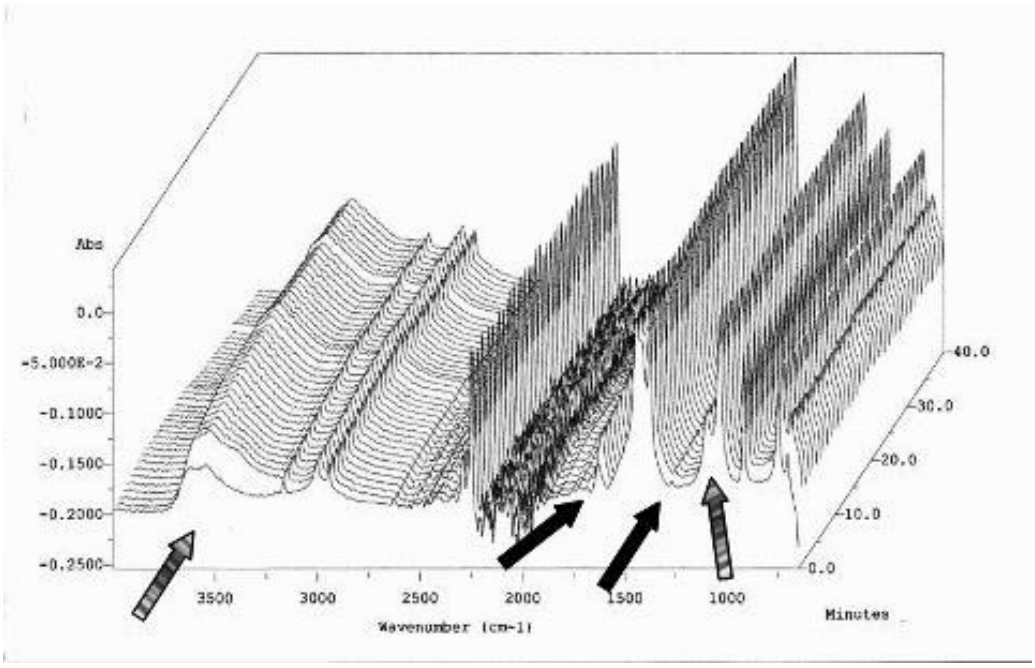


Figure 2. Reaction profile of the Fe-catalysed oxidation of ethylbenzene.

In Figure **3** are reported, for comparison, the spectrum of pure acetonitrile and one taken from the reaction profile (t = 20 min).

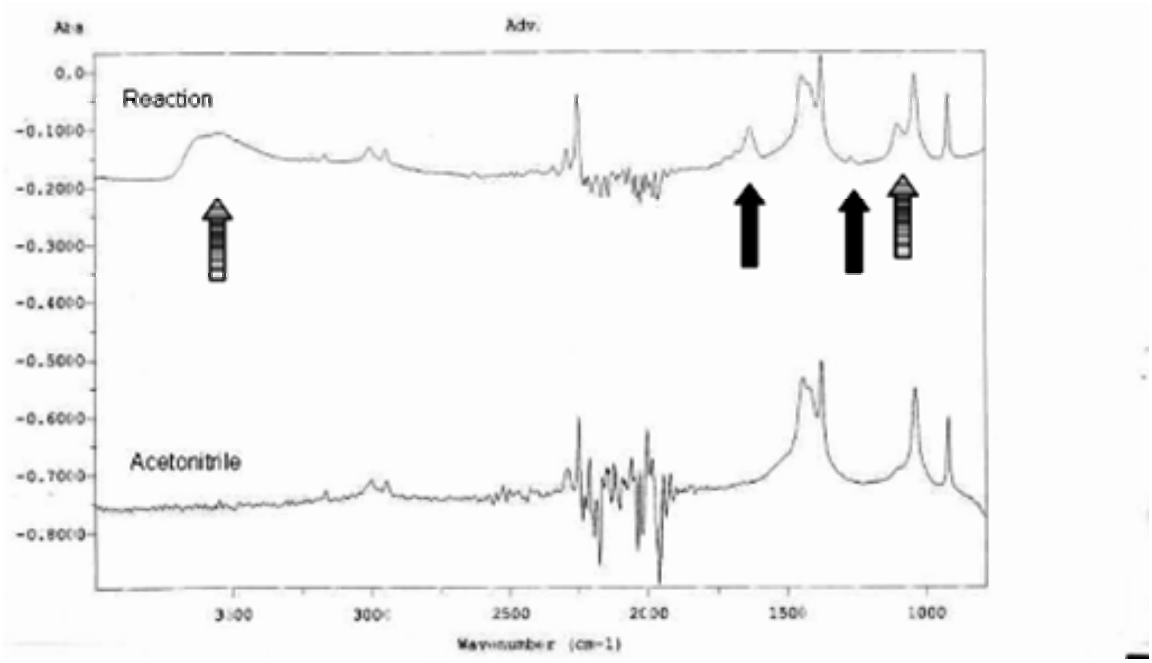
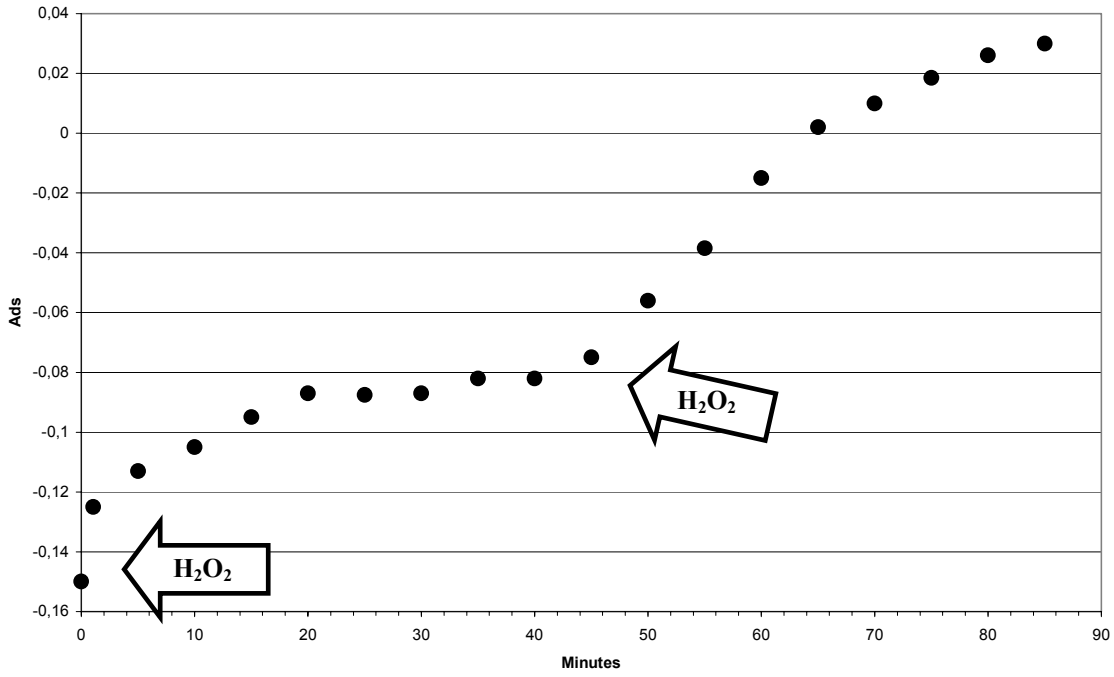


Figure 3. Pure solvent and reaction mixture spectra: comparison.

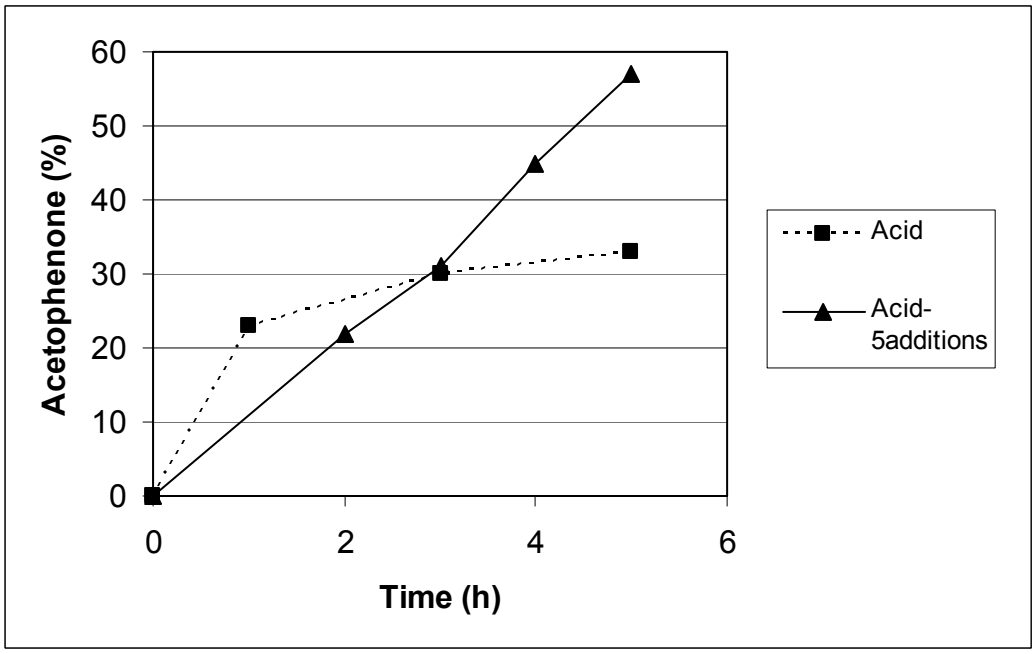
The black arrows indicate two characteristic peaks corresponding to the newly formed acetophenone (the others are covered by the solvent), one at 1269 cm^{-1}, due to the stretching and bending of the C-C-C bond, and the second at 1674 cm^{-1}, due to the stretching of CO group.

It was then possible to evaluate the rate of formation of acetophenone vs. time, as shown in Graph **2**. Upon the addition of hydrogen peroxide, acetophenone is rapidly formed in the first minutes, but then, probably because of the consumption of H_2O_2, the formation rate decreases to reach a plateux after *ca*. 20 minutes. Indeed, after the addition of the second equivalent of oxidant, the rate drastically increased, until the hydrogen peroxide is again consumed in the production of acetophenone. These observations indicate the possibility of shortening the reaction time by more frequent addition of H_2O_2, i.e. every twenty minutes instead of every hour.



Graph 2. Formation of acetophenone vs. time.

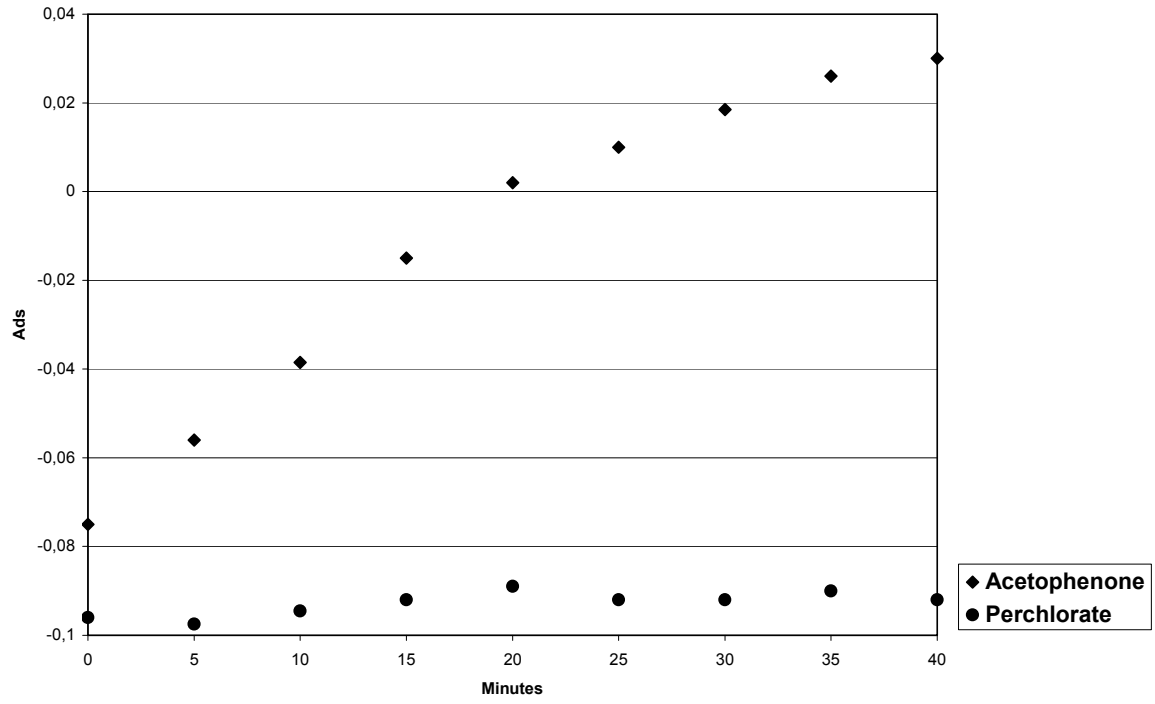
The addition all in once of the oxidant (5 eq.), however, was detrimental for the reaction, as shown in Graph **3**.



Graph 3. Addition of hydrogen peroxide: influence on acetophenone formation.

The decomposition of hydrogen peroxide and the oxidation of the substrate are two competitive processes. When the oxidant is present in low concentration, the two reactions proceed simultaneously until the oxidant is completely consumed and a new portion is added. In this case, the oxygen atoms can be efficiently inserted in the ethylbenzene and the waste of H_2O_2 through iron-catalysed decomposition is limited, resulting in an increasing yield in acetophenone during the reaction course (up to 58%). On the contrary, when hydrogen peroxide is added all in once, the decomposition process proceeded faster then the oxidation reaction and large part of the oxidant is wasted in water and oxygen, before it could be used for the transformation of ethylbenzene. The curve for this case displayed a plateaux after *ca*. three hours and the yield in acetophenone did not exceed 33%.

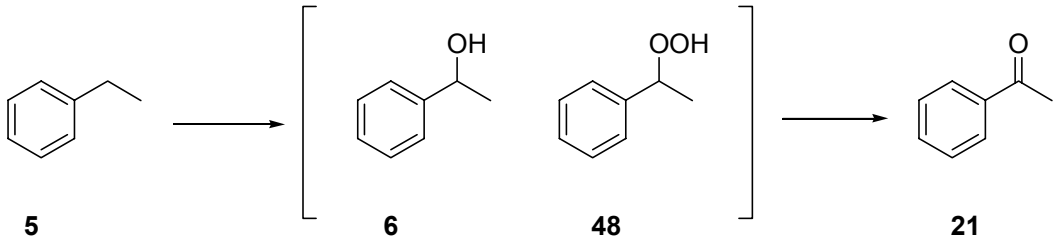
Perchlorate coming from the iron source showed a signal of medium intensity at 1100 cm^{-1}, as shown by the striped arrow in Figure **3**. Comparison of the absorbance variation during the reaction course for both perchlorate and acetophenone indicated a non-participative role of the latter in the oxidation process (Graph **4**).



Graph 4. Not-participative role of perchlorate in the oxidation of ethylbenzene.

An important aim of *in situ* IR investigations was to collect informations about the reaction mechanism and to understand if ethylbenzene **5** is directly oxidised to acetophenone **21** or if

intermediates, such as 1-phenylethanol **6** or the corresponding hydroperoxide **48**, are involved (Scheme **9**).



Scheme 9. Possible intermediates involved in Fe-catalysed oxidation of ethylbenzene.

1-Phenylethanol should present characteristic bands for the stretching of C-O and of O-H at, respectively, 1085-1050 cm^{-1} and 3650-3584 cm^{-1}. The first is in the region of the solvent absorbance and the latter is covered by the broad signal (Figure **3**, striped arrow, 3600-3200 cm^{-1}) formed during the reaction. It was therefore not possible to deduce something about its involvement as reaction intermediate.

Infrared spectra of 1-phenylethyl hydroperoxide **48**, both neat and in solution, have been reported in literature.[68] The region between 3300 and 3750 cm^{-1}, where the characteristic band of the OOH should appear, presented the broad peak already seen above and none of the other characteristic peaks reported for this hydroperoxide was found in the collected infrared spectra. Although is not possible to exclude the formation of 1-phenylethyl hydroperoxide as labile intermediate that quickly decomposes to the corresponding ketone, no evidences were found for the formation of a stable hydroperoxide as product of the oxidation of ethylbenzene.

2.3.7 Studies of CH Activation in Ionic Liquids

A source of chemical waste that is often unavoidable arises from the use of volatile molecular solvents.[69] In view of this, we considered the possibility of switching from acetonitrile to ionic liquids as solvent system. Ionic liquids appear very attractive as novel reaction media

[68] a) K. Sugamoto, Y.-I. Matsushita, T. Matsui, *J. Chem. Soc., Perkin Trans. I* **1998**, 3989; b) Y. Tatsuno, S. Otsuka, *J. Am. Chem. Soc.* **1981**, *103*, 5832.

[69] For recent reviews and book, see: a) T. Welton, *Chem. Rev.* **1999**, *99*, 2071; b) P. Wasserscheid, W. Keim, *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; *Angew. Chem.* **2000**, *112*, 4519; c) R. A. Sheldon, *Chem. Commun.* **2001**, 2399 and references therein; d) *Ionic Liquids in Synthesis*, (Eds. P. Wasserscheid, T. Welton), Wiley-VCH, Weinheim/New York, **2003**.

toward greener processes in organic synthesis and are widely used in green chemistry.[70] In fact, having a negligible vapour pressure, their loss into the environment by evaporation is minimal; this property may offer environmental advantages in industrial processes. Ionic liquids possess several other appealing properties including a high flash point, thermal stability, immiscibility with some organic solvents, and the capacity to dissolve a wide range of organic, inorganic and organometallic compounds. Room temperature ionic liquids are composed only of ions ("molten salts"). Figure **4** shows some typical constitutive anions and cations. An important feature is that variation of the anion or of the properties of the cation can be used to optimise yield and selectivity or modulate the miscibility of reaction components.

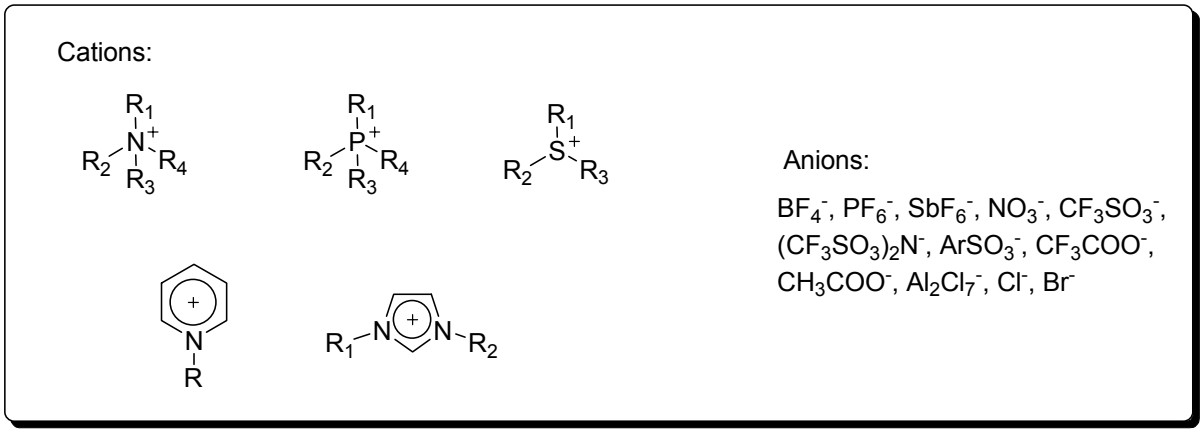
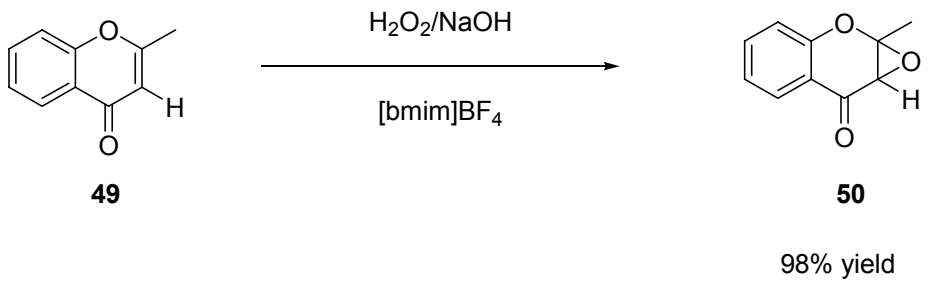


Figure 4. Typical constitutive anions and cations of ionic liquids.

Ionic liquids have been employed in a variety of organic reactions such as hydrogenation,[71] Heck reactions,[72] hydroformylation,[73] alkoxycarbonylation,[74] and allylic substitution.[75] Song and co-worker first proved that oxidation could advantageously be performed in ionic liquid.[76] The chiral (salen)Mn-catalysed epoxidation of various olefins, such as 2,2-dimethylchromene, could clearly be accelerated with the addition of ionic liquid, with both excellent yields and enantiomeric excesses. There are few examples of the use of hydrogen

[70] R. D. Rogers, K. R. Seddon, *Ionic Liquids: industrial applications for green chemistry*, ACS symposium series 818; ACS: Washington, DC, **2002**.
[71] See for example: a) P. J. Dyson, D. J. Ellis, T. Welton, *Chem. Commun.* **1999**, 25; b) R. A. Brown, P. Pollet, E. Mckoon, C. A. Eckert, C. L. Liotta, P. G. Jessop, *J. Am. Chem Soc.* **2001**, *123*, 1254.
[72] See for example: D. E. Kaufmann, M. Nouroozian, H. Henze, *Synlett* **1996**, 1091.
[73] See for example: L. Xu, W. Chen, J. Ross, J. Xiao, *Org. Lett.* **2001**, *3*, 295.
[74] See for example: D. Zim, R. F. De Souza, J. Dupont, A. L. Monteiro, *Tetrahedron Lett.* **1998**, *39*, 7071.
[75] See for example: L. Ross, W. Chen, L. Xu, L. Mao, *Organometallics* **2001**, *20*, 138.
[76] C. E. Song, E. J. Roh, *Chem.Commun.* **2000**, 837.

peroxide and its derivatives in ionic liquid and they mainly concerned the epoxidation of olefins.[77] Fabrizi, Bernini and co-workers reported, for example, a convenient procedure to epoxidise chromone, isoflavone and chalcone derivatives using alkaline hydrogen peroxide (Scheme **10**).[77a]

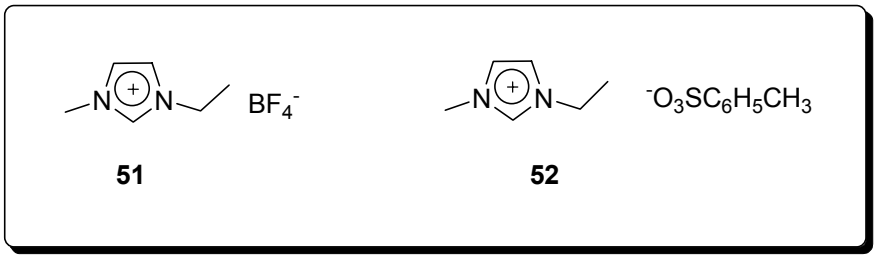


49 **50**

98% yield

Scheme 10. Epoxidation of chromones in ionic liquids by Fabrizi and Bernini.

To the best of our knowledge, no iron-catalysed reaction has been reported occurring in ionic liquids. Two ionic liquids were chosen to test our protocol, 1-ethyl-3-methyl imidazolium tetrafluoroborate ([emim]BF_4) **51** and 1-ethyl-3-methyl imidazolium tosylate ([emim]$ArSO_3$) **52** (Figure **5**).



51 **52**

Figure 5. 1-Ethyl-3-methyl imidazolium tetrafluoroborate ([emim]BF_4) **51** and 1-ethyl-3-methyl imidazolium tosylate ([emim]$ArSO_3$) **52**.

The choice of this particular cation was due to its insensitivity to both oxygen and water (even if it is hygroscopic), necessary feature for our operating conditions. The oxidation of ethylbenzene was used as test reaction and the results obtained are reported in Table **8**.

[77] a) R. Bernini, E. Mincione, A. Coratti, G. Fabrizi, G. Battistuzzi, *Tetrahedron* **2004**, *60*, 967; b) G. S. Owens, M. M. Abu-Omar, *Chem. Commun.* **2000**, 1165.

Table 8. Oxidation of ethylbenzene in ionic liquids

Entry	Solvent system	Additive	Results[a]
1	[emim]BF_4	–	No Conversion
2	[emim]BF_4	AcOH	No Conversion
3	[emim]BF_4/CH_3CN 1:1	AcOH	< 5% conversion
4	[emim]tosyl	–	Decomposition IL
5	[emim]tosyl	AcOH	Decomposition IL

Reaction conditions: ethylbenzene (1 mmol), $Fe(ClO_4)_2$ (0.1 mmol), aq. H_2O_2 (30%, 5 mmol; added within 4 h) in solvent system (1 mL) at rt for 5 h. [a] GC/MS and GC analysis using nitrobenzene as internal standard.

Ionic liquids do not represent a suitable solvent for iron-catalysed oxidation by hydrogen peroxide. The use of mixed system [emim]BF_4/CH_3CN also gave poor result and the addition of acetic acid did not enhance the reactivity (Table **8**, entries 1-3). When [emim]tosyl was used, ethyltosylate was recovered in the organic phase after work-up. The reaction was repeated with a batch of [emim]tosyl previously extracted with diethylether to remove any impurity and ethyltosylate was again found as product of ionic liquid decomposition (Table **8**, entries 4-5).

2.3.8 Conclusion

An iron-catalysed oxidation system for saturated hydrocarbons, using hydrogen peroxide as oxidant, has been developed, providing a promising tool for large-scale applications.

The method exhibited great advantages: the reaction proceeds under truly catalytic conditions, the catalyst does not require any ligand, and water is the only by-product formed. The presence of an additive, i.e. a carboxylic acid, was found to enhance the system and the effect of different acids was studied, indicating acetic acid and benzoic acid as the best ones. Various solvent systems were considered, such as, for example, ionic liquids and benzotrifluoride, and acetonitrile was found to be the most suitable. To extend the scope of the reaction, several substrates were tested, such as arylalkanes, cycloalkanes and alcohols. Arylalkanes were easily converted into the corresponding ketones with good selectivities and the less reactive and more challenging cycloalkanes gave the corresponding alcohols and ketones with yields comparable to the best reported in literature so far. The system presented

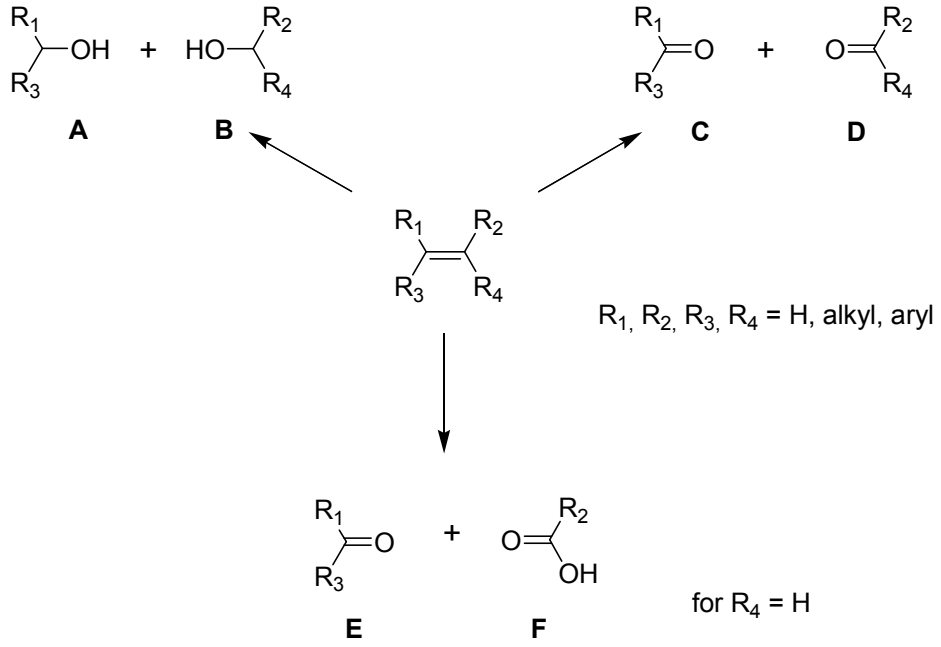
peculiar selectivity parameters (i.e. 3°/2° value of 3.67, ratio cyclohexanol/cyclohexanone *ca*. 1 and low reactivity of cyclohexanol), that are consistent with the involvement of both an alkylhydroperoxide or a Fe(OOH) species. *In situ* IR studies showed that a rapid addition of hydrogen peroxide to the system was detrimental for the transformation of ethylbenzene into acetophenone and that perchlorate did not act as an oxidising agent. Although the formation of 1-phenylethanol or of the corresponding hydroperoxide as intermediates could have not been unequivocally excluded by *in situ* IR analysis, no evidences have been found of their involvement.

3. Fe-Catalysed Oxidative Cleavage of Double Bonds

3.1 Introduction

Oxidative cleavage of olefins is an interesting process, which allows degradation of large compounds or the introduction of oxygen-containing functionalities into complex molecules.[78]

Depending on the choice of the oxidant, reaction conditions and work-up, various products can be obtained. Ketones and secondary alcohols can be easily prepared from compounds containing trisubstituted alkenes, while primary alcohols and carboxylic acids are the main products when the alkene contains a secondary carbon (Scheme **11**). Due to their susceptibility to further oxidation, aldehydes are the most difficult to obtain and therefore require selective oxidants and mild conditions.



Scheme 11. Oxidative cleavage of double bonds: possible products.

Two main methodologies are available for the preparation of ketones and aldehydes: ozonolysis, or the reaction with an oxidant in the presence of a metal catalyst.

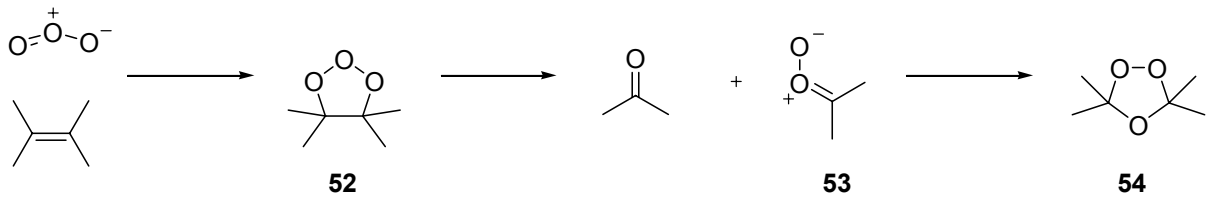
[78] R. W. Fischer, W. A. Herrmann, T. Weskamp, in: *Transition Metals for Organic Synthesis,* Vol. 2 (Eds. M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd edn., **2004**, 427.

The conversion of tetrasubstituted double bonds to the corresponding ketones is easily achieved using a number of oxidants. However, if the alkene is trisubstituted or less, the product will be either an aldehyde or a carboxylic acid. With the exception of ozonolysis, all the methods involve a metal complex as oxidant, alone (metal oxide in stoichiometric amount) or in combination with a co-oxidant (catalytic conditions). The existing methods will be discussed on the basis of the nature of the oxidant.

3.1.1 Ozonolysis

Ozonolysis is the standard method for the direct oxidative cleavage of olefins and yields aldehydes or carboxylic acids depending on the method of work-up.[79] Although ozone is hazardous and serious accidents involving explosions have been reported,[80] the procedure is well-developed and widely applied.

The reaction has been intensively studied,[78,81] and, even if some details are not completely understood, the mechanism proposed by Criegee is commonly accepted (Scheme **12**).[82]



Scheme 12. Mechanism of ozonolysis proposed by Criegee.[82]

The product of the first step, a [1,3] dipolar cycloaddition, is the rather unstable "primary" ozonide **52**, which decomposes *via* a reverse [1,3] cycloaddition to give a carbonyl compound and the carbonyl ylide **53**.

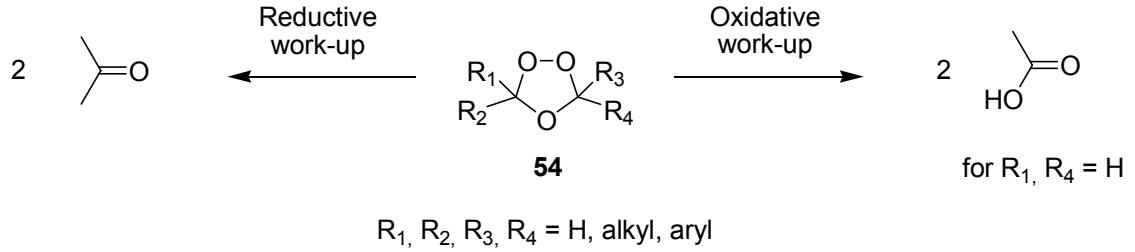
[79] a) J. S. Belew, *Oxidation Techniques and Applications in Organic Synthesis*, Vol. 1 (Eds. R. L. Augustine), Dekker, New York, **1969**, 259; b) S. D. Razumovskii, G. E. Zaikov, *Russ. Chem. Rev. (Engl. Transl.)* **1980**, *49*, 1163; c) P. S. Bailey, *Ozonation in Organic Chemistry*, Vol. 1 (Edn. W. S. Trahanosky), Academic Press, New York, **1978**; d) P. S. Bailey, *Chem. Rev.* **1958**, *58*, 925.

[80] a) K. Koike, G. Inoue, T. Fukuda, *J. Chem. Eng. Jpn.* **1999**, *32*, 295; b) R. A. Ogle, J. L. Schumacher, *Process Saf. Prog.* **1998**, *17*, 127.

[81] a) A. H. Haines, *Methods for the Oxidation of Organic Compounds*, Academic Press, Toronto, **1985**, 117; b) R. L. Kuczkowski, *Acc. Chem. Res.* **1983**, *16*, 42; c) W. Carruthers, *Some Modern Methods of Organic Synthesis*, Cambridge University Press, New York, 2nd ed., **1978**, 355.

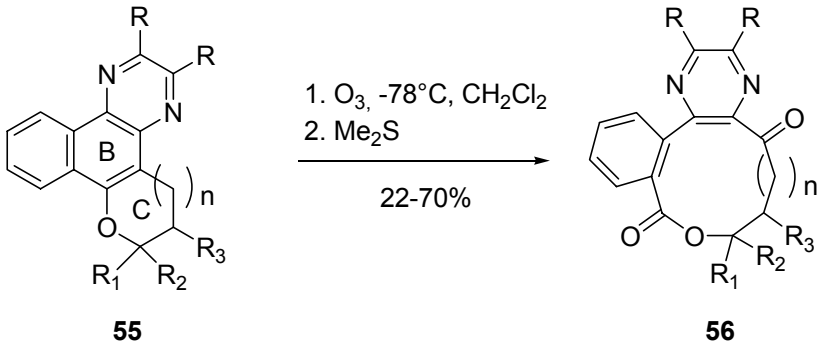
[82] R. Criegee, *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 745; *Angew. Chem.* **1975**, 86, 765.

These intermediates recombine to form the more stable secondary ozonide **54** that yields carbonyl compounds (aldehydes and ketones) or carboxylic acids upon reductive or oxidative work-up, respectively (Scheme **13**).



Scheme 13. Decomposition of secondary ozonide **54**.

This method has been shown to be a useful and versatile tool in organic chemistry. A wide range of synthetic approaches includes, in their pathway, an ozonolysis step so that the technique has been demonstrated on various substrates. Estèvez-Braun and Ravelo, for example, recently reported the synthesis of 9- and 10-membered macrolactones *via* ozonolysis of the enol double bond shared by rings B and C in the 1,4-diazaphenenthrene precursors **55** (Scheme **14**).[83]

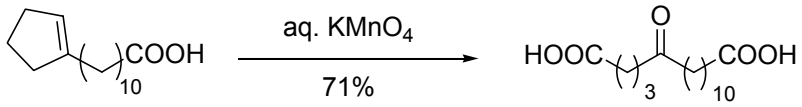


Scheme 14. Synthesis of 9- and 10-membered macrolactones *via* ozonolysis.[83]

[83] E. Pèrez-Sacau, J. Soto-Delgado, A. Estèvez-Braun, A. G. Ravelo, *Tetrahedron* **2005**, *61*, 437.

3.1.2 Permanganate

The main products obtained from the cleavage of carbon-carbon double bonds with permanganate are carboxylic acids, derived from the oxidation of intermediate aldehydes. Scheme **15** depicts an example of products that are normally obtained when alkenes react with aqueous potassium permanganate.[84]



57 **58**

Scheme 15. MnO_4-mediated oxidative cleavage.

The addition of a phase-transfer agent, such as quaternary ammonium or phosphonium salts, solubilises the permanganate ion in non-aqueous solvents, where it reacts with alkenes to produce a cyclic intermediate[85] which then decomposes to give aldehydes or the corresponding α-diol upon treatment with acid or a mild base, respectively. Moreover, under phase-transfer conditions, permanganate selectively cleaves aryl-substituted double bonds in the presence of alkyl-substituted double bonds or other oxidisable functional groups.[86]

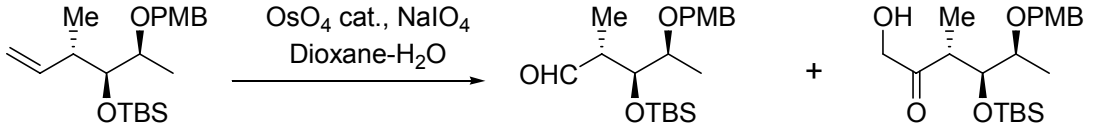
3.1.3 Osmium Tetroxide and Sodium Periodate

The one-pot combination of two well-known reactions, namely osmium tetroxide hydroxylation of an olefin and periodate cleavage of vicinal diols, is an efficient technique for obtaining carbonyl compounds.[87] Catalytic amounts of expensive and poisonous osmium tetroxide are sufficient because periodate oxidises the lower valence form of osmium to the tetroxide, thus regenerating the hydroxylating agent. This method has the advantage of not proceeding beyond the aldehydic oxidation state and affords the same products produced by ozonisation followed by reductive cleavage. The reaction is usually carried out in a mixed

[84] S. D. Sabnis, H. H. Mathur, S. C. Bhattacharyya, *J. Chem. Soc.* **1965**, 4580.
[85] T. Ogino, K. Mochizuki, *Chem. Lett.* **1979**, 443.
[86] R. Rathore, S. Chandrasekaran, *J. Chem. Res. (S)*, **1986**, 458.
[87] a) R. Pappo, D. S. Allen Jr., R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478; b) D. G. Lee, *Oxidation Techniques and Applications in Organic Synthesis*, vol. 1 (Ed. R. L. Augustine), Dekker, New York, **1969**.

solvent system containing water and dioxane, acetone, acetic acid or tetrahydrofurane. Non-aqueous solvents can be employed if a phase-transfer agent is added or by using periodic acid in tetrahydrofurane.

Recently, Jin and co-workers reported an improved procedure for the oxidative cleavage of monosubstituted olefins.[88] They found that addition of 2,6-lutidine drastically increased the reaction yield by suppressing the undesired formation of α-hydroxy ketone side products, such as compound **61** (Scheme **16**).

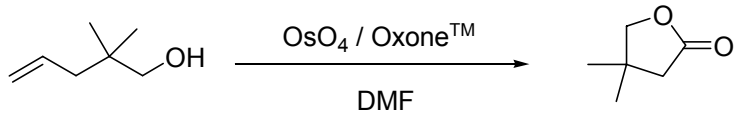


59 **60** **61**

No base	60-64%	30-25%
2,6-lutidine	90%	6%

Scheme 16. Improved procedure for the oxidative cleavage of monosubstituted olefins.[88]

The major drawbacks of this method are the high toxicity and the price of osmium tetroxide. To overcome these issues and render this reagent applicable to large-scale operations, several strategies have been adopted by different groups to immobilise the catalyst on soluble and insoluble supports, with various levels of success.[89] Recently, Borhan and co-workers[90a] employed Oxone™ ($2KHSO_5$, $KHSO_4$, K_2SO_4) as a mild oxidant for the OsO_4-mediated oxidative cleavage of olefins to their corresponding aldehydes and carboxylic acids.



62 **63**

85%

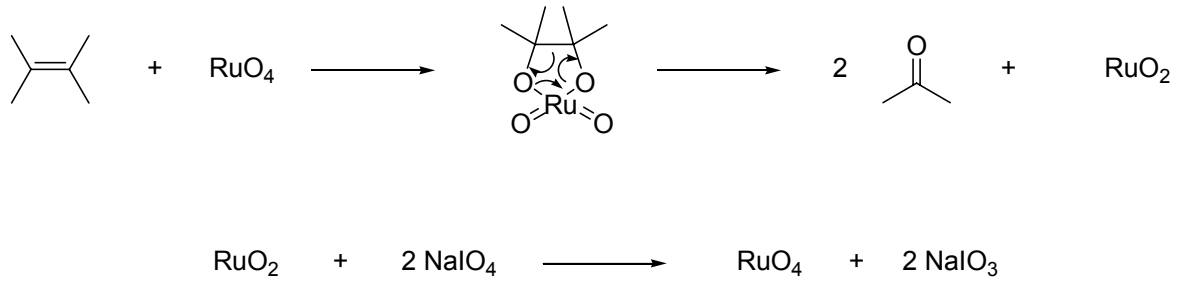
Scheme 17. OsO_4-promoted oxidative cleavage of olefins with Oxone™.[90b]

[88] W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, *Org. Lett.* **2004**, *6*, 3217.
[89] See for example: a) G. Cainelli, M. Contento, F. Maniscalchi, L. Plessi, *Synthesis* **1989**, 47; b) S. Kobayashi, T. Ishida, R. Akiyama, *Org. Lett.* **2001**, *3*, 2649; c) S. V. Ley, C. Ramarao, A.-L. Lee, N. Østergaad, S. C. Smith, I. M. Shirley, *Org. Lett.* **2003**, *5*, 185.
[90] a) B. R. Travis, R. S. Narayan, B. Borhan, *J. Am. Chem. Soc.* **2002**, *124*, 3824; b) J. M. Schomaker, B. R. Travis, B. Borhan, *Org. Lett.* **2003**, *5*, 3089.

This protocol was coupled with intramolecular trapping by an alcohol moiety to form lactones and thus showed that a mild osmium-catalysed tandem oxidative cleavage/oxidative lactonisation reaction can be used to prepare lactones from hydroxyl olefins (Scheme **17**).[90b]

3.1.4 Ruthenium-Catalysed Systems

Ruthenium is one of the few transition metals suitable for use as a catalyst for single–step cleavage of olefinic double bonds. Ruthenium tetroxide reacts with carbon-carbon double bonds to give cyclic ruthenate(VI) esters, like osmium tetroxide, but yielding only cleavage products (Scheme **18**).[91]

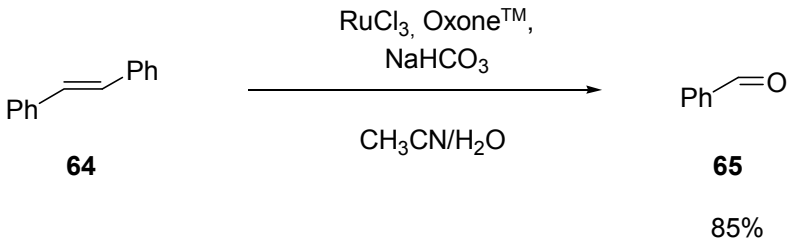


Scheme 18. Mechanism of ruthenium-catalysed oxidative cleavage of olefins.

Due to its reactivity, RuO_4 is commonly replaced with catalyst precursors, such as $RuCl_3$, Ru(acac) and RuO_2, in the presence of a co-oxidant, mostly an organic peracid or periodate, which continuously regenerates the active species. Sharpless and co-workers[92] demonstrated that addition of acetonitrile to the traditional biphasic CCl_4/H_2O solvent system for RuO_4 leads to a greatly improved system. The previous systems, although very effective, presented problems such as slow or incomplete reactions, probably due to an inactivation of the ruthenium catalyst. Mostly, this happened in the presence of carboxylic acids, either added as co-oxidant or generated during the course of the oxidation. Sharpless and co-workers suggested that the formation of lower valent ruthenium carboxylate complexes was responsible for the loss of catalytic activity, whereas use of acetonitrile, which acts as a ligand for the lower valent ruthenium(III/II), avoids the formation of undesired carboxylate complexes.

[91] F. M. Dean, J. C. Knight, *J. Chem. Soc.* **1962**, 4745.
[92] P. H. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936.

Recently, Yang and co-worker reported an efficient protocol with ruthenium chloride as catalyst and Oxone™ as the primary oxidant.[93] A wide range of olefins, such as symmetric stilbenes, trisubstituted aryl olefins and chalcones were smoothly converted into the corresponding aldehydes in good to excellent yields (Scheme **19**).



Scheme 19. Oxidative cleavage by Yang.[93]

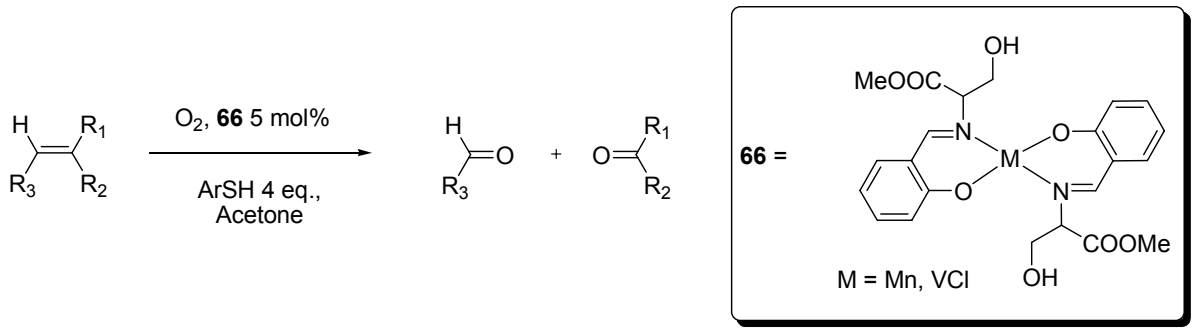
3.1.5 Rhenium-Catalysed Systems

Methylrheniumtrioxide (MTO) was first prepared in 1979,[94] but was only much later recognised, by Herrmann and co-workers, as a powerful catalyst for the efficient activation of hydrogen peroxide.[95] After tuning the reaction conditions, MTO, along with others alkylrhenium oxides, was found to catalyse epoxidations, didhydroxylations and cleavage of carbon-carbon double bonds.[96] The conversion of olefins to the corresponding aldehydes in moderate to excellent yields can be achieved by choosing the right solvent and the optimal oxidant/substrate ratio. A dehydrating agent or azeotropic distillation are employed to suppress hydrolysis of the catalyst during the reaction. Recently, Weskamp and co-worker reported the one-pot transformation of olefins to aliphatic, as well as aromatic, carboxylic acids. Addition of HBF_4 to the MTBE/H_2O_2/MTO system resulted in the direct oxidation of the formed aldehydes to their corresponding carboxylic acids with a selectivity of up to 60% at complete conversion.[97] Emerson and Abu-Omar successfully employed the MTO/(H_2O/CH_3CN)/H_2O_2 system in the transformation of cyclic β-diketones to carboxylic acids, obtaining excellent yields and selectivities.[98]

[93] D. Yang, C. Zhang, *J. Org. Chem.* **2001**, *66*, 4814.
[94] I. R. Beattie, P. J. Jones, *Inorg. Chem.* **1979**, *18*, 2318.
[95] W. A. Herrmann, in: *Organic Peroxygen Chemistry*, (Ed. W. A. Herrmann), Springer-Verlag: Berlin, **1993**, 130.
[96] For a review, see: F. E. Kühn, M. Groarke, in: *Applied Homogeneous Catalysis with Organometallic Compounds*, (Eds. B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2002**, *3*, 1304.
[97] W. A. Hermann, T Weskamp, J. P. Zoller, R. W. Fischer, *J. Mol. Catal.* **2000**, *153*, 49.
[98] M. M. Abu-Omar, J. H. Emerson, *Organometallics* **1996**, *15*, 3543.

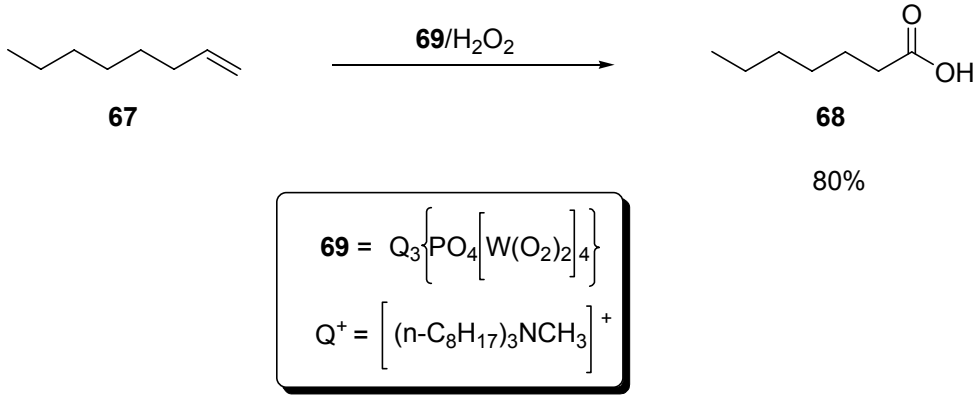
3.1.6 Other Systems

Vanadium and manganese complexes have been used efficiently in the presence of molecular oxygen and thiophenols for the oxidative cleavage of a wide range of olefins (Scheme **20**).[99] The β-hydroperoxidisulfide formed in situ from thiyl radical addition to the double bond undergoes transition metal-catalysed decomposition followed by oxygen trapping to provide the corresponding aldehydes and ketones in up to 98% yield.



Scheme 20. Oxidative cleavage of trisubstituted olefins by Jugè and co-workers.[99]

The use of aqueous hydrogen peroxide in the presence of tungsten-derivatives under homogeneous conditions represents an interesting system for the cleavage of alkenes to carboxylic acids.[100]



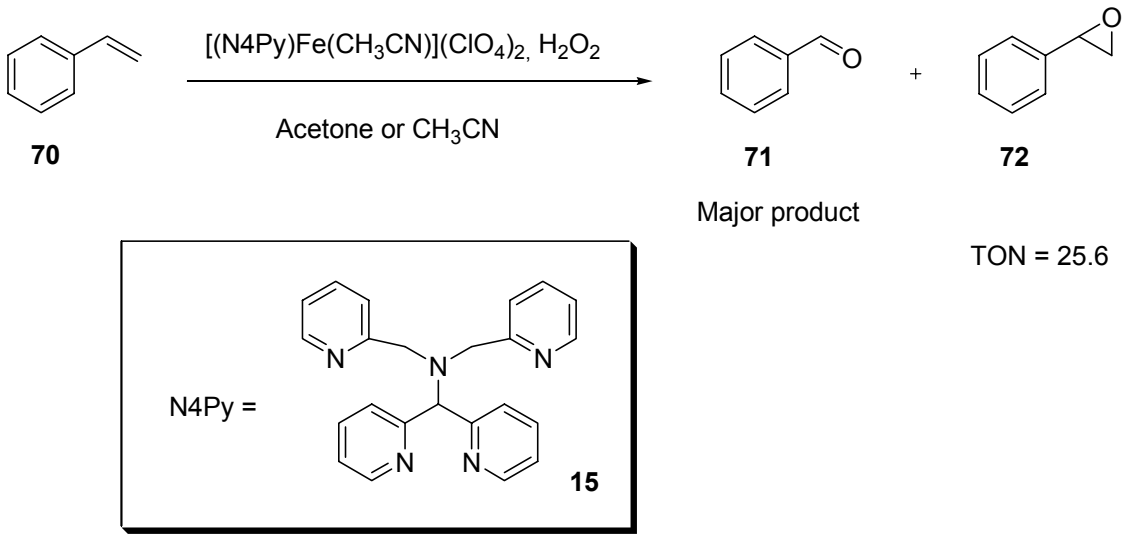
Scheme 21. An example of tungsten-derivatives mediated oxidative cleavage.

[99] X. Baucherel, J. Uziel, S. Jugé, *J. Org. Chem.* **2001**, *66*, 4504.
[100] a) Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida, M. Ogawa, *J. Org. Chem.* **1988**, *53*, 3587; b) T. Oguchi, T. Ura, Y. Ishii, M. Ogawa, *Chem. Lett.* **1989**, 857; c) E. Antonelli, R. D'Alosio, M. Gambero, T. Fiorani, C. Venturello, *J. Org. Chem.* **1998**, *63*, 7190; d) C. D. Brooks, L. Huang, M. McCarron, R. A. W. Johnstone, *Chem Commun.* **1999**, 37.

Medium and long-chain alkenes were cleaved by the system **69**/H_2O_2 in absence of organic solvent under two-phase conditions in good to high yields (Scheme **21**).[100a] The reaction of aqueous H_2O_2 and catalytic amount of a heteropolyacid, adsorbed onto magnesium, aluminium or zinc oxide, leads to complete cleavage of small alkenes to carbonyl compounds.[100d]

3.2 Goal of the Study

In spite of the fact that iron belongs to the same group as osmium and ruthenium on the periodic table, to date no report has appeared about a Fe-based protocol for the oxidative cleavage of double bonds. In addition, only recently the use of hydrogen peroxide as oxidant in this class of reaction has been described, in combination with MTO[96] or POM[100] as the metal catalyst. Interestingly, Feringa and Que observed formation of benzaldehyde (**71**) as major product when styrene was oxidised by a non-heme iron complex in the presence of hydrogen peroxide (Scheme **22**).[101] The overall low yields (2.2%) and the need for a large excess of oxidising agent make this system of scarce synthetic value. However, this study helped to demonstrate the involvement in the process of a radical oxidant, derived from the homocleavage of the low-spin Fe(III)OOH intermediate generated during the reaction.



Scheme 22. Styrene cleavage/epoxidation catalysed by iron in the presence of N4Py ligand by Feringa and Que.[101]

[101] G. Roelfes, M. Lubben, R. Hage, L. Que, B. L. Feringa, *Chem. Eur. J.* **2000**, *6*, 2152.

Prompted by these observations and by our previous results in the Fe-catalysed oxidation of hydrocarbons,[102] we wondered about the possibility to extend the scope of the $Fe(ClO_4)_2/CH_3COOH/H_2O_2$ system to the oxidative cleavage of double bonds and we aimed to develop a new clean and efficient method for this interesting transformation.

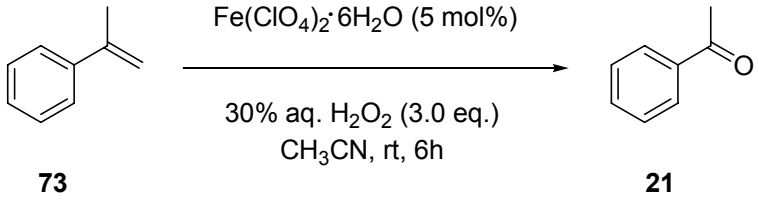
[102] C. Pavan, J. Legros, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 709.

3.3 Results and Discussion

3.3.1 Preliminary Experiments and Catalyst Optimisation

We chose as test substrate α-methylstyrene, an easily available olefin. The oxidative cleavage of α.α-disubstituted olefins leads to the formation of a ketone and formaldehyde.

To our delight, in the presence of iron(II) perchlorate and aqueous hydrogen peroxide, α-methylstyrene was completely consumed within only one hour affording acetophenone as major product (Equation **2**). Although, according to the literature on that topic,[103] epoxidation is supposed to be an easier reaction, α-methylstyrene oxide was not detected.



73 **21**

Equation 2.

As previously described for the CH activation, acetonitrile plays an important role in this system. When other solvents, such as acetone and methanol, were used, we obtained poor conversions even with longer reaction time (up to 3 days) and in the absence of solvent the reaction proved to be almost explosive and therefore difficult to control.

An important drawback of the above described protocol is constituted by the spontaneous and quick evolution of gas from decomposition of hydrogen peroxide and the subsequent increase in temperature. The reaction mixture reached and bypassed the boiling point of acetonitrile (81-83 °C), this fact representing a safety issue in the presence of perchlorate. A first solution could be the replacement of iron perchlorate with of a different iron salt. We tested different iron sources, chosen among the most common and inexpensive ones, and found out that only few of them are suitable (Table **9**).

As already noticed in the case of CH activation, iron(II) acetylacetonate and iron(II) acetate failed in activating the hydrogen peroxide (Table **9**, entries 2 and 3). On the other side, iron(II) chloride and iron(III) nitrate showed a modest to good activity in transforming α-methylstyrene in acetophenone (Table **9**, entries 4 and 5), even if still inferior to iron(II)

[103] For recent examples: G. Dubois, A. Murphy, T. P. D. Stack, *Org. Lett.* **2003**, *5*, 2469.

perchlorate. These results induced us to look for another way to overcome the major drawback of this protocol, since iron(II) perchlorate remained the best choice regarding conversion and selectivity.

Table 9. Iron-catalyzed oxidative cleavage of α-methylstyrene with aqueous H_2O_2

Entry	[Fe]	Time (h)	Conversion (%)[a]	Selectivity (%)[a,b]
1	$Fe(acac)_2$	24	–	–
2	$Fe(OAc)_2$	24	–	–
3	$Fe(NO_3)_2 \cdot 9H_2O$	4.5	66	80
4	$Fe(ClO_4)_2 \cdot 6H_2O$	4.5	98	80
5	$FeCl_2 \cdot 4H_2O$	4.5	36	58

Reaction conditions: α-methylstyrene (1 mmol), Fe salt (5 mol%) and aq. H_2O_2 (35%, 3 mmol) in acetonitrile (3 mL). [a] Measured by GC analysis with nitrobenzene (40 mol%) as internal standard. [b] Selectivity = mmol acetophenone/mmol converted substrate.

As already reported for the Fe-catalysed oxidation of unreactive substrates, the addition of organic molecules with coordinating properties, such as carboxylic acids, can enhance the reaction efficiency and suppress the catalase activity typical of Fe/H_2O_2 systems. As suggested by our previous studies (see Chapter 2.3.2), we added acetic acid (30 mol%) to the reaction medium prior to the addition of the oxidant.

The impact of this reaction modification is reported in Table **10** and graphically shown in Graph **5**. Although no quick evolution of gas was anymore noticed, the temperature increased to *ca*. 60 °C upon addition of hydrogen peroxide. The system then slowly returned to room temperature. As precaution, we cooled the vessel at 0 °C for the first hour and then allowed the reaction to reach room temperature.

Under this improved operative conditions the reaction became very well behaved and the undesiderable exothermicity was no longer observed. In the iron(II) perchlorate-catalysed system the reaction time was shortened to 4.5 hours with no significant loss in selectivity and conversion (Table **10**, entry 1).

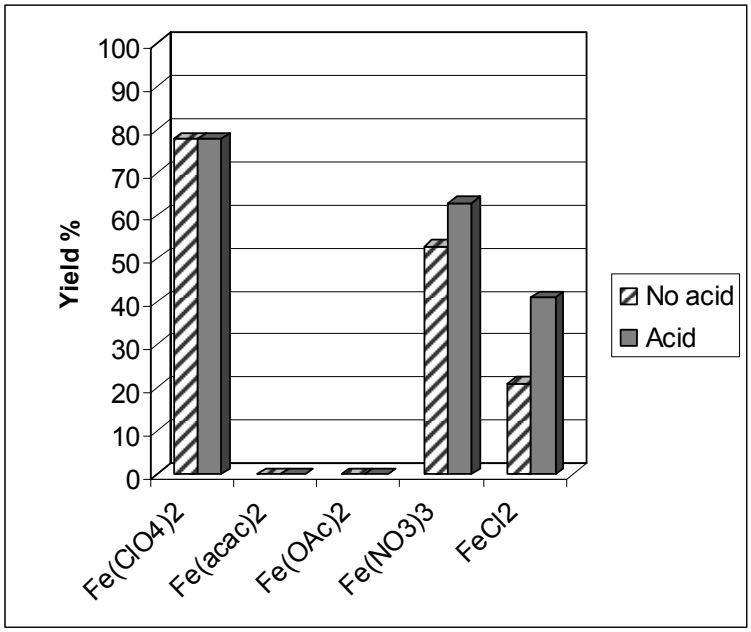
Table 10. Iron-catalysed oxidative cleavage of α-methylstyrene with aqueous H_2O_2 and various iron sources.

Entry	[Fe]	Additive	Time (h)	Conv.[a](%)	Selectivity[a,b] (%)	TON
1	$Fe(ClO_4)_2 \cdot 6H_2O$	–	6	98	80	15.7
2		AcOH	4.5	95	82	15.7
3	$Fe(acac)_2$	–	24	–	–	–
4		AcOH	24	–	–	–
5	$Fe(OAc)_2$	–	24	–	–	–
6		AcOH	24	–	–	–
7	$Fe(NO_3)_2 \cdot 9H_2O$	–	4.5	66	80	10.6
8		AcOH	4.5	76	83	12.6
9	$FeCl_2 \cdot 4H_2O$	–	4.5	36	58	4.2
10		AcOH	4.5	64	64	8.2
11		AcOH	24	88	59	10.4

Reaction conditions: α-methylstyrene (1 mmol), Fe salt (5 mol%) and aq. H_2O_2 (35%, 3 mmol) in acetonitrile (3 mL). [a] Measured by GC analysis with nitrobenzene (40 mol%) as internal standard. [b] Selectivity = mmol acetophenone/mmol converted substrate.

The effect of the additive was more dramatic in the case of iron(II) chloride and iron(III) nitrate (Graph **5**). The system catalysed by iron(II) chloride was almost double-yielding in acetophenone (from 21% to 41%) in 4.5 hours and gave 52% yield if let running 24 hours. The iron(III) nitrate-containing system smoothly converted α-methylstyrene in acetophenone in 63% yield, with a gain of 20% on the one without acid.

Iron(II) acetate and iron(II) acetylacetonate, on the other side, did not benefit from the additive and the starting material was recovered unconverted even after 24 hours (Table **10**, entries 2 and 3).



Graph 5. Yield in acetophenone with and without acetic acid.

Considering the evident benefits of the additive on the protocol, we tried to optimise the system screening different acetic acid concentrations. Since $FeCl_2$ seemed to be the most sensitive iron source, it was chosen as test catalyst (Table **11**).

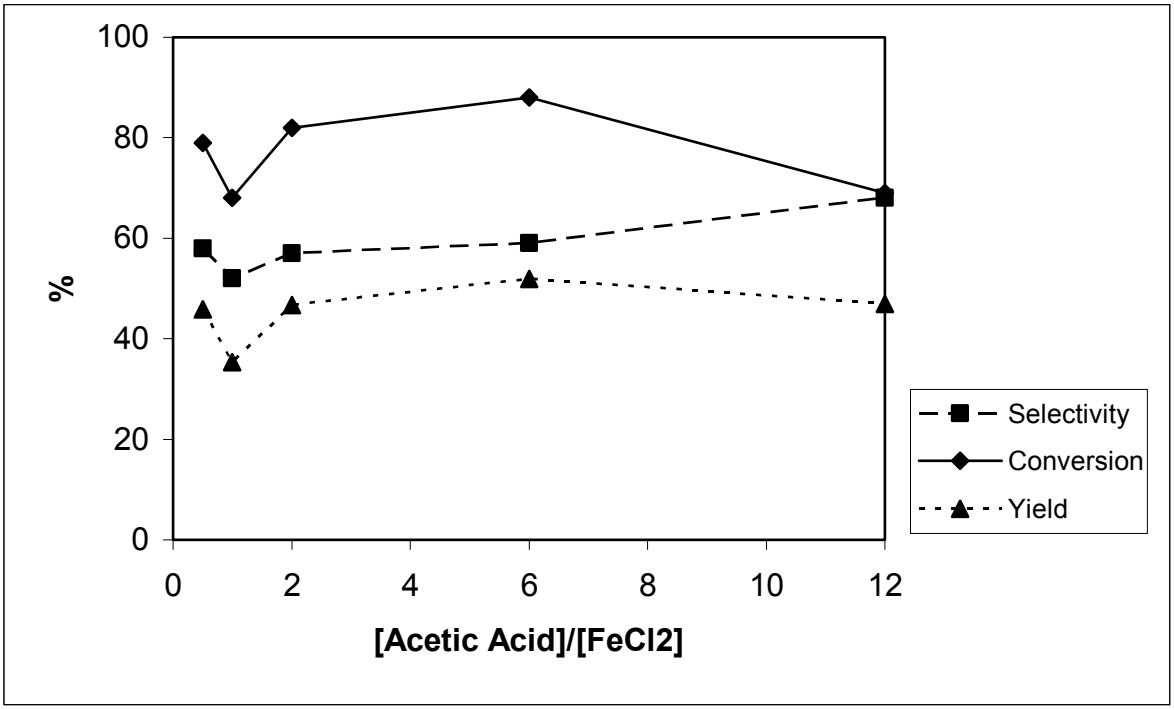
Table 11. Iron(II) chloride catalysed oxidative cleavage of α-methylstyrene with aqueous H_2O_2.

Entry	Additive (eq.)	Time (h)	Conversion[a] (%)	Selectivity[a,b] (%)
1	AcOH (0.025)	24	79	58
2	AcOH (0.05)	24	68	52
3	AcOH (0.1)	24	82	57
4	AcOH (0.3)	24	88	59
5	AcOH (0.6)	24	69	68
6	$PhCO_2H$ (0.3)	24	89	69
7	$PhCO_2H$ (0.6)	24	61	71
8	$AcONa{\cdot}3H_2O$ (0.3)	4.5	<5	–

Reaction conditions: α-methylstyrene (1 mmol), Fe salt (5 mol%) and aq. H_2O_2 (35%, 3 mmol) in acetonitrile (3 mL). [a] Measured by GC analysis with nitrobenzene (40 mol%) as internal standard. [b] Selectivity = mmol acetophenone/mmol converted substrate.

At lower and higher concentrations (Table **11**, entries 1, 2 and 5)), the effect is less evident and the results are similar to the ones obtained with no additive.

In Graph **6** the dependency of conversions, selectivities and yields on [acetic acid]/[$FeCl_2$] ratio are shown.

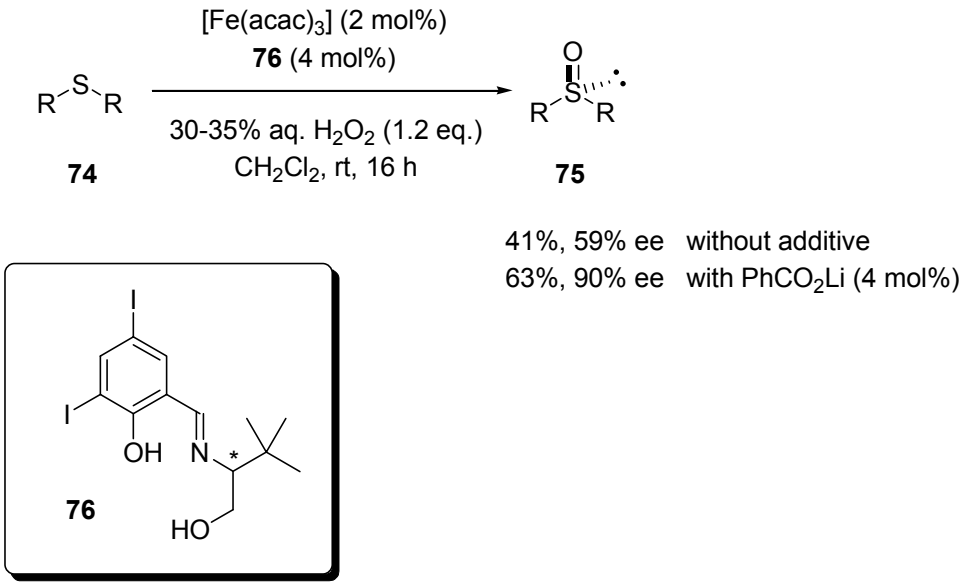


Graph 6. Effect of acetic acid ratio on oxidative cleavage of α-methylstyrene to acetophenone.

The best yield remained that obtained with the acid ratio initially chosen, 30 mol%, even if this can be reduced to 10 mol% with no significant loss in conversion and selectivity. This outcome could be explained by supposing the formation of clusters involving Fe, acetic acid and the solvent itself.

We already showed that benzoic acid is an effective additive in Fe-catalysed oxidations, and it was therefore interesting to test it also in Fe-catalysed oxidative cleavage. We added, respectively, 30 and 60 mol% of benzoic acid to the $FeCl_2$-containing system and found results comparable to those obtained for acetic acid (Table **11**, entries 6 and 7), in line with the data observed for the iron-catalysed CH-activation.

Recently, it was found in our group that carboxylates can drastically enhance the performance of Fe-catalysed sulfoxidations (Scheme **23**).[104]



Scheme 23. Carboxylate-enhanced system for the enantioselective oxidation of sulfides.[104]

Unfortunately, addition of sodium acetate to the reaction mixture had a detrimental effect on the oxidative cleavage and, because of quick decomposition of hydrogen peroxide, no conversion was observed (Table **11**, entry 8).

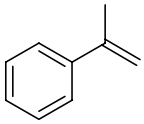
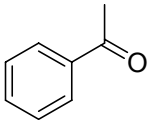
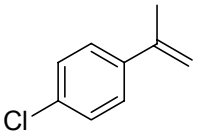
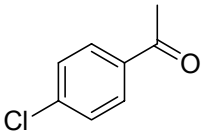
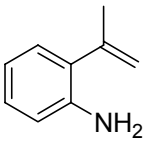
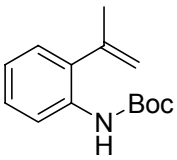
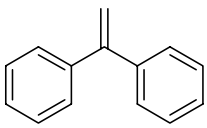
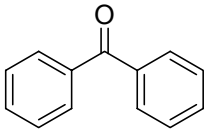
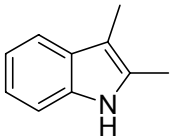
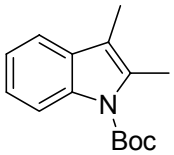
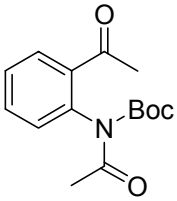
As shown by this preliminary screening, the system iron(II) perchlorate/AcOH/H_2O_2 proved to be the most efficient one in the oxidative cleavage of α-methylstyrene. It was therefore interesting to investigate the effect of iron amount on the substrate conversion. We tried to decrease the loading of Fe(II) perchlorate and found that the lowest limit for which the system maintained a good efficiency was 3.5 mol%. Using this catalyst loading we obtained complete conversion of substrate in only 5 hours, but with a decreased yield (54%). The use of less catalyst resulted in prolonged reaction time or in incomplete conversion.

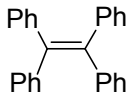
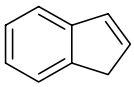
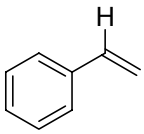
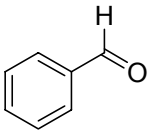
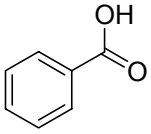
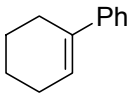
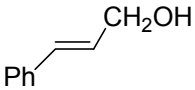
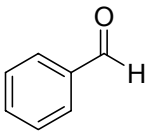
3.3.2 Substrate Scope

In order to verify the effective applicability of this method, various olefins were tested and the results obtained are reported in Table **12**.

[104] J. Legros, C. Bolm, *Angew. Chem. Int. Ed.* **2004**, *43*, 4225; *Angew. Chem.* **2004**, *116*, 4321.

Table 12. Iron-catalysed oxidative cleavage of various substrates with aqueous H_2O_2.

Entry	Substrate	Major Product	Conversion[a] (%)	Yield (%)
1	 **73**	 **21**	100	78
2	 **77**	 **78**	100	55
3	 **79**	–	–	–
4	 **80**	–	–	–
5	 **81**	 **29**	100	54
6	 **82**	Mixture	54	–
7	 **83**	 **84**	75	–[b]

8	 **85**	–	No conversion	–
9	 **86**	–	No conversion	–
10	 **70**	 **71**	100	50
		 **87**		50
11	 **88**	Mixture	100	–
12	 **89**	Mixture	95	–[c]
13	 **90**	 **71**	75	–[b]

Reaction conditions: substrate (1 mmol), Fe salt (5 mol%) and aq. H_2O_2 (35%, 3 mmol) in acetonitrile (3 mL). [a] Measured by GC analysis with nitrobenzene (40 mol%) as internal standard. [b] Mixture 1 : 3 substrate/product. [c] 1-phenylpentanone isolated.

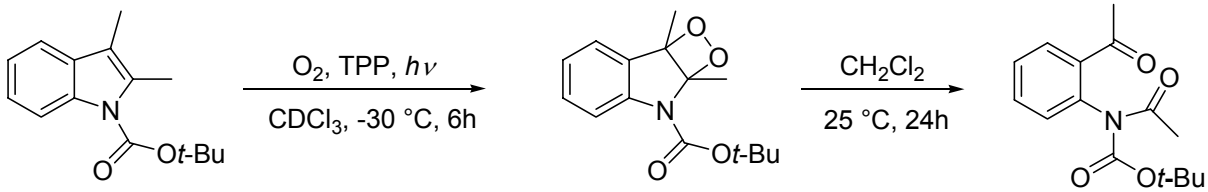
A substitution in para position seemed to be not detrimental for the oxidative cleavage and 4-chloro-α-methylstyrene (**77**) was smoothly and selective converted in the corresponding 4-chloroacetophenone (**78**) in good yield (Table **12**, entry 2). On the other hand, the introduction of an amino group in ortho position completely inhibited the reaction, and the

result remained the same also in the presence of a Boc-protected amino group. This outcome can be explained in view of a possible coordination of the iron by the Lewis-basic nitrogen atom of the substrate (Table **12**, entries 3 and 4).

The substitution of the methyl group in α with a phenyl group left untouched the efficiency of the protocol and benzophenone (**29**) was easily obtained from 1,1-diphenylethene (**81**) in 54% yield (Table **12**, entry 5).

2,3-Disubstituted indoles are common substrates of various dioxygenases that selectively catalyse their complete conversion to the corresponding carbamates.[105] Usually, this is performed with non-benign reagents, such as sodium periodate,[106] nitrous acid[107] and potassium permanganate,[108] with ozonolysis or, as reported recently, with plant cell culture in presence of H_2O_2 with excellent yield.[109] We subjected 2,3-dimethylindole (**82**) to Fe-cataysed oxidative cleavage under standard conditions but, disappointingly, after 5 hours, 54% of substrate was converted in a mixture of various oxygenated products, among which the desired o-acetylaminoacetophenone represents the 6%.

The oxidative cleavage mechanism of unprotected indoles is reported to go through the formation of a labile dioxetane that soon decomposes to give the final product.[110] Protected indoles, on the contrary, are known to give more persistent isolable dioxetanes that can, for example, thermally decompose to the corresponding carbamates (Scheme **24**).[111] We supposed that the lack of selectivity was partially due to the presence of the secondary amine and that Boc-protecting the substrate could lead to a more selective reaction.



Scheme 24. Oxidative cleavage of *N*-acylated indoles with oxygen: formation of stable dioxetane.

[105] a) P. Feigelson, F. O. Brady, in: *Molecular Mechanism of Oxygen Activation*, (Ed. O. Hayashi), Academic Press, New York, **1974**, 87; b) Y. Saeki, M. Nozaki, S. Senoh, *J. Biol. Chem.* **1980**, *255*, 8465.
[106] L. J. Dolby, D. L. Booth, *J. Am. Chem. Soc.* **1966**, *88*, 1049.
[107] J. R. Mahajan, B. J. Nunes, H. C. Aravjo, G. A. L. Ferreira, *J. Chem. Res. (S)* **1979**, 284.
[108] R. Sreekumar, R. Padmakumar, *Tetrahedron Lett.* **1997**, *38*, 5143.
[109] M. Takemoto, Y. Iwakiri, Y. Suzuki, K. Tanaka, *Tetrahedron Lett.* **2004**, *45*, 8061.
[110] See for example: a) R. J. Sundberg, *Chemistry of Indoles*, Academic Press, New York, **1970**; b) W. J. Houlihan, *Indoles*, part 1, John Wiley, New York, **1972**.
[111] W. Adam, D. Reinhardt, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1503.

And indeed, with the protected substrate **83**, the main product was the desired **84**, although only by 75% conversion after 5 hours.

In light of our results, we can postulate that under the $Fe/H_2O_2/AcOH$ system conditions the unprotected indole is quickly transformed to the corresponding carbamate that then undergoes further oxidative transformations, while the protected, partially inactivated, indole generates a more stable intermediate, which slowly decomposes to the final product.

Aldehydes are the most difficult carbonyl compounds to be obtained by oxidative cleavage, due to their sensibility to further oxidations. Usually ozone or a combination of osmium tetroxide and sodium periodate are recommended for their preparation. Under our standard conditions, styrene was completely converted to an equimolar mixture of benzaldehyde and benzoic acid (Table **12**, entry 10), and upon further addition of hydrogen peroxide, the major product detected was the acid **87** that clearly derives from further oxidation of the aldehyde and not from a direct oxidation of the substrate. Cinnamoyl alcohol was efficiently transformed in benzaldehyde, revealing a high selectivity of the system for the cleavage of double bonds even in the presence of an easily oxidisable group, such as an alcohol (Table **12**, entry 13).

Indene is another common substrate for oxidative cleavage. It can be cleaved with different oxidants, such as ozone, potassium chromate and oxygen to give several derivatives bearing different oxygenated groups. Unfortunately, the $Fe/H_2O_2/CH_3COOH$ system proved to be ineffective and no carbonyl products were detected (Table **12**, entry 9). The same inertness was noticed for tetraphenylethylene **85** (Table **12**, entry 8).

The direct oxidation of cyclohexene to adipic acid remains a paramount reaction of organic chemistry. Adipic acid is an important chemical, whose production is necessary for the manufacture of nylon-6,6, which is used in carpet fibers, upholstery, tire reinforcements, auto parts, apparel and other products. Most industrial processes of adipic acid production use nitric acid oxidation of cyclohexanol, cyclohexanone, or both, which are accessible from benzene.[112] The emission of nitrous oxide derived from the worldwide production of adipic acid represents 5 to 8% of the global anthropogenic emission of N_2O, which is commonly thought to cause global warming and ozone depletion[113] as well as acid rain and smog. Therefore, the development of environmentally friendly practical procedures for the oxidation of cyclohexene is highly desiderable. The first example of a green process for this

[112] D. D. Davis, D. R. Kemp, in: *Kirk-Ohmer Encyclopedia of Chemical Technology*, vol. 1, (Eds. J. I. Kroschwitz, M. Howe-Grant), Wiley, New York, **1991**, 466.
[113] R. E. Dickinson, R. J. Cicerone, *Nature* **1986**, *319*, 109.

important transformation was described by Noyori and co-worker in 1998.[114] Noyori's system uses hydrogen peroxide as oxidant, produces water as the only by-product and is made possible through the presence of a catalytic amount of a tungsten oxide and a phase-transfer catalyst. Unfortunately, its industrial application is still not possible as 4 moles of hydrogen peroxide are consumed per mole adipic acid and its cost is therefore prohibitive. Recently, an alternative benign method for direct oxidation of cyclohexene to adipic acid in a nearly quantitative yield was proposed by Deng and co-workers.[115] They replaced the expensive phase-transfer catalyst of the above protocol with organic acids, such as oxalic and succinic acid, but the process still needs large amount of hydrogen peroxide. Adipic acid can also be obtained by a biocatalytic strategy that uses *Escherichia Coli* to convert D-glucose into *cis,cis*-musconic acid, suppressing the problems of petroleum-based feedstocks and generation of undesired by-products.[116] However, also this process is too expensive to be scaled-up. Among the "not green" approaches to this reaction, ozone, along with osmium tetroxide and permanganate, represent still the reagents of choice[117] for the oxidative cleavage of cyclohexene and derivatives to the corresponding acids, aldehydes and alcohols.

Our iron-catalysed oxidative cleavage of cyclohexene gave a complex mixture of oxygenated products (Table **12**, entry 11). 1-Phenylcyclohexene, considered to be less reactive, gave a comparable result (Table **12**, entry 12).

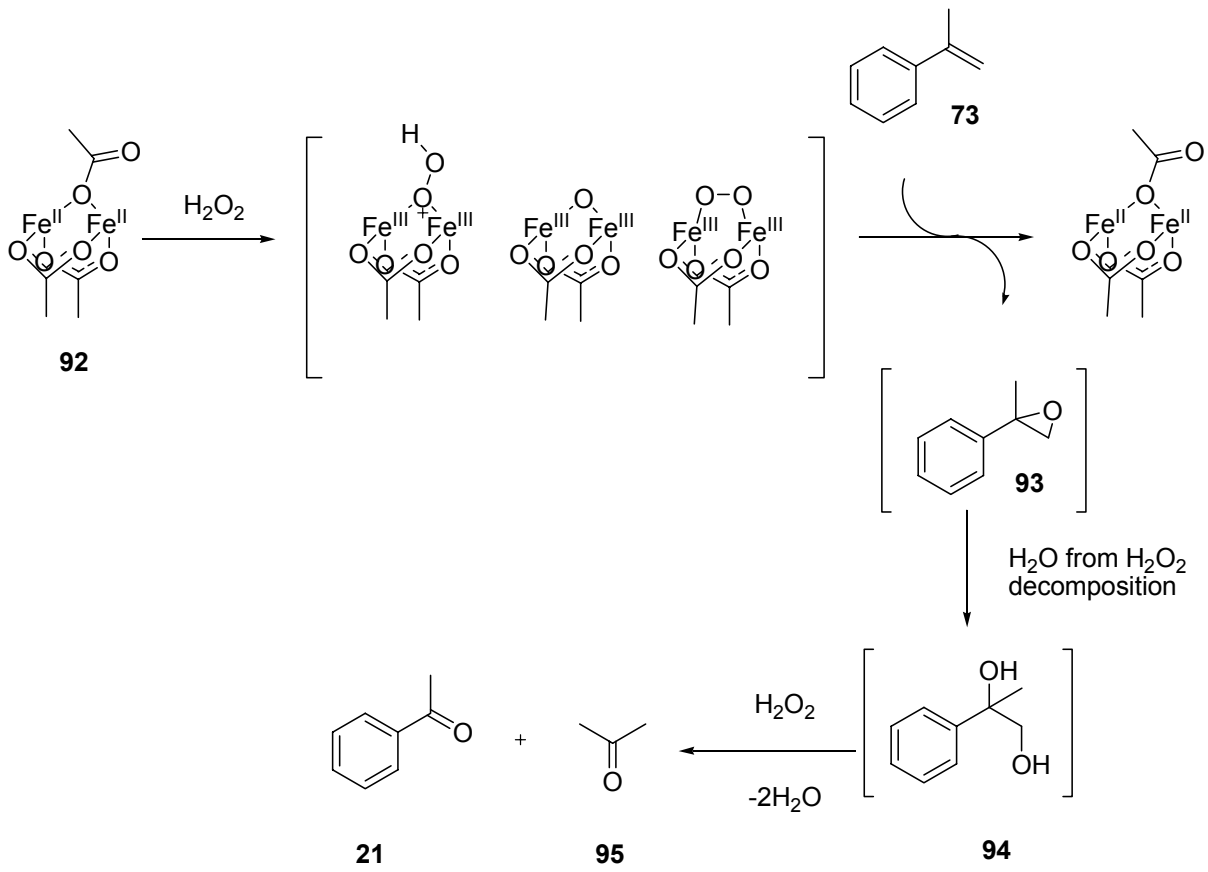
Although disappointingly, these results are similar to those reported for ruthenium-catalysed cleavage of 1-phenylcyclohexene that gives in most cases a mixture of all possible oxygenation products (acid, aldehyde, epoxide and diol).[118]

3.3.3 Proposed Mechanism

Considering the novelty of the system, no literature data are available about mechanicistic studies and possible pathways. Taking into account the numerous studies conducted on the activation of hydrogen peroxide by iron and the different species supposed to be intermediates,[101] we proposed a possible mechanism for this new protocol. The *in situ*

[114] a) K. Sato, M. Aoki, R. Noyori, *Science* **1998**, 1646; b) C. Bolm, O. Beckmann, O. A. G. Dabard, *Angew. Chem. Int. Ed.* **1999**, *38*, 907; *Angew. Chem.* **1999**, *111*, 957; c) R. Noyori, M. Aoki, K. Sato, *Chem. Commun.* **2003**, 1977.
[115] Y. Deng, Z. Ma, K. Wang, J. Chen, *Green Chem.* **1999**, *1*, 275.
[116] K. M. Draths, J. W. Frost, *J. Am. Chem. Soc.* **1994**, *116*, 399.
[117] M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, Washington, DC, **1990**, 77.
[118] See for example: a) D. Yang, C. Zang, *J. Org. Chem* **2001**, *66*, 4814; b) S. Wolfe, S. K. Hasan, J. R. Campbell, *J. Chem. Soc. D* **1970**, 1420.

formation of diiron species in the presence of carboxylic acids is well described and the activation of the oxidant could happen through the formation of Fe(III)-OOH species,[101] or equivalent, as shown in Scheme **25**. Epoxidation of the starting material, hydrolysis of the newly formed epoxide and oxidation of the diol by hydrogen peroxide could be involved as intermediate passages, leading to the final products.

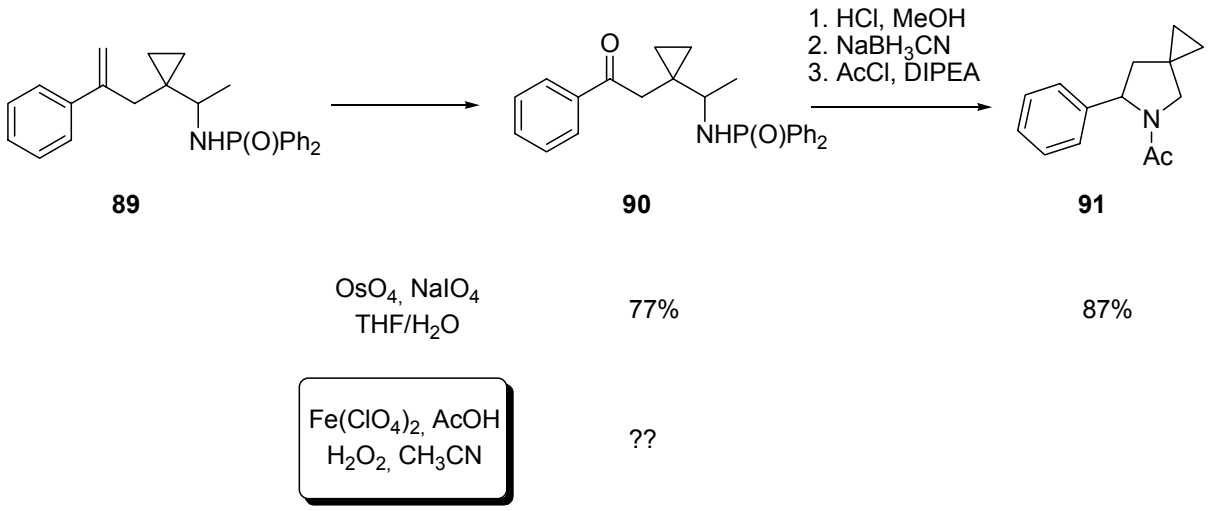


Scheme 25. Proposed mechanism for the Fe-catalysed oxidative cleavage.

3.3.4 Conclusion

In summary, we demonstrated the applicability of the $Fe(ClO_4)_2/CH_3COOH/H_2O_2$ system to the oxidative cleavage of double bonds. The reaction conditions were studied and optimised, demonstrating the importance of the presence of an additive, namely acetic acid, to enhance the feature of the system. Substrates with various substitution pattern were considered, revealing a limitation of the applicability of the protocol to α,α-disubstituted styrenes, which were easily and selectively transformed into the corresponding acetophenone derivatives in good yields. Although the new methodology here reported failed in being of general

application, nevertheless it could represent an alternative to other, more toxic, systems, as, for example, in the synthesis of azaspirocycles reported by Wipf and co-workers.[119] The oxidative cleavage of the starting material propargyl phosphinamide represents a key step in this synthetic route and is here performed with the $OsO_4/NaIO_4$ system (Scheme **26**). The use the new iron-based method could help to improve the protocol from both the economic and environmental point of view, by avoiding the use of toxic and expensive osmium tetroxide.



Scheme 26. Synthesis of azaspirocycles by Wipf and co-workers.[119]

[119] P. Wipf, C. R. J. Stephenson, M. A. A. Walczak, *Org. Lett.* **2004**, *6*, 3009.

4. Studies towards Enantioselective CH Activation with TACN

4.1 Introduction

Cyclic polyamines represent an extremely interesting class of organic molecules, particularly in view of the numerous applications and peculiar properties of their metal complexes.[120] Among them, the small cyclic triamine 1,4,7-trimethyltriazacyclononane (TM-TACN)[121] (**97**) (Figure **6**) has received considerable attention.

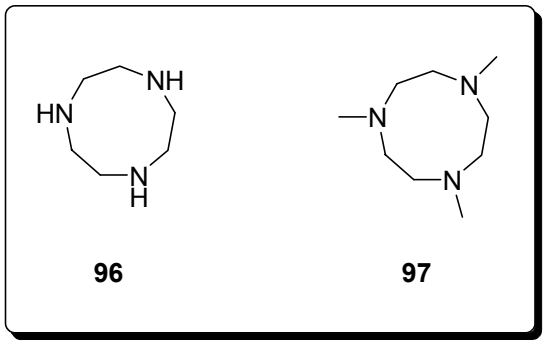


Figure 6. Triazacyclonanane (TACN) **96** and trimethyltriazacyclononane (TM-TACN) **97**.

4.1.1 Triazacyclononanes Complexes

Coordination complexes of transition metals with substituted triazacyclononanes have been proposed as structural and functional models for the metallic core of protein-complexed metal-containing redox enzymes.[122] An iron-TM-TACN complex has also been shown to be an effective DNA-cleavage agent for biochemical purposes.[123]

Interest in TACN-derived catalysts for alkene epoxidation with hydrogen peroxide largely originates from work at Unilever on detergent additives to oxidise organic staining

[120] For reviews see for example: a) M. Mitewa, P. R. Bontchev, *Coord. Chem. Rev.* **1994**, *135*, 129; b) E. Kimura, *Tetrahedron* **1992**, *48*, 6175.
[121] a) K. Wieghardt, P. Chaudhuri, B. Nuber, J. Weiss, *Inorg. Chem.* **1982**, *21*, 3086; b) K. Wieghardt, S. Brodka, K. Peters, E. M. Peters, A. Z. Simon, *Naturforsch. B* **1987**, *42*, 279.
[122] See for example: a) K. Wieghardt, *Angew. Chem. Int. Ed.* **1989**, *28*, 1153; *Angew. Chem.* **1989**, *101*, 1149; b) K. Wieghardt, K. Pohl, U. Bossek, B. Nuber, J. Weiss, *Naturforsch. B* **1988**, *43b*, 1184; c) A. A. Belal, P. Chaudhuri, I. Fallis, L. J. Farrugia, R. Hartung, N. M. McDonald, B. Nuber, R. D. Peacock, J. Weiss, K. Wieghardt, *Inorg. Chem.* **1991**, *30*, 4397.
[123] G. C. Silver, W. C. Trogler, *J. Am. Chem. Soc.* **1995**, *117*, 3983.

materials.[124] Excellent bleaching properties were observed, but these were associated with unwanted fabric damage following prolonged washing cycles. Besides their activity as powerful bleaching and hygiene-delivering agents, preformed or *in-situ* generated metal complexes of TM-TACN have been shown to be active catalysts in the oxidation (epoxidation[125] and dihydroxylation[126]) of olefins, sulfides[127] and alcohols,[128] often with H_2O_2 as terminal oxidant. Recently, Shul'pin *et al.* have described the oxidation of simple hydrocarbons to alcohols and ketones with H_2O_2, catalysed by a binuclear Mn(IV) complex of TM-TACN in the presence of acetic acid.[129] The peculiar catalytic activity of TACN-metal complexes have been ascribed to the relatively small size of the ring, which forces endodentate orientation of the three electron pairs on the nitrogens and allows only facial coordination modes in octahedral complexes (contrary to others polyazamacrocycles, such as Cyclam[130] or porphyrines[131]).

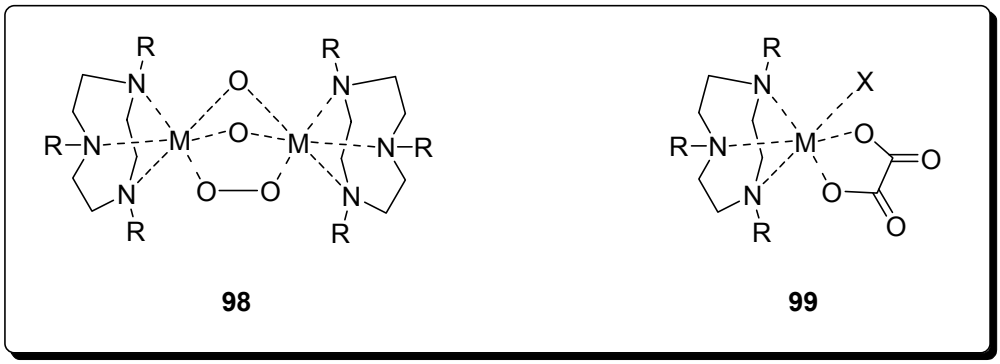


Figure 7. Examples if c*is*-dioxo and fac-μ-trioxo complexes formed by triazacyclononanes.

[124] a) R. Hage, J. E. Iburg, J. Kerschner, J. H. Koek, L. M. Lempers, R. J. Martens, U. S. Racherla, S. W. Russell, T. Swarthoff, M. R. P. van Vliet, J. B. Warnaar, L. van der Wolf, B. Krijnen, *Nature* **1994**, *369*, 637; b) J. H. Koek, E. W. M. J. Kohlen, S. W. Russell, L. van der Wolf, P. F. ter Steeg, J. C. Hellemons, *Inorg. Chim. Acta* **1999**, *295*, 189; c) T. L. Favre, R. Hage, K. van der Helm-Rademaker, J. H. Koek, R. J. Martens, T. Swathoff, M. R. P. van Vliet, *Eur. Pat.* 91 458 397, **1991**.

[125] a) D. De Vos, T. Bein, *Chem. Commun.* **1996**, 917; b) D. De Vos, B. F. Sels, M. Reynaers, Y. V. S. Rao, P. A. Jacobs, *Tetrahedron Lett.* **1998**, *39*, 3221; c) A. Berkessel, C. A. Sklorz, *Tetrahedron Lett.* **1999**, *40*, 7965.

[126] D. E. De Vos, S. de Wildeman, B. F. Sels, P. J. Grobet, P. A. Jacobs, *Angew. Chem. Int. Ed.* **1999**, *38*, 980; *Angew. Chem.* **1999**, *111*, 1033.

[127] R. W. Hay, T. Clifford, N. Govan, *Transition Met. Chem.* **1998**, *23*, 619; b) D. H. R. Barton, W. Li, J. A. Smith, *Tetrahedron Lett.* **1998**, *39*, 7055.

[128] a) W.-H. Fung, W.-Y. Yu, C.-M. Che, *J. Org. Chem.* **1998**, *63*, 2873; b) C. Zondervan, R. Hage, B. L. Feringa, *Chem. Commun.* **1997**, 419.

[129] a) G. B. Shul'pin, J. R. Lindsay-Smith, *Russ. Chem. Bull.* **1998**, *47*, 2379; b) G. B. Shul'pin, G. Süss-Fink, L. S. Shul'pina, *J. Mol. Cat. A* **2001**, *170*, 17 and references therein.

[130] For reviews, see: a) F. C. J. M. van Veggel, W. Verboom, D. N. Reinhoudt, *Chem. Rev.* **1994**, *94*, 279; b) M. D. Ward, *Chem. Soc. Rev.* **1995**, 121.

[131] For reviews, see for example: a) B. Meunier, *Chem. Rev.* **1992**, *92*, 1411; b) M. K. Stern, J. T. Groves, in: *Manganese Redox Enzymes*, (Ed. V. Pecoraro), VCH: New York **1992**, 233.

The cooperative interaction of the three nitrogens, the macrocyclic effect and the absence of retro-donation resulted in a remarkable stability for complexes where the metal possesses a high oxidation state. The constraint to facial coordination, moreover, grants facile access to uncommon *cis*-dioxo and fac-μ-trioxo configurations (in cases where oxygen atoms complete the coordination sphere) as shown in Figure **7**

Although many transition metal mononuclear complexes have been described,[132] the most common and functionally interesting structures for TM-TACN-metal complexes in high oxidation states are binuclear complexes bearing bridged μ-oxo ligands.[133]

4.1.2 Synthesis: General Approaches

The synthesis of triazacyclononanes is far from trivial. The formation of middle-size rings is less energetically favoured in comparison to the smaller five- and six-membered homologues. Two main strategies have been developed for the synthesis of *N*-substituted 1,4,7-triazacyclononanes.

The most commonly employed method contemplates the assessment of the cyclic nine-membered moiety and subsequent introduction of substituents on nitrogen atoms. This approach is also motivated by the existence of an efficient synthesis of the simple TACN skeleton by Searle and Gene,[134] later improved by Madison and co-workers,[135] based on the classical protocol by Richman and Atkins[136] The two possible disconnections pathways offered by this method are shown in Scheme **27**.

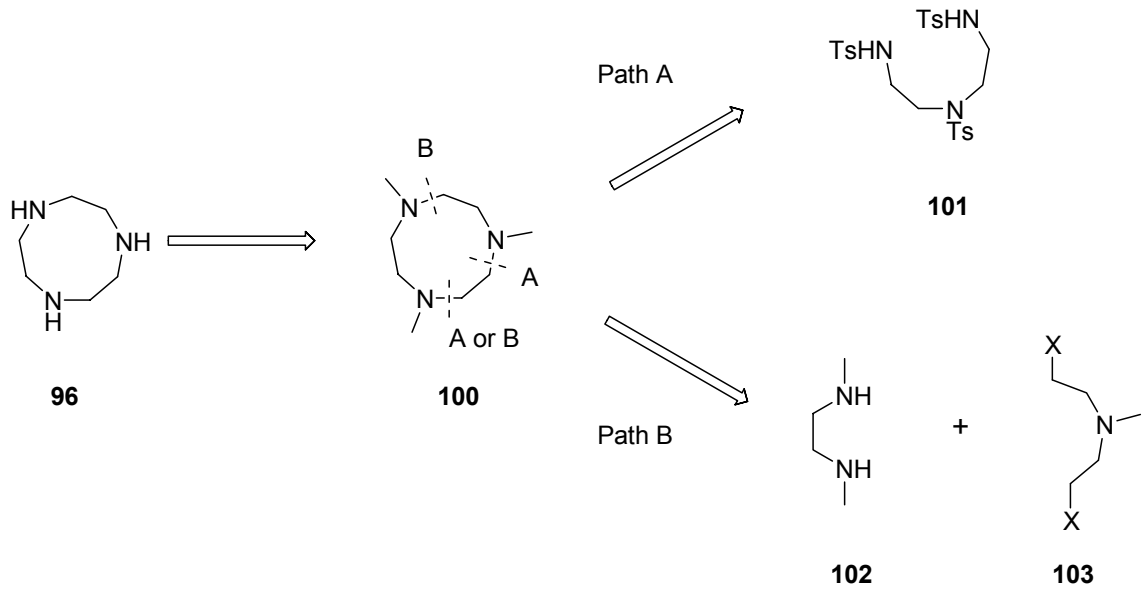
[132] V. C. Quee-Smith, L. Del Pizzo, S. H. Jureller, J. L. Kerschner, R. Hage, *Inorg. Chem.* **1996**, *35*, 6461; b) W.-C. Cheng, W.-Y. Yu, K.-K. Cheung, C.-M. Che, *J. Chem. Soc., Chem Commun.*, **1994**, 1063; c) S.-M. Au, S.-B. Zhang, W.-H. Fung, W.-Y. Yu, C -M. Che, K.-K. Cheung, *Chem. Commun.* **1998**, 2677; d) W.-C. Cheng, W.-Y. Yu, K.-K. Cheung, C.-M. Che, *J. Chem. Soc., Dalton Trans.* **1994**, 57; e) M. C. W. Chan, F.-W. Lee, K.-K. Cheung, C.-M. Che, *J. Chem. Soc., Dalton Trans.* **1999**, 3197; f) B. Qian, L. M. Henling, J. C. Peters, *Organometallics* **2000**, *19*, 2805; g) N. A. H. Male, M. E. Skinner, P. J. Wilson, P. Mountford, M. Schröder, *New J. Chem.* **2000**, *24*, 575.

[133] a) K. Wieghardt, U. Bossek, B. Nuber, J. Weiss, J. Bonvoisin, M. Corbella, S. E. Vitols, J. J. Girerd, *J. Am. Chem. Soc.* **1988**, *110*, 7398; b) J. H. Koek, S.W. Russell, L. van der Wolf, R. Hage, J. B. Warnaar, A. L. Spek, J. Kerschner, L. Del Pizzo, *J. Chem. Soc., Dalton Trans.* **1996**, 353; c) P. Neubold, K. Wieghardt, B. Nuber, J. Weiss, *Inorg. Chem.* **1989**, *28*, 459; d) S. C. Payne, K. S. Hagen, *J. Am. Chem. Soc.* **2000**, *122*, 6399; e) R. Hage, E. A. Gunnewegh, J. Niël, F. S. B. Tjan, T. Weyhermüller, K. Wieghardt, *Inorg. Chim. Acta* **1998**, *268*, 43; f) S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Jr. Young, C. J. Cramer, L. Que Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11555.

[134] G. H. Searle, R. J. Gene, *Aust. J. Chem.* **1984**, *37*, 959.

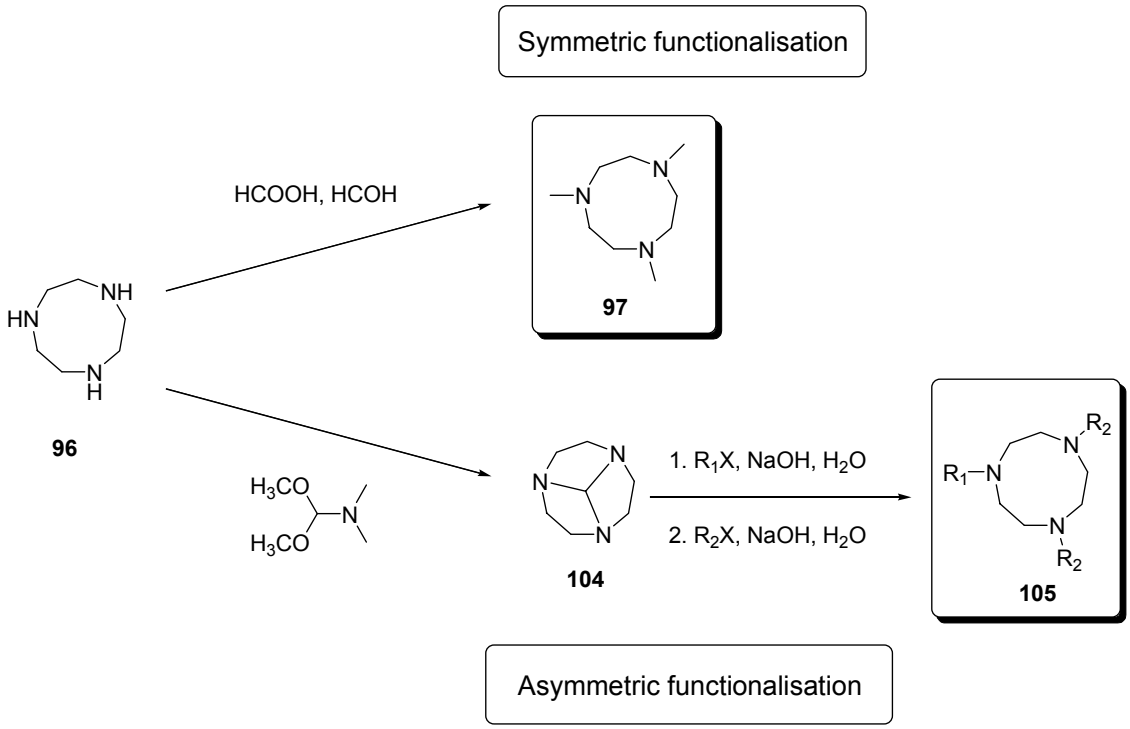
[135] S. A. Madison, D. J. Batal, *U. S. Pat.*, 5 284 944, **1994**.

[136] a) J. E. Richman, T. J. Atkins, *J. Am. Chem. Soc.* **1974**, *96*, 2268; b) J. E. Richman, T. J. Atkins, W. F. Oettle, *Org. Synth.* **1978**, *58*, 86.



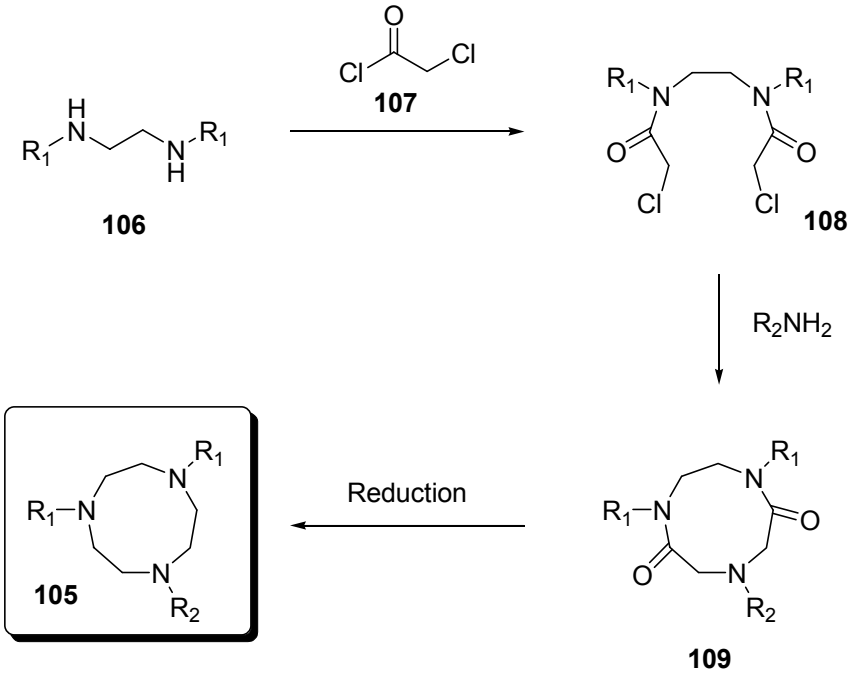
Scheme 27. Possible disconnections via Richman-Atkins cyclisation.

The final deprotection step, besides requiring harsh conditions, is also generally low-yielding. Compound **96** can be then symmetric substituted, for example by methylation (Path A, Scheme **28**), or asymmetric functionalised (Path B, Scheme **28**), offering a wide range of substitution patterns.



Scheme 28. Possible functionalisation pathways of TACN.

An alternative and more flexible approach to the synthesis of asymmetric substituted triazacyclononane was developed by Bradshaw and Krakowiak.[137] The cyclic moiety is obtained first as amide **109** and then reduced to the corresponding cyclic triamine **105**, as shown in Scheme **29**.



Scheme 29. *Crab-like* cyclisation approach by Bradshaw and Krakowiak.[137]

Innumerable variations of the basic triazacycle have been described in the literature, employing the first or the second route, and different groups, such as aliphatic and aromatic,[138] allylic,[139] polyfluorinated alkyl chains (for fluorous biphasic catalysis),[140] have been introduced in alternative to the original methyl groups as nitrogen substituents.

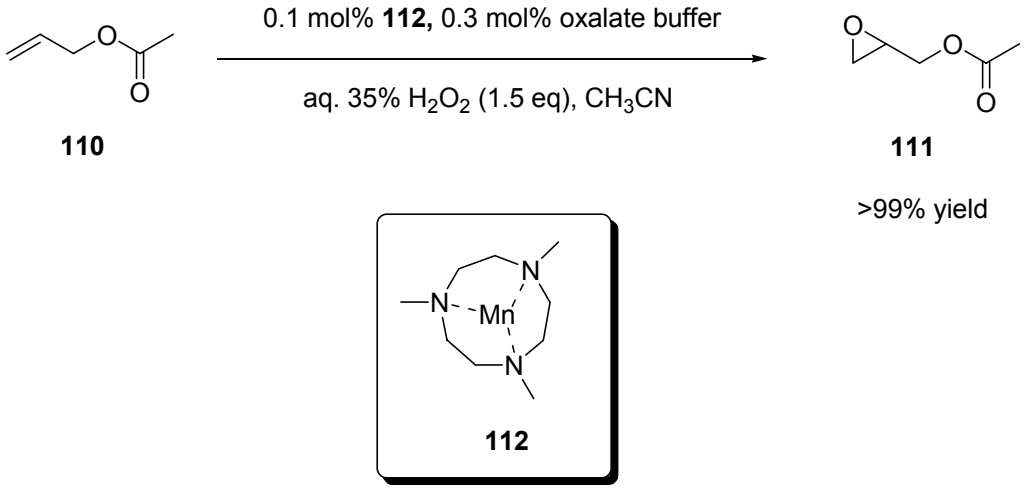
[137] See for example: a) K. E. Krakowiak, J. S. Bradshaw, N. K. Dalley, W. Jiang, R. M. Izatt, *Tetrahedron Lett.* **1989**, *30*, 2897; b) K. E. Krakowiak, J. S. Bradshaw, R. M. Izatt, *J. Heterocyclic Chem.* **1990**, *27*, 1585.
[138] See for example: a) P. C. McGowan, T. J. Podesta, M. Thornton-Pett, *Inorg. Chem.* **2001**, *40*, 1445; b) G. H. Walf, R. Benda, F. J. Litterst, U. Stebani, S. Schmidt, G. Lattermann, *Chem. Eur. J.* **1998**, *4*, 93.
[139] L. J. Farrugia, P. A. Lovatt, R. D. Peacock, *Inorg. Chim. Acta* **1996**, *246*, 343.
[140] J.-M. Vincent, A. Rabion, V. K. Yachandra, R. H. Fish, *Angew. Chem. Int. Ed.* **1997**, *36*, 2346; *Angew. Chem.* **1997**, *109*, 2438.

4.1.3 Application of Metal-Triazacyclononane Complexes

4.1.3.1 Mn-TACN Complexes Catalysed Epoxidations

Manganese complexes based on TM-TACN have been found to be active catalysts for the epoxidation of olefins, but the system efficiency was limited by their pronounced catalase activity. De Vos and Bein improved the system by carrying out the reaction in acetone at 0 °C. Under these conditions, simple disubstituted olefins were converted into the corresponding epoxides with TON up to 1000[141a] and benzylic alcohols were easily converted to benzaldehydes.

The same research group showed that the addition of oxalate buffer as co-ligand strongly improves the epoxidising activity of the Mn-TACN catalyst.[142] Simple disubstituted olefins, especially terminal ones, were converted to the corresponding epoxides in up to 99% yield, as shown in Scheme **30**.



Scheme 30. Epoxidation of olefins catalysed by Mn-TMTACN **112** by De Vos and Bein.[142]

Berkessel and Sklorz further improved the system employing ascorbic acid as co-ligand.[125c] Under these new conditions, methyl acrylate was converted to its epoxide in 97% yield and 2-pentanol yielded 2-pentanone in almost quantitative yield. Recently, the combination of $[Mn_2O_3(TM\text{-}TACN)_2](PF_6)_2$ with glyoxylic acid methylester methylhemiacetal and hydrogen

[141] a) D. E. De Vos, T. Bein, *Chem. Commun.* **1996**, 917; b) C. Zondervan, R. Hage, B. L. Feringa, *Chem. Commun.* **1997**, 419.
[142] D. E. De Vos, B. F. Sels, M. Reynaers, Y. V. Subba Rao, P. A. Jacobs, *Tetrahedron Lett.* **1998**, *39*, 3221.

peroxide has been demonstrated particularly active in epoxidation as well as in *cis*-dihydroxylation of olefins.[143]

Another way to suppress the catalase activity peculiar of metal-TM-TACN complexes is the heterogenisation of the catalyst. Jacobs and co-workers reported the first example of heterogeneous manganese triazacyclononane active in epoxidation and *cis*-hydroxylation of olefins (Figure **8**).[126] The catalyst was formed *in situ* and disubstituted olefins were epoxidised with selectivity up to 90%.

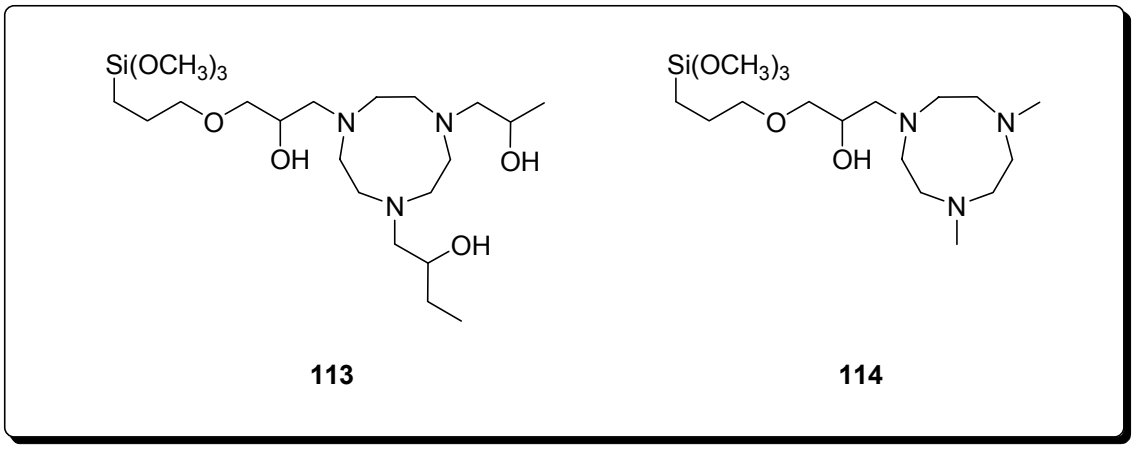


Figure 8. Heterogenisation of triazacyclononanes by Jacobs. [126]

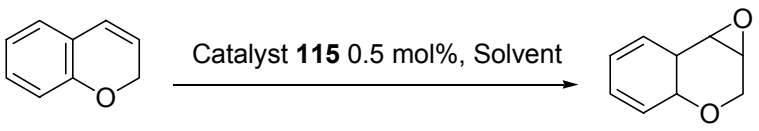
Recently, a new polymeric manganese 1,4,7-triazacyclononane complex has been developed by Bolm and co-workers and employed for the epoxidation of olefins with selectivity up to 100%.[144]

Chiral TACN

The impressive number of TACN derivatives described in the literature contrasts with the very few known examples of chiral variations of the azacyclononane skeleton. This is even more surprising, considering the rich application scope of the corresponding metal complexes, and, accordingly, the potential for asymmetric catalysis in a variety of synthetically useful reactions. Moreover, the nitrogen atoms of the cycle, which are involved in the ligation of the metal active centres, are in close proximity with sp^3 hybridised carbon

[143] J. Brinksma, L. Schmieder, G. van Vliet, R. Boaron, R. Hage, D. E. De Vos, P. L. Alsters, B. L. Feringa, *Tetrahedron Lett.* **2002**, *43*, 2619.
[144] A. Grenz, S. Ceccarelli, C. Bolm, *Chem. Commun.* **2001**, 1726.

atoms: replacement of these with stereogenic carbon centres offers an easy handle for introduction of chirality. The first report of a chiral analogue of TM-TACN **97** employed in catalysis appeared in patent in 1995.[145] Beller and co-workers synthesised 1,4,7-trimethyl-2,3-cyclohexano-1,4,7-triazacyclononane **115** (Figure **9**) starting from enantiopure *N,N'*-dimethyl-cyclohexyldiamine and successfully applied its manganese complex to the enantioselective epoxidation of olefins with enantiomeric excesses up to 90% (Scheme **31**).



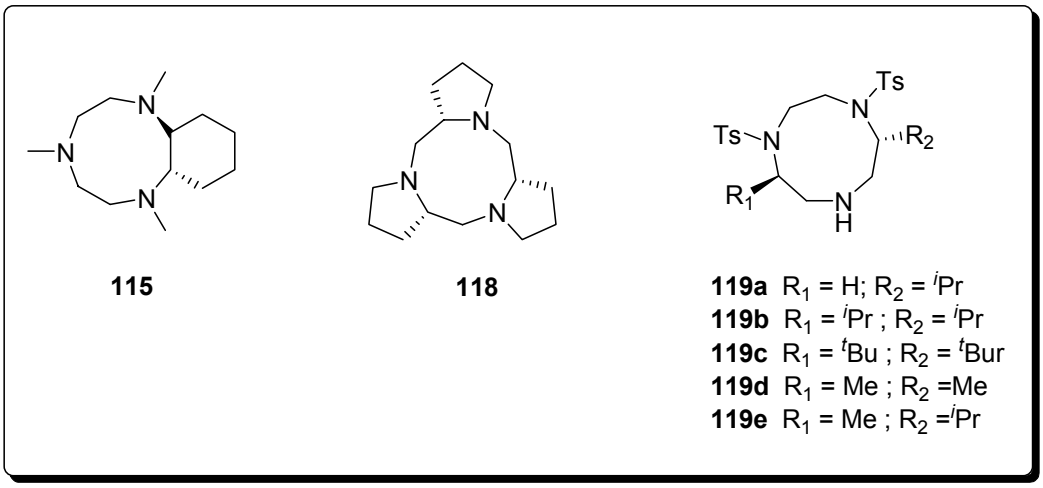
116 **117**

H_2O_2 35 % ee 80 %
yield 25 %

$NaIO_4$ or TBHP ee up to 90%

Scheme 31. Enantioselective epoxidation of chromene **116** by Beller.[145]

Despite the interest in triazacyclononanes there are few examples of the synthesis of chiral analogues where, as in case above, the stereochemistry is directly associated with the macrocyclic ring itself.



115 **118**

119a R_1 = H; R_2 = ^{i}Pr
119b R_1 = ^{i}Pr ; R_2 = ^{i}Pr
119c R_1 = ^{t}Bu ; R_2 = ^{t}Bur
119d R_1 = Me ; R_2 =Me
119e R_1 = Me ; R_2 =^{i}Pr

Figure 9. Examples of chiral triazacyclononanes bearing the stereocenters on the ring.

[145] M. Beller, A. Tafelsh, R. W. Fisher, B. Scharbert, DE 19523891, **1995**.

Gibson and co-workers devoted many studies to the development of a straightforward pathway for the synthesis of TACN bearing one or two stereocenters on the macrocyclic ring. Isopropyl substituted 1,4,7-triazacyclononane **119a** (Figure **9**) was accessed through an *in situ* sequential cyclisation method, using as chirality source (*L*)-valine methyl ester hydrochloride.[146] Macrocycles **119b-e** (Figure **9**) bearing two stereocenters on the cycle were obtained via Richman-Atkins cyclisation involving the use of chiral bistosamides, readily prepared by the ring opening of chiral tosyl aziridines, as the nucleophilic components in the cyclisation.[147] Independently, Kim and co-workers reported the synthesis of compound **119b** by azide opening of enantiopure aziridine.[148]

In situ epoxidations were carried out using macrocycle **119b** by application of the stereoselective method of Berkessel and Sklorz involving manganese(II) acetate with an ascorbate/ascorbic acid co-ligand system. Styrene gave (*R*)-styrene oxide in up to 23% ee with poor to moderate yields.

Recently, Bolm and co-workers reported the synthesis of the enantiopure C_3-symmetric trispyrrolidine-1,4,7-triazacyclononane **118** by reduction of (*L*)-proline-derived cyclotripeptide **120**. Its dinuclear manganese complex showed catalytic activity in the epoxidation of vinylarenes and styrene was converted to (*S*)-styrene epoxide with 24% ee.[149]

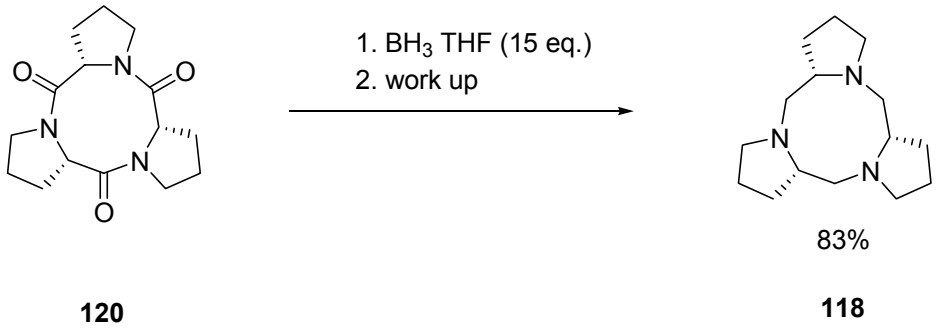
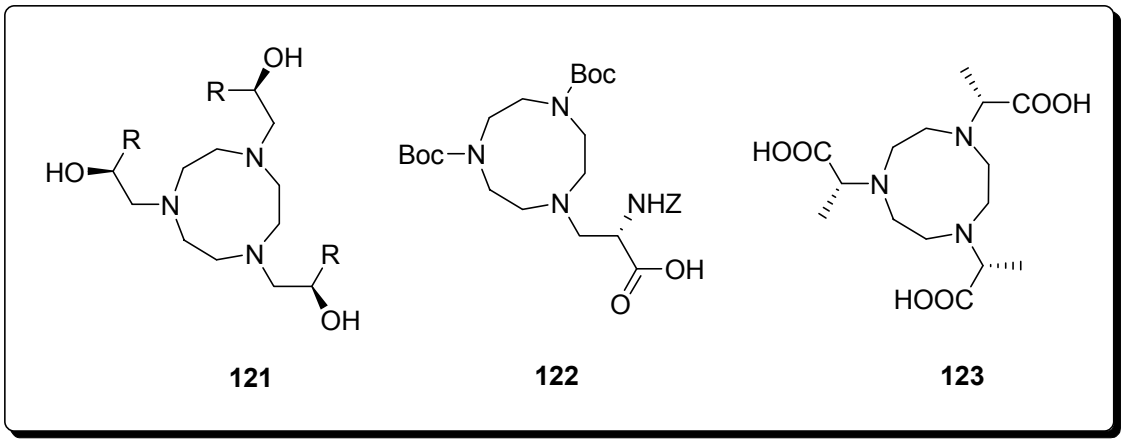


Figure 10. Synthesis of trispyrrolidine-1,4,7-triazacyclononane **118** by Bolm and co-workers.[149]

Chiral TACN systems bearing the chirality source on the pendant arm have been mainly synthesised by reaction of the TACN's nitrogens with chiral epoxides, yielding cycles **121**

[146] G. Stones, G. Argouarch, A. R. Kennedy, D. C. Sherrington, C. L. Gibson, *Org. Biomol. Chem.* **2003**, *1*, 2357.
[147] a) G. Argouarch, C. L. Gibson, G. Stones, D. C. Sherrington, *Tetrahedron Lett.* **2002**, *43*, 3795. b) See also: J. E. W. Scheuermann, F. Ronketti, M. Motevalli, D. V. Griffiths, M. Watkinson, *New J. Chem.* **2002**, *26*, 1054.
[148] B. M. Kim, S. M. So, H. J. Choi, *Org. Lett.* **2002**, *6*, 949.
[149] C. Bolm, N. Meyer, G. Raabe, T. Weyhermüller, E. Bothe, *Chem. Commun.* **2000**, 2435.

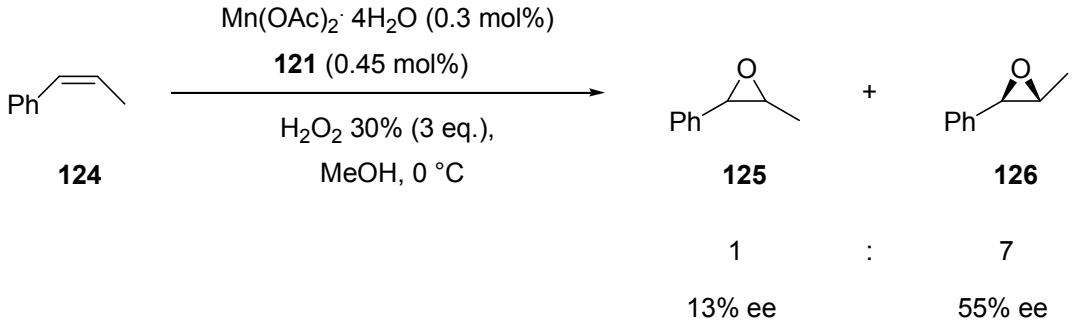
(Figure **11**) bearing an oxygenated stereogenic centre (an additional ligation site) on the β position in the side chains.[150]



121 **122** **123**

Figure 11. Examples of chiral triazacyclononanes bearing the stereocenters on the pendant arms.

The structure of these systems has been studied in detail and Bolm and co-workers demonstrated the activity of their Mn complexes in the enantioselective epoxidation of olefins with H_2O_2.[151] *Cis*-β-methylstyrene was smoothly converted in the corresponding epoxide with a ratio *cis*/*trans* 1:3 and enantiomeric excess for the major isomer of 55%, the best one reported so far for triazacyclononanes with chiral pendant arm (Scheme **32**).



Scheme 32. Enantioselective epoxidation of *cis*-β-methylstyrene by Bolm.[149]

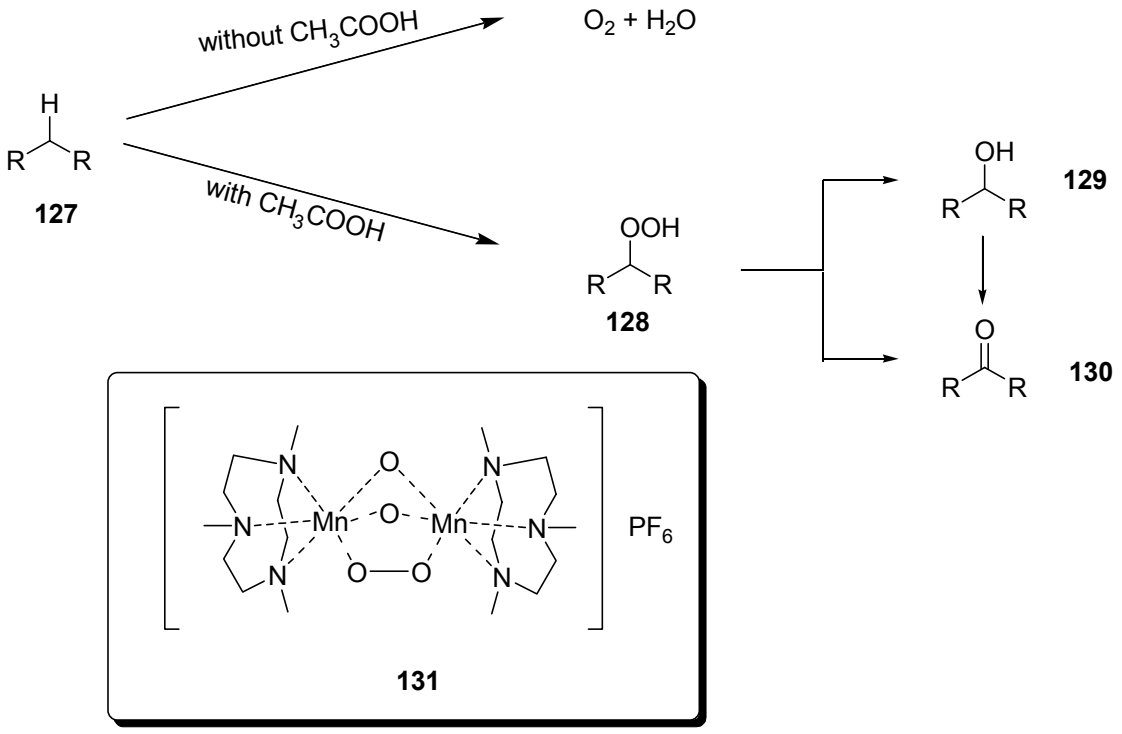
Chiral TACN have been also applied to reactions other than catalysed oxidations. For example, reaction of one nitrogen atoms of the TACN ring with (*L*)-serine-β-lactone, led to

[150] a) I. A. Fallis, L. J. Farrugia, N. M. Mc Donald, R. D. Peacock, *J. Chem. Soc., Dalton Trans.* **1993**, *18*, 2759; b) A. A. Belal, L. J. Farrugia, R. D. Peacock, J. Robb, *J. Chem. Soc., Dalton Trans.* **1989**, 931.
[151] C. Bolm, D. Kadereit, M. Valacchi, *Synlett* **1997**, 687.

the chiral protected triazacycle **122** (Figure **11**), which was employed for the construction of functionalised oligopeptides.[152]

4.1.3.2 Metal-TACN Complexes Catalysed CH Activation

Transition metal complexes of triazacyclononanes have emerged as a promising class of catalysts for the oxidation of saturated hydrocarbons with various oxidants.[153] In particular, it has recently been found that the dinuclear manganese(IV) complex $[LMn^{IV}(O)_3Mn^{IV}L]PF_6$ **131**, where L is TM-TACN, catalyses oxygenation of some alkanes by either peroxyacetic acid or hydrogen peroxide in the presence of carboxylic acids.[154] Higher alkanes, such as cyclohexane, *n*-pentane, *n*-heptane, and methylbutane, were oxidised by hydrogen peroxide at 20 °C in acetonitrile solution to afford initially the corresponding alkyl hydroperoxides **128** as the predominant products.



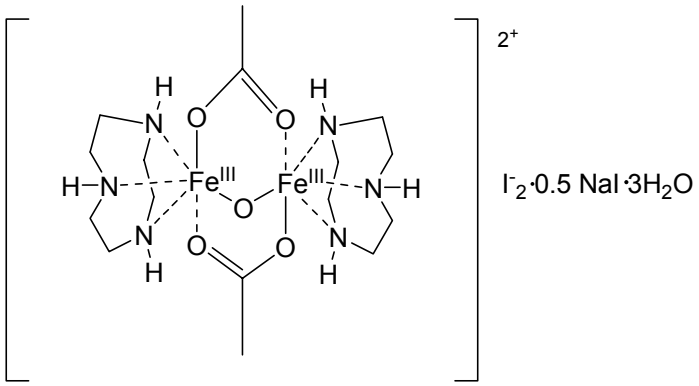
Scheme 33. Alkane oxidations catalysed by Mn-TM-TACN **131** by Shul'pin and co-workers.[154]

[152] a) P. Rossi, F. Felluga, P. Scrimin, *Tetrahedron Lett.* **1998**, *39*, 7159; b) F. Formaggio, M. Crisma, P. Rossi, P. Scrimin, B. Kaptein, Q. B. Broxterman, J. Kamphuis, C. Toniolo, *Chem. Eur. J.* **2000**, *6*, 4498.
[153] See for example: M. Contel, C. Izuel, M. Laguna, P. R. Villuendas, P. J. Alonso, R. H. Fish, *Chem. Eur. J.* **2003**, *9*, 4168.
[154] G. B. Shul'pin , G. Süss-Fink, L. S. Shul'pina, *J. Mol. Cat. A* **2001**, *170*, 17 and references therein.

Later in the course of the reaction these compounds decomposed to produce the corresponding ketones **130** and alcohols **129**, as depicted in Scheme **33**. In the absence of carboxylic acid, usually acetic acid, no alkane oxidation occurs.

Turnover numbers (TONs) for cyclohexane attained 3300 after 2 hours and the yield of oxygenated products (alkylhydroperoxide, ketone and alcohol) was 46% based on the alkane. Although the oxidant efficiency is only 30%, these results are among the best obtained to date for cyclohexane oxidation by hydrogen peroxide.[155] The system H_2O_2-**131**-CH_3COOH also transforms secondary alcohols into the corresponding ketones with quantitative yields at room temperature within few minutes. The oxygenation of *cis*- and *trans*-1,2-dimethylcyclohexane by peroxyacetic acid and **131** afforded tertiary alcohols with a marked preference for retention of stereochemistry (up to 91% for *cis*-1,2-dimethylcyclohexanol).Moreover, terminal aliphatic olefins are epoxidised and dimethylsulfide is selectively converted into dimethyl sulfoxide. More recently, Srinivas and co-workers reported the unique properties of the Mn-TM-TACN/H_2O_2 system in the oxidation of benzylic position. *In situ* prepared catalyst in the presence of carboxylate buffers selectively converted ethylbenzene in 1-phenylethanol and acetophenone with a selectivity for benzylic position up to 91%.[156]

The binuclear iron complex of TACN **132** has been found to be active in the oxygenation of alkanes by hydrogen peroxide in the presence of pyrazine-2-carboxylic acid (PCA) with TON up to 240 in the oxidation of cyclohexane (Figure **12**).[157]



132

Figure 12. Fe-TACN **132**, active catalyst in the oxidation of alkanes by H_2O_2.[157]

[155] For a review, see: U. Schuchardt, D. Cardoso, R. Sercheli, R. Pereira, R. S. da Cruz, M. C. Guerreiro, D. Mandelli, E. V Spinacè, E. L. Pires, *Applied Catalysis A: General* **2001**, *211*, 1.
[156] T. H. Bennur, S. Sabne, S. S. Deshpande, D. Srinivas, S. Sivasanker, *J. Mol. Cat. A:* **2002**, *185*, 71.
[157] G. B. Shul'pin, G. V. Nizova, Y. N. Kozlov, L. Gonzalez Cuervo, G. Süss-Fink, *Adv. Synth. Cat.* **2004**, *346*, 317.

Although the catalyst **132** resulted less active than the Mn-containing complex **131**, these results were remarkable and proved the activity of Fe-TACN complexes in the CH activation of hydrocarbons.

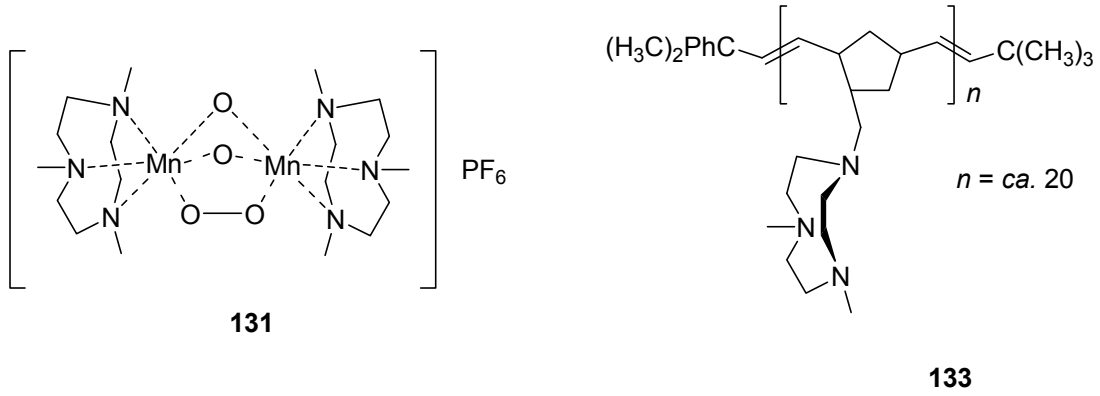
4.2 Goal of the Study

Inspired by the extensive and remarkable work of Shul'pin and co-workers in this area, we aimed to develop an enantioselective CH oxidation system based on triazacyclononanes.
Two approaches have been explored:

- Synthesis of new chiral triazacyclononanes and their application in the homogeneous Mn- and Fe-catalysed oxidation of hydrocarbons.
- Use of the achiral Mn-TM-TACN complex **131** in combination with chiral additives, i.e. carboxylic acids, towards the enantioselective and diastereoselective CH activation of arylalkanes.

4.3 Results and Discussion

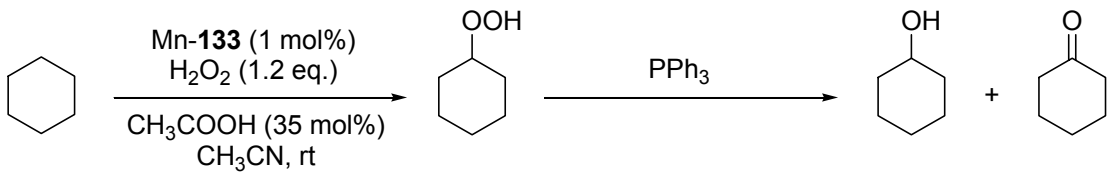
The system Mn(II)-compound **133** has been recently described as an efficient catalyst in the epoxidation of simple olefins by hydrogen peroxide in aqueous acetone-methanol medium in the presence of sodium oxalate.[144] Such a catalyst appeared relevant to compound **131**, proved to be very active in the oxygenation of some alkanes by H_2O_2 in the presence of acetic acid[158] (Figure **13**), and was therefore interesting to investigate the catalytic activity of a Mn(IV)-compound **133** complex in the oxidation of different unreactive substrates.[159]



131 **133**

Figure 13. Mn-TMTACN complex **131** and polymeric system **133**.

Due to the low solubility of **133** in acetonitrile, *in situ* formation of the active catalyst was unsuccessful and the Mn(IV) complex of the polymeric 1,4,7-triazacyclononane was prepared following a standard protocol.[133a,b] The oxidation of cyclohexane in acetonitrile at room temperature in the presence of acetic acid gave as main products the corresponding alkylhydroperoxide **134**, that, upon treatment with triphenylphosphine, decomposed in cyclohexanol and cyclohexanone (Scheme **34**).

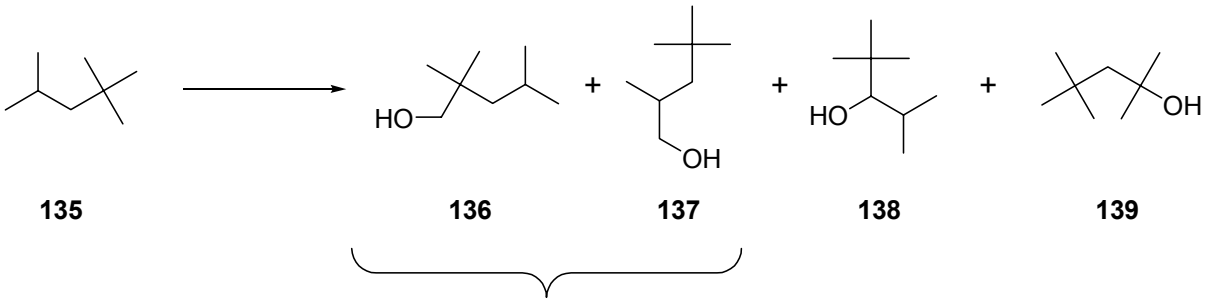


18 **134** **19** **20**

Scheme 34. Mn-**133**-catalysed oxidation of cyclohexane.

[158] G. B. Shul'pin, G. Süss-Fink, J. R. Lindsay Smith, *Tetrahedron* **1999**, *55*, 5345.
[159] G. V. Nizova, C. Bolm, S. Ceccarelli, C. Pavan, G. B. Shul'pin, *Adv. Synth. Cat.* **2002**, *344*, 899.

The oxidation of branched alkanes, such as isooctane, gave the two regioisomers of primary alcohols as major products, whereas the secondary and tertiary were formed in traces. This selectivity parameter is reversed in comparison with what found with related systems, such as O_2-H_2O_2-*hν*, where hydroxyl radical are invoked in the mechanism (Scheme **35**).



H_2O_2-**131**-CH_3CO_2H	1	:	5	:	**55**
O_2-H_2O_2-*hν*	1	:	2	:	**6**
O_2-H_2O_2-$FeSO_4$	1	:	3	:	**6**
H_2O_2-VO_3^--PCA	1	:	4	:	**9**
H_2O_2-**Mn(IV)-133**-CH_3CO_2H	**>95**		Traces		Traces

Scheme 35. Selectivity parameters in the oxidation of branched alkanes.

Moreover, the reaction proceeds without stereoselectivity in the oxidation of *cis*-decalin, giving a mixture of *trans*- and *cis*-decalols in a ratio of 1.5, whereas the homogeneous dinuclear Mn(IV) catalyst **131** gave 0.12. These studies demonstrated that C_1-symmetric triazacyclononanes are also effective ligands in the Mn-catalysed oxidation of poorly reactive substrate. Moreover, it was established that this polymeric system, although showing high selectivity for the oxidation of primary carbons, presents a lack of regioselectivity.

4.3.1 Synthetic Strategy

Inspired and encouraged by these results, we believed that C_1-symmetric chiral triazacyclononanes could lead to the enantioselective oxidation of alkanes in a homogeneous system.

On the basis of the previous system, we designed the synthesis of new of C_1-symmetric TACN bearing a chiral fragment on a nitrogen atom in α-position (Figure **14**), so that the stereogenic centre is directly bound to the nitrogen, an arrangement that, to the best of our knowledge, was previously reported in the literature only once.[160]

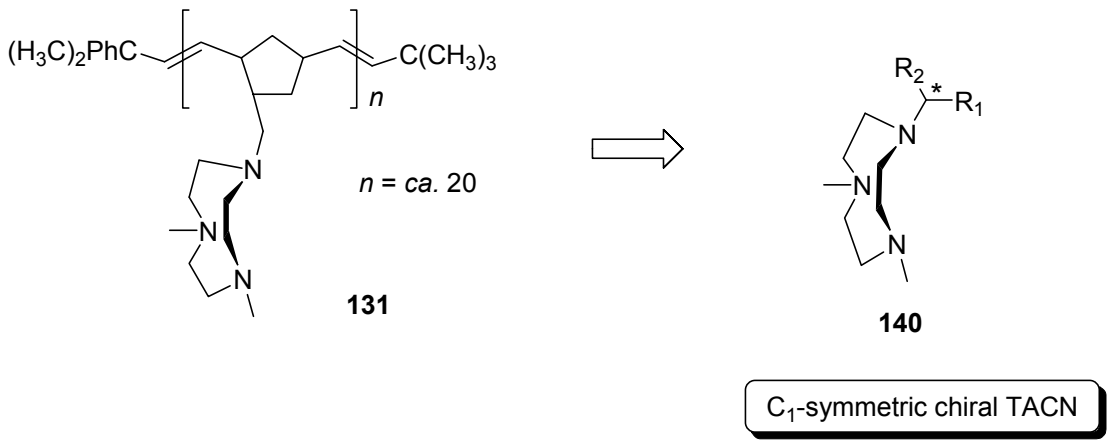
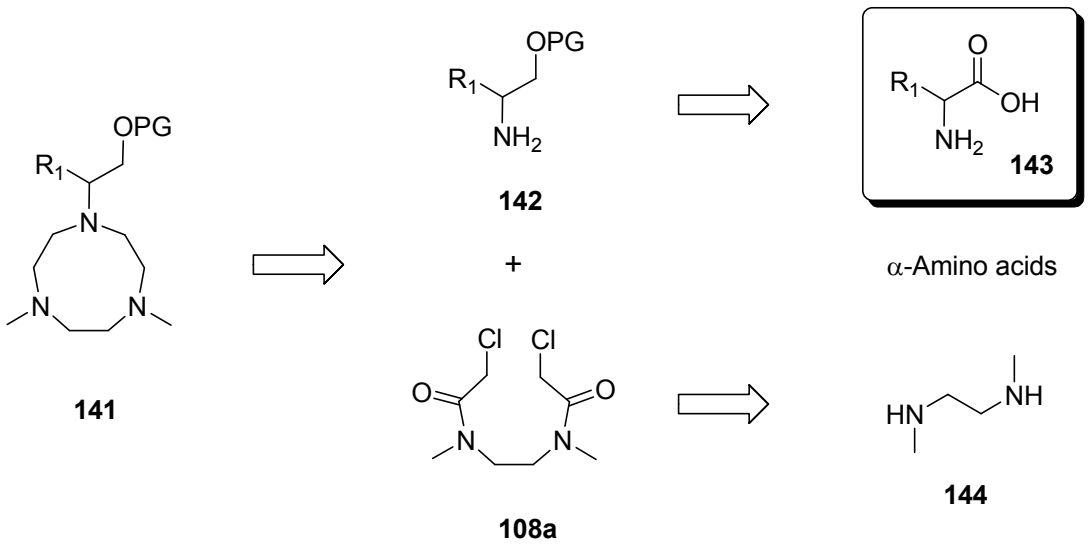


Figure 14. Towards the synthesis of new C_1-symmetric chiral TACN: approach.

We envised in the *Crab-like*[137] cyclisation method a flexible and versatile synthetic approach for the introduction of the stereocenter at the desired position, as shown in Scheme **36**.



Scheme 36. Synthesis of new chiral C_1-symmetric TACN: synthetic approach.

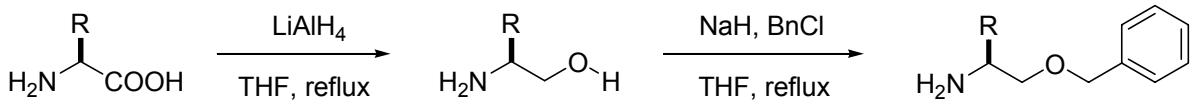
[160] D. A. Dixon, M. Shang, A. G. Lappin, *Inorg. Chim. Acta* **1999**, *290*, 197.

The possibility to employ different amines in the cyclisation protocol grants to this approach unpaired flexibility, which well compensate the moderate yields. For our purpose, α-amino acids **143** furnished the convenient α substitution and were therefore chosen as readily available enantiopure starting materials. Amines **142** were obtained by reduction and O-protection of the amino acids and cyclised with the bischloroamide **108a** to give the desired chiral C_1-symmetric triazacyclononanes.

4.3.2 Synthesis of Chiral C_1-Symmetric Triazacyclononanes Derived from Amino Acids

4.3.2.1 Synthesis of Protected Amino Alcohols

(*S*)-Valine **143a** and (*R*)-phenylglicine **143b** were chosen as starting material. Reduction with $LiAlH_4$ easily provided the corresponding aminoalcohol, (*S*)-valinol **145a** and (*R*)-phenylglicinol **145b**, in quantitative yield. O-Benzyl aminoalcohols were obtained by refluxing compounds **142a,b** with NaH and benzyl chloride for 48 hours.[161] Upon basic work-up and flash chromatography purification, the desired products **142a,b** were obtained as yellow oils with yields up to 90% (Scheme **37**).



R = (*S*)-^{i}Pr **143a**
R = (*R*)-Ph **143b**

R = (*S*)-^{i}Pr **145a**
R = (*R*)-Ph **145b**

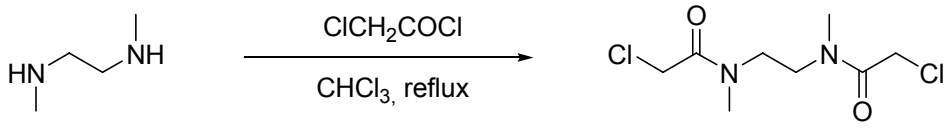
R = (*S*)-^{i}Pr **142a**
R = (*R*)-Ph **142b**

Scheme 37. Synthesis of *O*-benzylprotected aminoalcohols **142a,b**.

4.3.2.2. Synthesis of *N*,*N*'-dimethyldichloroamide

N,*N*'-Dimethyldichloroamide **108a** was synthesised by refluxing *N*,*N*'-dimethyl-ethylendiamine **144** with two equivalent of chloroacetylchloride in chloroform for 12 hours and obtained as an amorphous solid after crystallisation from ethanol (Scheme **38**).

[161] S. K. Patel, K. Murat, S. Py, Y. Vallée, *Org. Lett.* **2003**, *5*, 4081.

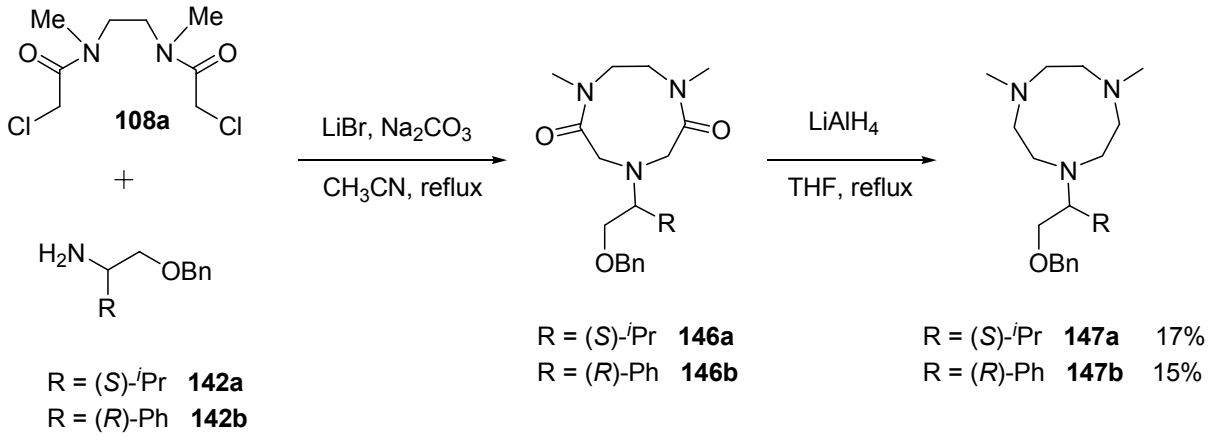


144 **108a**

Scheme 38. Synthesis of *N,N'*-dimethyldichloroamide **108a**.

4.3.2.3 Synthesis of C_1-Symmetric Triazacyclononanes

The C_1-symmetric triazamacrocycle was then prepared using the *Crab-like* cyclisation method. The amide portion of the starting material works as protecting group for the nitrogen atoms and increases the reactivity of the chloro-substituted carbon towards nucleophilic substitution. *N,N'*-dimethylchloroamide **108a** and protected aminoalcohols **142a,b**, respectively, were refluxed in acetonitrile for 6 hours in the presence of lithium bromide. The latter acts as a template to favour the formation of the medium-sized nine-membered ring and it also restrains the parallel reaction of intermolecular substitution of the second amine group. The crude cyclic bisamides **146a,b** were directly reduced with $LiAlH_4$ without any further purification to give macrocycles **147a,b** (Scheme **39**). Purification of these compounds is not trivial. Due to their strong basicity, separation by flash chromatography required a very short column and has been performed with a highly polar solvent mixture, such as methanol/ammonium hydroxide. Triazacyclononane **147a** and **147b** were obtained as colourless oils in, respectively, 17% and 15% yield over two steps.



R = (*S*)-^{i}Pr **142a**
R = (*R*)-Ph **142b**

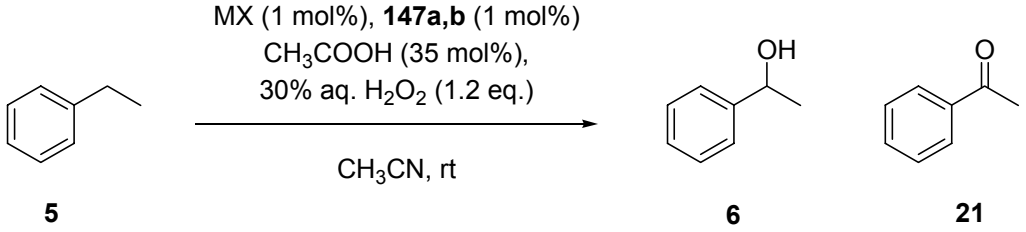
R = (*S*)-^{i}Pr **146a**
R = (*R*)-Ph **146b**

R = (*S*)-^{i}Pr **147a** 17%
R = (*R*)-Ph **147b** 15%

Scheme 39. Synthesis of C_1-symmetric triazacyclononanes **147a,b**.

4.3.3 Enantioselective CH Activation Studies

The new C_1-symmetric TACN **147a,b** were then tested as potential ligands for the enantioselective oxidation of alkanes. Ethylbenzene (**5**) was chosen as test substrate and manganese and iron as metals. Following the reaction conditions previously reported,[159] acetic acid was added as co-ligand and hydrogen peroxide was employed as terminal oxidant. The complexes were formed *in situ* by mixing the metal salt and the ligand in acetonitrile (Equation **3**).



Equation 3.

$Mn(OAc)_2$, already shown to form active complexes with triazacyclononanes in the epoxidation and CH activation, was chosen as manganese source. Complexes of $Fe(ClO_4)_2$ and, for example, TM-TACN[162] have been isolated and proposed as model diiron centers for biological systems and *in situ* formed species have been reported as catalyst for the oxidation of ethylbenzene by hydrogen peroxide.[163] This metal salt was therefore initially chosen as iron source. $Mn(OAc)_2$ gave no conversion, whereas $Fe(ClO_4)_2$ showed some activity. Under these conditions, 1-phenylethanol and acetophenone were the only products formed, the alcohol **6** being the major one. A slightly asymmetric induction was detected (<10%), that decreased during the course of the reaction. Considering the low conversion observed, some control experiments were conducted in order to understand if a ligand effect of triazacyclononanes **147a,b** is present. In the absence of iron(II) perchlorate or of the ligand, the reaction does not occur (Table **13**, entries 1 and 2). When the metal is present, but the ligand is missing, the major product formed is acetophenone (Table **13**, entry 3), thus indicating a different mechanism involved in the presence or in the absence of compounds **147a,b**.

[162] P. Chauduri, K. Wieghardt, B. Nuber, J. Weiss, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 778; *Angew. Chem.* **1985**, *97*, 774.
[163] M. Klopstra, R. Hage, R. M. Kellogg, B. L. Feringa, *Tetrahedron Lett.* **2003**, *44*, 4581.

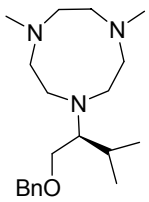
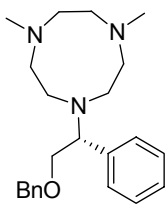
Table 13. Oxidation of ethylbenzene with different systems.

Entry	Metal	Ligand	Conversion (%)[a]	Alcohol:ketone[a]
1	–	–	0	–
2	–	+	0	–
3	+	–	5	1:4

Reaction conditions: ethylbenzene (1 mmol), iron perchlorate (0.01 mmol), aq. H_2O_2 (30%, 1 mmol), CH_3COOH (35 mol%) in CH_3CN (2.5 mL) at rt for 24 h. [a] Determined by GC analysis using nitrobenzene as internal standard.

Comforted by this test and in an attempt to improve the initial result, the nature of iron source was addressed and in Table **14** the results obtained with iron(II) perchlorate and iron(III) chloride are reported.

Table 14. Oxidation of ethylbenzene catalysed by Fe-TACN complexes

Entry	Ligand	Iron salt	Time(h)	Conv.(%)[a]	Alcohol:ketone[a]	ee[a] (%)
1			24	5	2:1	9 (*R*)
2		$Fe(ClO_4)_2$	48	6	1:1	9 (*R*)
3			96	7	1:1.2	5 (*R*)
4			24	3	5:1	4 (*R*)
5	**147a**	$FeCl_3$	48	5	3.5:1	4 (*R*)
6			96	7	2:1	4 (*R*)
7			24	3	3:1	9 (*S*)
8		$Fe(ClO_4)_2$	48	6	1.3:1	8 (*S*)
9			96	7	1:1	5 (*S*)
10			24	3	3.5:1	8 (*S*)
11	**147b**	$FeCl_3$	48	6	3:1	6 (*S*)
12			96	8	2:1	5 (*S*)

Reaction conditions: ethylbenzene (1 mmol), iron salt (0.01 mmol), ligand **147a,b** (1 mol%), aq. H_2O_2 (30%, 1 mmol), CH_3COOH (35 mol%) in CH_3CN (2.5 mL) at rt. [a] Determined by GC analysis using nitrobenzene as internal standard.

Unfortunately, no improvements were observed either in the conversions or in the enantiomeric excesses. Although in the presence of iron(III) chloride the formation of 1-phenylethanol is slightly favoured, no gain in asymmetric induction was obtained.

We then considered the influence of acetic acid and modified its amount and its ratio to hydrogen peroxide. The results are reported in

Table **15**.

Table 15. Oxidation of ethylbenzene: reaction conditions screening.

Entry	H_2O_2	Acetic acid	Time(h)	Conv.(%)[a]	Alcohol:ketone[a]	ee[a] (%)
1	50 mol%	–	24	24	1.2:1	rac
2	50 mol%	35 mol%	24	4	2:1	rac
			48	12	3:1	rac
3	100 mol%	35 mol%	24	3	2:1	10% (*R*)
			48	4	1:1	5% (*R*)
4	50 mol%	50 mol%	24	9	2:1	9% (*R*)
			48	12	1:1	5% (*R*)
5[b]	100 mol%	35 mol%	18	3	3.2:1	rac
			24	4	3:1	4% (*R*)

Reaction conditions: ethylbenzene (1 mmol), ligand **147a** (1 mol%), iron perchlorate (1 mol%), 30% aq. H_2O_2 (x mol%) in CH_3CN (2.5 mL), CH_3COOH (x mol%) at rt for 24 h. [a] Determined by GC analysis using nitrobenzene as internal standard; [b] 5 mol% of catalyst were used.

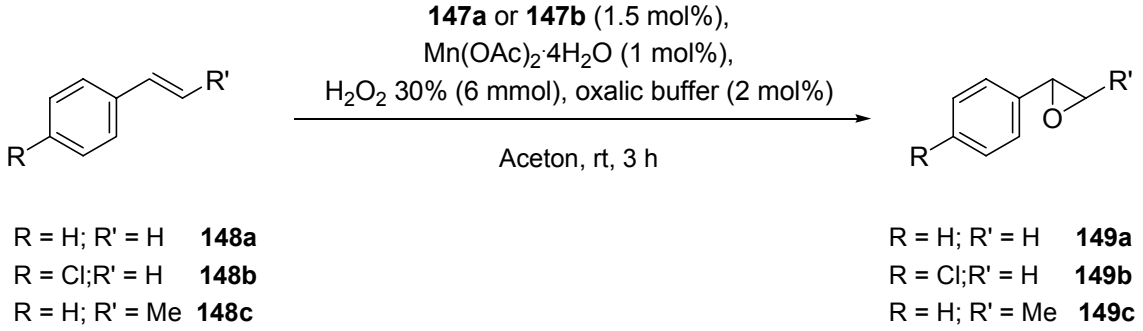
In the absence of acetic acid, the reaction proceeded faster and 24% of ethylbenzene was converted in 24 hours, giving an equimolar mixture of acetophenone and 1-phenylethanol, with no asymmetric induction (Table **15**, entry 1). Acetic acid slowed down the reaction favouring the formation of 1-phenylethanol with initial enantiomeric excesses up to 10% (Table **15**, entries 2-4). Increasing the amount of catalyst (5 mol%) did not beneficially affect the enantioselectivity neither the conversion, although a higher ratio alcohol/ketone was found (Table **15**, entry 5).

Despite the modest activity, the systems have proved capable of transferring the chiral information into the catalytic process and represent the first example of enantioselective CH-activation catalysed by *in situ* formed Fe(II)-TACN complexes.

4.3.4 Enantioselective Epoxidation Studies

Enantioselective epoxidation of olefins catalysed by chiral Mn-TACN complexes has attracted great attention in the past years. Most of the effective systems reported to date employed triazacyclononanes bearing the stereocenter on the ring,[145] but only one example has been described with chiral fragments on nitrogen atoms.[151]

To the best of our knowledge, chiral C_1-symmetric triazacyclononanes have not yet revealed their potential as ligand in the asymmetric epoxidation of olefins. Therefore, amino acid derived TACNs **147a** and **147b** have been tested using simple olefins as substrates and hydrogen peroxide as terminal oxidant. In Table **16** are reported the results obtained under the conditions shown in Equation **4**.



Equation 4.

The olefins **148a-c** were transformed into corresponding epoxides **149a-c** with moderate to good conversion (up to 70%, Table **16**, entry 3). The azamacrocycle **147b**, derived from (*R*)-phenylglycine, proved capable of transferring chiral information and converted styrene (**148a**) in (*S*) styrene oxide with 17% ee (Table **16**, entry 1). The asymmetric induction decreased for *trans*-β-methylstyrene (**148b**) and 4-chlorostyrene (**148c**) to, respectively, 10 and 5 % ee (Table **16**, entries 2-3). Oxidation of the chosen substrates catalysed by Mn-triazacyclononane **147a** complex gave the corresponding epoxides **149a-c** with low ee (≤6%).

Table 16. Mn-TACN catalysed enantioselective epoxidation of olefins

Entry	Substrate	147a		147b	
		Conv. (%)[a]	ee[a]	Conv. (%)[a]	ee[a]
1	Styrene (**148a**)	53	6 (*R*)	63	17 (*S*)
2	*Trans*-β-methylstyrene (**148b**)	18	rac	22	10 (*S*)
3	4-Chlorostyrene (**148c**)	34	2 (*R*)	70	5 (*S*)

Reaction conditions: substrate (1 mmol), compound **147a** or **147b** (1.5 mol%), $Mn(OAc)_2$ (1 mol%), H_2O_2 (4 mmol + 2 mmol), oxalic buffer (2 mol%) in acetone for 3 h. [a] Determined by GC analysis.

Although the enantiomeric excesses obtained are only modest, these novel C_1-symmetric ligands have been proved active in the Mn-catalysed epoxidation of simple olefins.

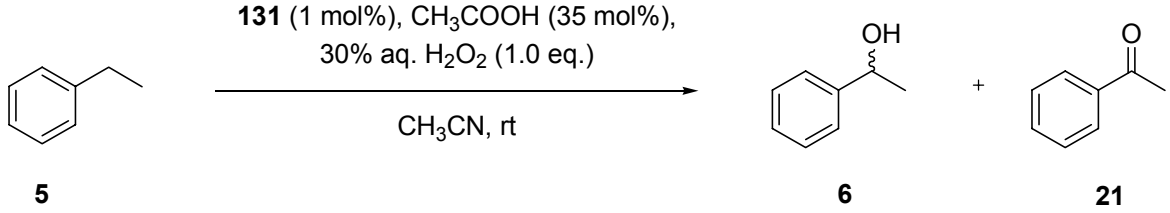
4.4 Studies on the Asymmetric CH Activation Using Carboxylic Acids as Chiral Promoters

Recently, Srinivas and co-workers reported the benzylic oxidation of ethylbenzene using an *in situ* formed Mn-TM-TACN complex as catalyst and hydrogen peroxide as terminal oxidant.[156] The activity and the selectivity of the catalyst in the presence of various buffers such as acetate, oxalate, tartrate and malonate, were investigated and the authors concluded that the carboxylic acid act as co-ligand in addition to acting as a buffer. The nature of the carboxylic acid and mode of coordination influence the redox behaviour of the Mn site, thus yielding to different selectivity in the benzylic oxidation. For example, in the presence of malonate or ascorbate, the only product detected was acetophenone, whereas oxalate buffer led to the formation of a 2:1 mixture ketone/alcohol. This strong additive effect has been studied also by Feringa and co-workers, who recently reported a carboxylic acid-promoted *cis*-hydroxylation and epoxidation of alkenes, where the carboxylic acid permitted the tuning of the catalyst selectivity towards *cis*-hydroxylation and epoxidation.[164]

It was therefore challenging the idea of using chiral carboxylic acids as additive, or co-ligands, to induce asymmetric benzylic oxidation.

[164] J. W. de Boer, J. Brinksma, W. R. Browne, A. Meetsma, P. L. Alsters, R. Hage, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 7990.

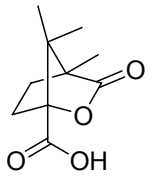
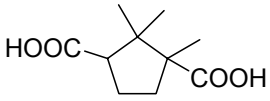
First, oxidation of ethylbenzene was conducted using Mn-TM-TACN complex **131** as catalyst and acetic acid as additive, under the reaction conditions proposed by Shul'pin and co-workers,[158] in order the test the activity of the system (Equation **5**).

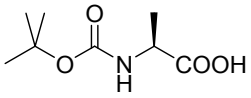
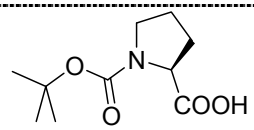


Equation 5

Ethylbenzene (**5**) was completely converted within one hour and the major products detected were 1-phenylethanol and acetophenone in 94:6 ratio. Under these conditions, the pre-formed catalyst proved to be more effective than *in situ* formed active species reported by Srinivas and co-worker.[156] Indeed, in the case of acetate buffer they observed a 1:2 ratio and a conversion of only 19% after 10 hours.

Table 17. Oxidation of ethylbenzene with various carboxylic acids as additive.

Entry	Acid	Time(h)	T(°C)	Conv.(%)[a]	alc/ket[a]	ee[a](%)	TON
1		1	rt	100	94:6	–	1150
2	acetic acid **150**	120	–22	75	13:87	–	863
3		1	rt	100	94:6	rac	1150
4	(-)-Camphanic acid **151**	120	–22	91	32:68	rac	1047
5	 D(+)-Camphoric acid **152**	1	rt	9	80:20	rac	104

6	 N-Boc-L-Alanine **153**	1	rt	20	4:1	rac	230
7	 N-Boc-L-Proline **154**	1	rt	5	4:1	rac	58

Reaction conditions: substrate (2.3 mmol, 1.0 eq), carboxylic acid (40 mol%), complex **131** (1.0 mol%), H_2O_2 (1.2 eq) in acetonitrile (5 mL). [a] Detected by GC analysis.

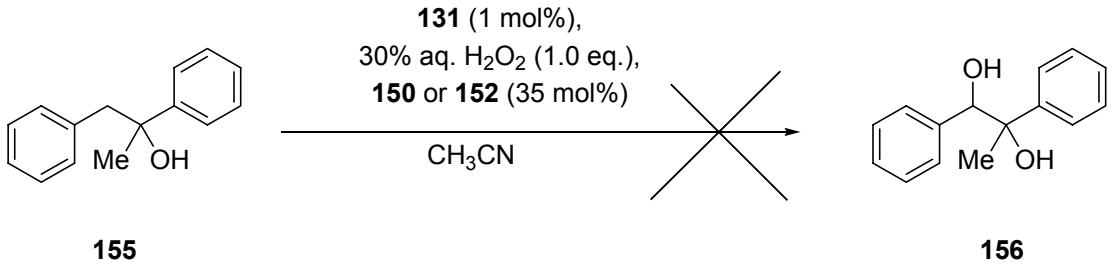
The major activity and selectivity showed by the Mn-TM-TACN/CH_3COH/H_2O_2 system prompted us to explore the possibility of chiral induction in the formation of 1-phenylethanol by mean of chiral carboxylic acids **151**-**154**. The results are reported in Table **17**.

(–)-Camphanic acid **151** showed high activity and selectivity for the formation of 1-phenylethanol (Table **17**, entry 3), comparable to that obtained with acetic acid (**150**). Although high TON has been attained, no chiral induction was observed. At lower temperature, the substrate was still present after 5 days and the reaction showed an inverted selectivity, with acetophenone as major product (Table **17**, entries 2 and 4). Unfortunately, the alcohol was produced only in its racemic form.

N-Boc-L-alanine- and *N*-Boc-L-Proline-containing systems gave poor to moderate conversions and 1-phenylethanol was obtained as racemate (Table **17**, entries 6 and 7).

Although dicarboxylate buffers have been reported to have a more pronounced effect on the *in situ* formed Mn-TM-TACN catalyst, the use of (+)-camphoric acid **152** was less than fruitful and the substrate was poorly converted without any asymmetric induction (Table **17**, entry 5). These latter additives showed also an inferior selectivity for 1-phenylethanol vs. acetophenone (4:1).

Acetic acid and camphanic acid greatly enhanced the oxidation of ethylbenzene, providing high selectivity for 1-phenylethanol and large TONs. In order to verify the possibility of diastereomeric induction, these two compounds have been used as additives in the oxidation of racemic 1,2-diphenyl-2-propanol, as shown in Equation **6**.



155 **156**

Equation 6.

Unfortunately, this substrate completely inhibited the reaction and only starting material was detected by NMR and GC analyses.

Although the nature of carboxylic acid has been proved important for the outcome of some Mn-TM-TACN catalysed oxidations, the use of chiral carboxylic acids failed in inducing both the enantioselective and the diastereoselective oxidation of hydrocarbons.

4.5 Conclusion

Transition metal complexes of triazacyclononanes are efficient and selective catalyst for the CH oxidation of unreactive substrate using hydrogen peroxide as oxidant. In particular, the polymeric system **133** have been proved to be able to oxidise simple alkanes, such as cyclohexane, giving the corresponding alkyl hydroperoxide as predominant product, and revealed peculiar selectivity parameters, that differentiate this system from those previously reported in literature. The synthesis of new soluble chiral triazacyclononanes, having similar C_1-symmetry, was achieved using readily available amino acids as source of chirality. The *Crab-like* methodology has been demonstrated to be the ideal synthetic approach and it granted the desired flexibility. Two new C_1-symmetric TACNs **147a** and **147b** were synthesised and employed in the Mn- and Fe-catalysed oxidation of ethylbenzene with H_2O_2 as oxidant and acetic acid as additive. Although only low conversion were obtained when iron was used as metal source, the system proved to be able of transferring the chiral information into the catalytic process, thus representing the first example of enantioselective CH-activation catalysed by *in situ* formed iron-TACN complexes. The newly synthesised chiral C_1-symmetric TACN demonstrated activity also in the enantioselective Mn-catalysed epoxidation of simple olefins, with moderate to good conversions and modest *ee*.

A second approach towards the enantioselective CH oxidation of hydrocarbons was studied, using the isolated complex **131** in combination with chiral carboxylic acids. Although the

effect of the additive on the efficiency of the system was undeniable proved, this protocol failed in inducing both the enantioselective and the diastereoselective oxidation of hydrocarbons.

5. Experimental Section

5.1 General remarks

All reactions involving air- or moisture-sensitive chemicals were carried out under argon atmosphere using standard Schlenk techniques.[165] The addition of all reagents as well as solvents was carried out with glass or polypropylene syringes equipped with V2A steel needles under an argon stream.

5.2 Solvents

The solvents were dried and purified by standard methods.[166]

Acetone: refluxed over P_2O_5, followed by distillation.

Acetonitrile: purchased in analytical pure form from Merck and used without further purification.

Diethyl ether: dried over KOH and Al_2O_3, heated under reflux over sodium/benzophenone-ketyl radical and then distilled.

Dichloromethane: distilled from calcium hydride.

Methanol: purchased in analytical pure form from Fluka or Merck and used without further purification.

Pentane: refluxed over calcium and then distilled.

Tetrahydrofurane: dried over KOH, heated under reflux over sodium/benzophenone ketyl radical and then distilled.

Toluene: refluxed over sodium/benzophenone ketyl radical and then distilled.

Triethylamine: refluxed over KOH, distilled under argon and then stored over KOH.

The absolute solvents were stored in Schlenk flasks over molecular sieves 4Å under inert atmosphere at room temperature. The solvents for column chromatography, recrystallisation and reactions work-up were distilled prior to use.

Commercial compounds where purchased from the companies Merck, Aldrich, Acros, Fluka, Lancaster, Strem. Hydrogen peroxide (aq. 30%) was purchased from Fluka and stored at 4

[165] D. F. Shriver, M. A. Drezdzon, *The Manipulation of Air-Sensitive Compounds*, Wiley, Chichester, **1986**.
[166] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, **1996**.

°C. The amino acids were kindly provided by Degussa AG. Ionic liquids were gently supplied by Dr. Solinas. The Mn-TM-TACN complex **131** was kindly donated by Prof. G. B. Shul'pin.

5.3 Determination of the physical data

^{1}H-NMR-Spectra:

^{1}H-NMR spectra were recorded at room temperature on a Varian VXR 300 (300 MHz), a Varian Gemini 300 (300 MHz) or a Varian Inova 400 (400 MHz) spectrometer. Chemical shifts are given in ppm (δ units) referring to tetramethylsilane as internal standard. Coupling constants *J* are given in Hertz and the multiplicities are reported as following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet).

^{13}C-NMR-Spectra:

^{13}C-NMR spectra were ^{1}H-broad band-decoupled and measured with a Varian VXR 300 (75 MHz), a Varian Gemini 300 (75 MHz), a Varian Inova 400 (100 MHz) spectrometer. Chemical shifts are given in ppm δ referring to tetramethylsilane as internal standard.

Mass spectrometry:

Mass spectra were detected using a Varian MAT 212 mass spectrometer or a Finnigan MAT 95 spectrometer with EI or CI ionisation. All values are given in atomic units of mass per elemental charge (*m/z*).

Infrared spectroscopy:

IR spectra were recorded on a Perkin-Elmer PE 1720X or on a Pelkin-Elmer PE 1760 FT spectrometer. Wave numbers (υ) of absorption maxima are listed in cm^{-1}. Only peaks with an intensity > 60% are given.

Optical rotatory power:

Optical rotation measurements were conducted on a Perkin Elmer 241 polarimeter at λ = 589 nm using CHROMASOLV® grade solvents.

Elemental Analysis:

Elemental analyses were recorded on a Heraeus CHN-O-RAPID instrument and on an Elemental Vario EL instrument.

5.4 Chromatographic methods

Flash-column chromatography

Separations by flash column chromatography were performed on silica gel 60, particle size 40-63 μm (230-240 mesh) purchased from Merck.

Thin-layer chromatography

Thin-layer chromatography (TLC) was performed using precoated aluminium backed plates (Merck silica gel 60 F_{254}). The detection was performed by using UV radiation (λ = 254 nm), by treatment with a solution of cerium(IV) ammonium sulphate and phosphomolybdic acid in H_2SO_4 or by a basic solution of potassium permanganate and development under hot air stream.

GC/MS Analysis:

GC/MS analyses were conducted on a HP 6890 Series gas-chromatograph, MSD 5973. The stationary phase was a HP-5 MS (30 m x 0,25 mm x 0.25 μm), He as carrier gas at 200 °C.

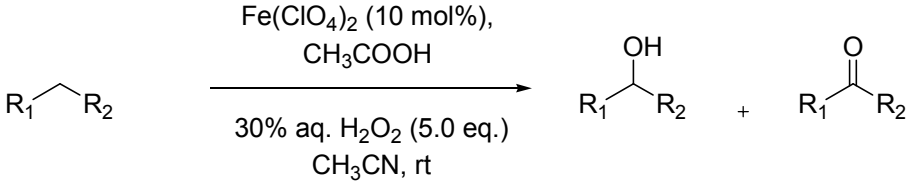
Gas chromatography:

Achiral gas chromatographic analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split mode injection system and a FID detector with mechanical pressure control using an Ultra 2 column (crosslinked 5% phenylpolysilphenylansiloxan) from Hewlett-Packard. Chiral gas chromatographic analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph with and without electronic pressure control (EPC), using a Cyclodex β-I/P (heptakis-(2,3,6-trimethyl)-β-cyclodextrin/polysiloxan) purchased from Chromatographie Service GmbH. FS-Phenyl-Sil columns (Chromatographie Service GmbH) were used as pre-columns. The data acquisition and data integration were performed with a Hewlett-Packard ChemStation (Rev.A.05.04[273]) which was connected to the gas chromatographs via buffered HP-IB interfaces. When a pressure value is given in conjunction with a temperature value the

pressure is to be considered as temperature dependent (EPC; constant flow). Otherwise the pressure given is meant to be a constant pressure on the column.

5.5 Fe-Catalysed CH Activation of Hydrocarbons

5.5.1 General Protocol for the Oxidation of Alkylarenes and Cycloalkanes



To a stirred solution of the substrate (1 mmol), $Fe(ClO_4)_2 \cdot 6H_2O$ (36.6 mg, 0.1 mmol), acetic acid (12.0 mg, 0.2 mmol) and nitrobenzene (internal standard, 24.6 mg, 0.2 mmol) in CH_3CN (5 mL) is added H_2O_2 (30% aq., 567 mg, 5 mmol) over 4 hours (1 mmol/h). After 5 hours, the reaction is quenched with MnO_2, filtered on Na_2SO_4 and analysed.

Conversion and selectivity values were calculated using the following equations:

$$\%\ \text{Conversion} = 100 - \left[\left(\frac{areaA/areaS}{initialRatio} \bullet 100\right)\right]$$

$$\%\ \text{Selectivity} = \left[\left(\frac{areaB/areaS}{initialRatio}\right) \bullet (rf) \bullet \left(100/\%conversion\right)\right] \bullet 100$$

Where: areaA = substrate area

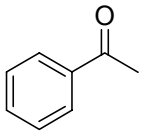
areaB = product area

areaS = standard area

initial ratio = area substrate/area standard before addition of the oxidant

rf = response factor = $\left(areaA/areaB\right) \bullet \left(HNMR(B)/HNMR(A)\right)$

5.5.1.1 Acetophenone (21)



Starting from ethylbenzene **5** (106 mg, 1 mmol) the product was obtained according to the general protocol after purification on silica gel (pentane/diethylether 3:1).

180 mg; yield = 50%

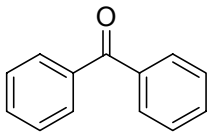
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 2H, arom C*H*), 7.50 (s, 1H, arom C*H*), 7.40 (s, 2H, arom C*H*), 2.54 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 197.8, 137.1, 133.0, 128.5, 128.2, 26.7.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 140 kPa N_2; 100 °C, 40 min, 10 °C/min, 200 °C, 10 min; t_R = 17.10 min.

The analytical data are in agreement with those of the commercial compound.

5.5.1.2 Benzophenone (29)



Starting from diphenylmethane **28** (168 mg, 1 mmol), the product was obtained according to the general protocol.

Conversion = 48%; Selectivity = 74%.

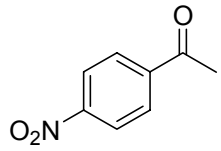
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.83-7.77 (m, 4H, arom C*H*), 7.62-7.55 (m, 2H, arom C*H*), 7. 51-7.44 (m, 4H, arom C*H*).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.7, 137.6, 132.4, 130.0, 128.3.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2; 120 °C, 10 min, 12 °C/min, 200 °C, 20 min; t_R = 23.05 min.

The analytical data are in agreement with those of the commercial compound.

5.5.1.3 1-(4-Nitro-phenyl)ethanone (27)



Starting from 4-nitroethylbenzene (**26**) (151.2 mg, 1 mmol), the product was obtained according to the general protocol.

Conversion = 65%; Selectivity = 74%.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 9.2 Hz, 2H, arom C*H*), 8.13 (d, *J* = 9.2 Hz, 2H, arom C*H*), 2.71 (s, 3H, CH_3).

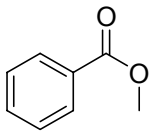
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 199.6, 152.8, 143.2, 129.7, 121.5, 29.6.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 140 kPa N_2; 100 °C, 40 min, 10 °C/min, 200 °C, 10 min; t_R = 47.45 min.

MS (GC/MS): *m/z* (%): 165 (M^+, 21), 150 (100), 104 (23), 92 (11), 76 (10).

The analytical data are in agreement with those reported in literature.[167]

5.5.1.4 Benzoic acid methyl ester (31)



Starting from 1-methoxymethylbenzene (**30**) (244.3 mg, 2 mmol), the product was obtained according to the general protocol, after purification on silica gel (pentane/diethylether 3:1).

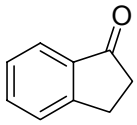
60 mg; yield = 22 %

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10-8.05 (m, 2H, arom C*H*), 7.61-7.55 (m, 1H, arom C*H*),7.46-7.41 (m, 2H, arom C*H*), 3.93 (s, 3H, CH_3).

[167] Z.-Z. Huang, Y. Tang, *J. Org. Chem.* **2002**, *67*, 5320.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 172.0, 133.8, 130.2, 128.5, 128.4, 52.3.
The data are in agreement with those reported in literature.[168]

5.5.1.5 Indan-1-one (33)



a) Starting from indane (**32**) (590 mg, 5 mmol), the product was obtained according to the general protocol, after purification on silica gel (pentane/diethylether 3:1).

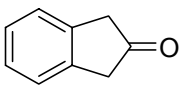
300 mg; yield = 46%

b) Starting from indan-1-ol (**35**) (134 mg, 1 mmol), the product was obtained according to the general protocol

Conversion = 100%; Selectivity = 57%
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.7 Hz, 1H, arom C*H*), 7.59 (t, *J* = 7.4 Hz, 1H, arom C*H*), 7.48 (d, *J* = 7.7 Hz, 1H, arom C*H*), 7.37 (t, *J* = 7.7 Hz, 1H, arom C*H*), 3.14 (t, *J* = 5.4 Hz, 2H, COC*H*$_2$CH$_2$), 2.72-2.68 (m, 2H, COCH$_2$C*H*$_2$).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 207.1, 155.2, 137.1, 134.6, 127.3, 126.7, 123.7, 36.2, 25.8.
GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2; 120 °C, 30 min, 20 °C/min, 200 °C, 5 min; t_R = 34.51 min.

The analytical data are in agreement with those reported in literature.[169]

5.5.1.6 Indan-2-one (38)



[168] M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, S. Tani, *Tetrahedron* **1999**, *55*, 13159.
[169] R. Takeuchi, H. Yasue, *J. Org. Chem.* **1993**, *58*, 5386.

Starting from indan-2-ol (**37**) (134 mg, 1 mmol), the product was obtained according to the general protocol.

Conversion = 57%; Selectivity = 26%.

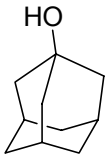
^{1}H-NMR (300 MHz, $CDCl_3$): δ =7.25 (m, 4H, arom C*H*), 3.55 (s, 4H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 215.1, 137.8, 127.4, 125.0, 44.1.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2; 120 °C, 30 min, 20 °C/min, 200 °C, 5 min; t_R = 32.00 min.

The analytical data are in agreement with those of the commercial compound.

5.5.1.7 Tricyclo[3.3.1.1^{3,7}]decan-1-ol (40)



Adamantane (**39**) (136.2 mg, 1 mmol) was dissolved in 10 mL CH_3CN/CH_2Cl_2 (1:1) and the product was obtained according to the general protocol.

Conversion = 24%; Selectivity = 40%

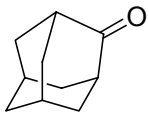
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.13 (br s, 3H, O*H*, OCH_AH_B), 1.73-1.58 (m, 12H, bridge CH_2, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 68.2, 45.3, 36.1, 30.7.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 16.62 min.

The analytical data are in agreement with those of the commercial compound.

5.5.1.8 Tricyclo[3.3.1.1^{3,7}]decan-2-one (41)



Adamantane (**39**) (136.2 mg, 1 mmol) was dissolved in 10 mL CH_3CN/CH_2Cl_2 (1:1) and the product was obtained according to the general protocol.

Conversion = 24%; Selectivity = 52%

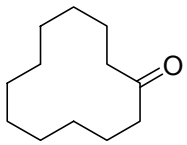
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.55 (br s, 3H, bridge C*H*$_2$, C*H*$_3$), 2.14-1.92 (m, 11H, bridge C*H*$_2$, C*H*$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 218.4, 47.0, 39.3, 36.3, 27.5.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 18.47 min.

The analytical data are in agreement with those of the commercial compound.

5.5.1.9 Cyclododecanone (43)



Starting from cyclododecane (**42**) (168.3 mg, 1 mmol), the product was obtained according to the general protocol.

Conversion = 10%; Selectivity = 50%

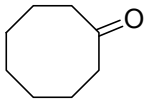
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.4-2.2 (m, 4H, COC*H*$_2$), 2.1-1.7 (s, 4H, bridge C*H*$_2$), 1.6-1.2 (m, 14H, bridge C*H*$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 212.3, 40.4, 23.7, 24.6, 24.1, 23.7.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 24.69 min.

The analytical data are in agreement with those of the commercial compound.

5.5.1.10 Cyclooctanone (45)



Starting from cyclooctane (**44**) (112.2 mg, 1 mmol), the product was obtained according to the general protocol.

Conversion = 55%; Selectivity = 44%

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41-2.36 (m, 4H, COC*H*$_2$), 1.90-1.81 (m, 4H, C*H*$_2$), 1.57-1.53 (m, 4H, C*H*$_2$), 1.50-1.30 (m, 2H, C*H*$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 218.4, 41.9, 27.1, 25.6, 24.6.

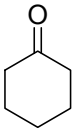
GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 12.26 min.

The analytical data are in agreement with those of the commercial compound.

5.5.2 Oxidation of Cyclohexane: Experiments in CD_3CN

To a stirred solution of the cyclohexane (**18**) (42 mg, 0.5 mmol), $Fe(ClO_4)_2 \cdot 6H_2O$ (18 mg, 0.05 mmol) and acetic acid (6 mg, 0.1 mmol) in CD_3CN (2.5 mL) H_2O_2 (30% aq., 283 mg, 2.5 mmol) is added over 4 hours (1.0 mmol/h). After 5 hours, the reaction is quenched with MnO_2 and filtered on Na_2SO_4. To an aliquot (700 μL) of the reaction mixture is added benzene (17.8 μL, 0.2 mmol) as internal standard and the solution is analysed *via* ^{1}H-NMR spectroscopy and gas chromatrography.

5.5.2.1 Cyclohexanone (20)



NMR yield = 20%

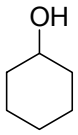
^{1}H-NMR (400 MHz, $CDCN_3$): δ = 2.28 (t, *J* = 6.73 Hz, 4H, COC*H*$_2$), 1.83 (m, 4H, C*H*$_2$), 1.70 (m, 2H, C*H*$_2$).

^{13}C-NMR (100 MHz, $CDCN_3$): δ = 210.6, 41.5, 26.9, 24.7.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 5.86 min.

The analytical data are in agreement with those of the commercial compound.

5.5.2.2 Cyclohexanol (19)



NMR yield = 20%

^{1}H-NMR (400 MHz, $CDCN_3$): δ = 3.48 (m, 1H, C*H*OH), 3.09 (br s, 1H, O*H*), 1.81 (m, 2H, C*H*$_2$), 1.70 (m, 2H, C*H*$_2$),1.52 (m, 1H, CH_AH$_B$),1.20 (m, 5H, CH$_A$$H_B$, C*H*$_2$).

^{13}C-NMR (100 MHz, $CDCN_3$): δ = 72.7, 35.2, 28.2, 22.1.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 5.66 min.

The analytical data are in agreement with those of the commercial compound.

5.5.3 General Protocol for i*n situ* IR Studies

The spectra were recorded using an ASI/ Mettler Toledo REACT IR 1000 with different intervals between the acquisition instances, each acquisition instance comprising 32 scans and a resolution of 8 cm^{-1}. Background spectra of each reaction component, i.e. ethylbenzene, $Fe(ClO_4)_2 \cdot 6H_2O$, acetophenone, 1-phenylethanol and acetic acid, respectively, were recorded first. The sequence of periodic acquisition was started when the oxidant was injected into the reaction mixture.

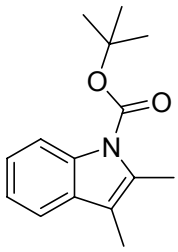
5.5.4 General Protocol for the CH Activation in Ionic Liquids

To a stirred solution of the ethylbenzene (**5**) (106.0 mg, 1.0 mmol), $Fe(ClO_4)_2 \cdot 6H_2O$ (36.6 mg, 0.1 mmol), acetic acid (12.0 mg, 0.2 mmol) and nitrobenzene (internal standard, 24.6 mg, 0.2 mmol) in solvent system (1 mL) is added H_2O_2 (30% aq., 567 mg, 5 mmol) over 4 hours (1 mmol/h). After 5 hours, the reaction is quenched with MnO_2, filtered on Na_2SO_4 and analysed.

5.6 Fe-Catalysed Oxidative Cleavage of Double Bonds

5.6.1 Synthesis of the Substrates

5.6.1.1 2,3-Dimethyl-indole-1-carboxylic acid *tert*-butyl ester (83)



To a NaH (360 mg, 15 mmol) suspension in THF (100 mL) was added the 2,3-dimethylindole (**82**) (1.45 g, 10 mmol) under inert atmosphere at 0 °C and let to react for ten minutes. Boc_2O (4.37 g, 20 mmol) was then added and the reaction was refluxed for 24 hours. After the addition of 0.2 N HCl, the mixture was extracted with CH_2Cl_2 (2 x 100 mL), the organic phase was dried over Na_2SO_4 and the solvent was evaporated to leave a yellow oil. The crude product was then purified by flash chromatography (pentane/diethyl ether 9:1).

430 mg; yield = 18%

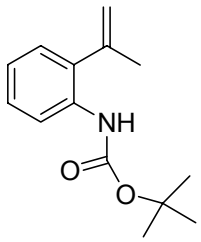
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 6.92 Hz, 1H, arom C*H*), 7.49 (d, *J* = 6.92 Hz, 1H, arom C*H*), 7.37-7.27 (m, 2H, arom C*H*), 2.59 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.76 (s, 9H, C(CH_3)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.9, 135.7, 132.8, 130.9, 123.4, 122.4, 117.8, 115.4, 113.8, 83.2, 28.4, 13.9, 8.7.

EI/MS: m/z (%): 245 (M^+, 47), 189 (100), 145 (58), 144 (55), 130 (20), 57 (68).

The analytical data are in agreement with those reported in literature.[170]

5.6.1.2 (2-Isopropenyl-phenyl)-carbamic acid *tert*-butyl ester (80)



A solution of 2-(prop-1-en-yl)benzenamine (**79**) (666 mg, 5.0 mmol) in THF (15 mL) containing Boc_2O (1.2 g, 5.5 mmol) was heated at reflux for two hours. The solvent was removed in vacuo, the residue dissolved in ethyl acetate and this solution was washed successively with 1 M acetic acid solution and brine. The organic phase was dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was crystallised from hexane to give a white solid.

280 mg; yield = 24%

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 1H, arom C*H*), 7.25 (t, *J* = 8.4 Hz, 1H, arom C*H*), 7.12 (dd, *J* = 5.9, 1.7 Hz, arom C*H*), 7.02 (t, *J* = 7.7, 7.3 Hz, 1H, arom C*H*), 6.85 (br s, 1H, N*H*), 5.38 (m, 1H, CH_ACH_B), 5.03 (m, 1H, CH_ACH_B), 2.08 (m, 3H, CH_3), 1.54 (s, 9H, $C(CH_3)_3$).

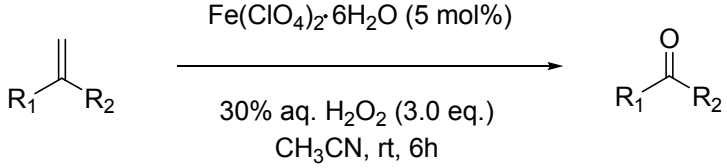
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 152.9, 142.8, 134.5, 127.8, 127.7, 122.6, 119.4, 116.8, 80.4, 28.4, 27.4, 24.4.

EI/MS: m/z (%): 234 (M+H, 5), 179 (11), 178 (100), 132 (3).

The analytical data are in agreement with those reported in literature.[171]

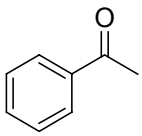
[170] D. Dhanak, C. B. Reese, *J. Chem. Soc. Perkin Trans. 1* **1986**, 2181.
[171] M. Arisawa, Y. Ando, M. Yamanaka, M. Nakagawa, A. Nishida, *Synlett* **2002**, 1514.

5.6.2 General Protocol for the Fe-catalysed Oxidative Cleavage of Double Bonds



To a solution of $Fe(ClO_4)_2 \cdot 6H_2O$ (36.6 mg, 0.1 mmol) and acetic acid (34.0 µL, 0.6 mmol) in CH_3CN (3.0 mL) is added a solution of substrate (2 mmol) in CH_3CN (3.0 mL). The reaction is cooled to 0 °C and H_2O_2 (30% aq., 582 mg, 6 mmol) is added to the previous solution. The reaction mixture is kept at this temperature one hour and then warmed to room temperature. After four hours, MnO_2 is added, followed by the addition of water. The aqueous phase is extracted with diethylether (3 x 10 mL). The combined organic phases are dried over $MgSO_4$, filtered and the solvent is removed under vacuo.

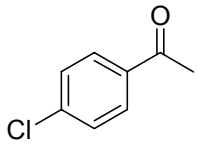
5.6.2.1 Acetophenone (21)



Starting from α-methylstyrene (**73**) (236.4 mg, 2 mmol), the product was obtained according to the general protocol, after purification of the crude by flash chromatography (pentane/diethylether 3:1).

187 mg; yield = 78%
For analytical data, see **5.5.1.1**.

5.6.2.2 1-(4-Chloro-phenyl)-ethanone (78)



Starting from 1-chloro-4-(prop-1-en-2-yl)benzene (**77**) (305.2 mg, 2 mmol), the product was obtained according to the general protocol, after purification of the crude product by flash chromatography (pentane/diethylether 3:1).

170 mg; yield = 55%

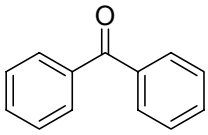
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (m, 2H, arom C*H*), 7.47 (m, 2H, arom C*H*), 2.64 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.9, 139.6, 135.5, 129.8, 128.9, 26.6.

MS (GC-MS): *m/z* (%): 154 (M^+, 30), 139 (100), 111 (40), 75 (12).

The analytical data are in agreement with those reported in literature.[172]

5.6.2.3 Benzophenone (29)

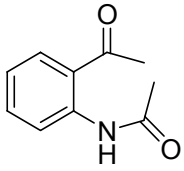


Starting from 1,1-diphenylethene (**81**) (360.5 mg, 2 mmol), the product was obtained according to the general protocol, after purification of the crude product by flash chromatography (pentane/diethylether 3:1).

197 mg; yield = 54%

For analytical data, see **5.5.1.2**.

5.6.2.4 *N*-(2-Acetyl-phenyl)-acetamide (157)



[172] J. E. Hong, W.-S. Shin, W. B. Jang, D. Y. Oh, *J. Org. Chem.* **1996**, *61*, 2199.

Starting from 2,3-dimethylindole (**82**) (290.4 mg, 2 mmol), the product was obtained according to the general protocol, after purification of the crude by flash chromatography (pentane/diethylether 3:1).

10.6 mg, yield = 6%

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.65 (br s, 1H, N*H*), 8.65 (d, *J* = 8.4 Hz, 1H, arom C*H*), 7.81 (d, *J* = 7.9 Hz, 1H, arom C*H*), 7.48 (dd, *J* = 8.4, 7.4 Hz, 1H, arom C*H*), 7.04 (t, *J* = 7.4 Hz, 1H, arom C*H*), 2.60 (s, 3H, CH_3), 2.16 (s, 3H, CH_3).

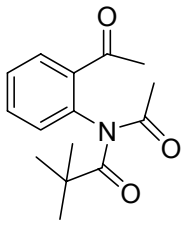
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 202.7, 169.4, 142.0, 135.1, 131.6, 122.3, 121.7, 120.7, 28.7, 25.7.

EI/MS: *m/z* (%): 177 (46), 135 (47), 134 (24), 120 (100), 92 (14).

IR (KBr): υ = 3238.9, 1690.2, 1652.6, 1585.3, 1527.8, 1451.8, 1363.0, 1309.7, 1241.5, 1164.8, 1007.8, 958.8, 759.8, 602.0.

The data are in agreement with those reported in literature.[111]

5.6.2.5 *N*-(2-acetylphenyl)-*N*-(pivaloyl)acetamide (84)



Starting from Boc-protected 2,3-dimethylindole (**83**) (245 mg, 1 mmol), the product was obtained according to the general protocol.

Conversion = 75%; NMR ratio 1:3 substrate/product

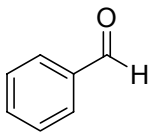
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 7.5, 1.5 Hz, 1H, arom C*H*), 7.51 (dt, *J* = 7.5, 1.5 Hz, 1H, arom C*H*), 7.40 (dt, *J* = 7.5, 1.5 Hz, 1H, arom C*H*), 7.12 (dd, *J* = 7.5, 1.5 Hz, 1H, arom C*H*), 2.60 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 1.33 (s, 9H, C(CH_3)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 198.4, 173.7, 152.1, 137.3, 134.6, 132.7, 130.4, 129.8, 128.1, 83.2, 28.6, 27.9, 26.7.

MS (GC-MS): *m/z* (%): 277 (M^+, 2), 234 (3), 177 (26), 162 (16), 135 (48), 120 (100), 92 (11).

The analytical data are in agreement with those reported in literature.[111]

5.6.2.6 Benzaldehyde (71)

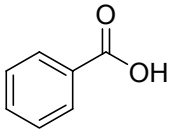


Benzaldehyde (**71**) was obtained from the oxidative cleavage of both styrene (**70**) (208 mg, 2 mmol) and cinnamoyl alcohol (**90**) (268 mg, 2 mmol), according to the general protocol.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.87 (s, 1H, C*H*O), 7.81-7.75 (m, 2H, arom C*H*), 7.60-7.52 (m, 1H, arom C*H*), 7.45-7.39 (m, 2H, arom C*H*).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 192.7, 134.6, 134.4, 129.9, 129.3.
GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 7.63 min.

The analytical data are in agreement with those of the commercial compound.

5.6.2.7 Benzoic acid (87)



Starting from styrene (**70**) (208 mg, 2 mmol), the product was obtained according to the general protocol.

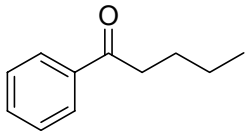
Conversion = 100%; Selectivity = 50%
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.60 (br s, 1H, COO*H*), 8.06-8.06 (m, 2H, arom C*H*), 7.54-7.49 (m, 1H, arom C*H*), 7.40-7.35 (m, 2H, arom C*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.6, 133.9, 130.3, 129.4, 128.5.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 140 kPa N_2; 40 °C, 3 min, 5 °C/min, 160 °C, 5 min, 40 °C/min, 240 °C, 10 min; t_R = 16.15 min.

The analytical data are in agreement with those of the commercial compound.

5.6.2.8 1-Phenyl-pentan-1-one (157)



Starting from 1-phenylcyclohexene (**89**) (317 mg, 2 mmol), the product was obtained according to the general protocol, after purification of the crude by flash chromatography (pentane/diethylether 9:1).

30.4 mg, yield = 9.4%

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.2 Hz, 2H, arom C*H*), 7.50-7.45 (m, 1H, arom C*H*), 7.38 (t, *J* = 7.2 Hz, 2H, arom C*H*), 2.90 (t, *J* = 7.4 Hz, 2H, CH_2), 1.68-1.62 (m, 2H,CH_2), 1.42-1.30 (m, 2H, CH_2), 0.88 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 200.6, 137.1, 132.9, 128.6, 128.1, 38.3, 26.5, 22.5, 13.9.

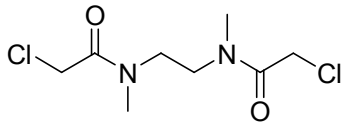
The analytical data are in agreement with those reported in literature.[173]

[173] D. Wang, Z. Zhang, *Org. Lett.* **2003**, *5*, 4645.

5.7 Studies towards the Enantioselective CH Activation with TACN

5.7.1 Synthesis of C_1-Symmetric Chiral Triazacyclononanes

5.7.1.1 2-Chloro-*N*-{2-[(2-chloro-acetyl)-methyl-amino]-ethyl}-*N*-methyl-acetamide (108a)



A solution of chloroacetylchloride (22.6 g, 0.2 mol) in chloroform (150 mL) is cooled to 0 °C and *N,N'*-dimethylethylendiamine (**144**) (8.8 g, 0.1 mol) in chloroform (30 mL) is added drop wise within 1 hour. The mixture is then refluxed for 12 hours. After cooling to room temperature, the solvent is removed completely and the residue is taken up with water and filtrated. After crystallisation from ethanol, an amorphous solid is obtained. Three conformational isomers are present (*cis*/*cis* : *cis*/*trans* : *trans*/*trans*; 70 : 28 : 2). Only characterisation for major isomer is reported.

14.5 g; yield = 60 %

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.99 (s, 4H, ClCH_2CO), 3.54 (s, 4H, CH_2N), 3.05 (s, 6H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.3, 45.4, 41.8, 36.3.

The analytical data are in agreement with those reported in literature.[174]

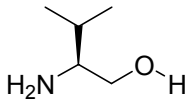
5.7.1.2 General Procedure for the Reduction of Amino Acids

A two-necked flask, charged with THF (94 mL) under inert atmosphere and, is cooled to 0 °C and $LiAlH_4$ (3.3 eq.) is added portionwise. The amino acid (1.0 eq.) is then added in small portions and the mixture is refluxed for 4 hours. The suspension is then cooled to 0 °C and is quenched adding dropwise H_2O (1.0 mL/g $LiAlH_4$), NaOH 15 % (0.8 mL/g $LiAlH_4$) and finally H_2O (3.0 mL/g $LiAlH_4$). The resulting colloid is diluted with Et_2O, treated with

[174] A. Grenz, *PhD Thesis*, Aachen, **2001**.

Na_2SO_4 and stirred overnight. The solids are filtered on Celite washing with Et_2O and the filtrate is evaporated leaving a solid.

(*S*)-2-Amino-3-methylbutan-1-ol (145a)



Starting from (*S*)-valine (**143a**) (6.6 g, 56 mmol), the product was synthesised according to the general procedure.

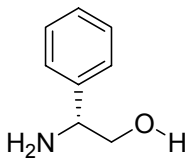
5.3 g; yield = 92 %

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.83-3.88 (m, 1H, CH_AH$_B$OH), 3.63-3.70 (m, 1H, CH$_A$$H_B$OH), 2.69-2.62 (m, 1H, H_2NC*H*), 2.59 (br s, 3H, NH_2, O*H*), 2.06-2.01 (m, 1H, C*H*(CH$_3$)$_2$), 1.01 (d, *J* = 7.2, 3H, CH_3), 0.96 (d, *J* = 7.2, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 63.91, 57.96, 30.43, 18.91, 17.94.

The analytical data are in agreement with those reported in literature.[175]

(*R*)-2-Amino-2-phenylethanol (145b)



Starting from (*R*)-phenylglycine (**143b**) (9.3 g, 56 mmol), the product was synthesised according to the general procedure.

6.8 g; yield = 88 %

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.18-7.21 (m, 2H, arom C*H*), 7.08-7.12 (m, 3H, arom C*H*), 4.23-4.19 (m, 1H, CH_AH$_B$OH), 3.95-4.01 (m, 3H, CH$_A$$H_B$OH, H_2NC*H*), 2.10 (br s, 3H, NH_2, O*H*).

[175] G. A. Smith, R. G. Gawley, *Org. Synth.* **1984**, *63*, 136.

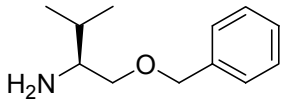
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.5, 128.6, 127.0, 67.5, 62.7.

The analytical data are in agreement with those reported in literature.[176]

5.7.1.3 General Procedure for the Synthesis of Protected Amino Alcohols

To a stirred solution of amino alcohol (1 eq.) in THF (1 mL/mmol amino alcohol) was added sodium hydride (60% dispersion, 1 eq.) in one portion and the resultant suspension was refluxed for 30 minutes. Benzyl chloride (1 eq.) was then added and the reaction mixture was refluxed for further 48 hours. On cooling, water was added and the solvent was removed *in vacuo*. The residue was treated with 6N KOH until pH 12 was reached and then extracted with dichloromethane. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil which upon column chromatography on silica gel yielded the desired compounds.

(*S*)-1-Benzyloxymethyl-2-methyl-propylamine (142a)



Starting from (*S*)-valinol **145a** (5.0 g, 48 mmol), the product was synthesised according to the general procedure.

8.3 g, Yield = 90 %

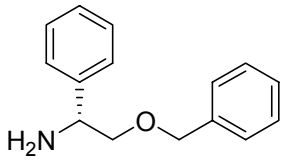
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.27-7.35 (m, 5H, arom C*H*), 4.60 (s, 2H, $C_6H_5CH_2O$), 3.71-3.75 (m, 1H, CH_AH_BOBn), 3.59-3.62 (m, 1H, CH_AH_BOBn), 2.77-2.74 (m, 1H, H_2NCH), 1.85-1.89 (m, 1H, $CH(CH_3)_2$), 1.35 (br s, 2H, NH_2), 0.90 (d, *J* = 6.9 Hz, 6H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.5, 127.6, 75.8, 75.0, 56.2, 32.9, 19.4, 18.1.

The analytical data are in agreement with those reported in literature.[177]

[176] A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, M. Druelinger, *J. Am. Chem. Soc.* **1981**, *103*, 3081.
[177] S. K. Patel, K. Murat, S. Py, Y. Vallée, *Org. Lett.* **2003**, *5*, 4081.

(*R*)-2-Benzyloxy-1-phenyl-ethylamine (142b)



Starting from (*R*)-phenylglycinol **145b** (5.0 g, 34.5 mmol), the product was synthesised according to the general procedure.

6.5 g; yield = 83 %

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.18-7.22 (m, 10H, arom C*H*), 4.54 (s, 2H, $C_6H_5CH_2O$), 4.20 (dd, *J* = 3.8, 9.0 Hz, 1H, H_2NCH), 3.66 (dd, *J* = 3.8, 9.0 Hz, 1H, CH_AH_BOH), 3.44 (t, *J* = 8.8 Hz, 1H, CH_AH_BOH), 1.81 (s, 2H, NH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 142.8, 137.6, 128.7, 128.6, 127.9, 127.5, 127.0, 75.0, 72.9, 60.5.

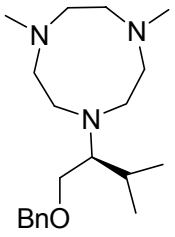
The analytical data are in agreement with those reported in literature.[178]

5.7.1.4 General Procedure for the Synthesis of C_1-Symmetric Chiral TACN

A 250 ml two necked flask was charged with LiBr (2 eq.), Na_2CO_3 (4 eq.), the bis-chloroamide **108a** (1 eq.) and CH_3CN (15 mL/mmol chloroamide). The resulting suspension was heated to reflux and a solution of the protected aminoalcohol (1 eq.) in CH_3CN (8 ml) is added dropwise. The mixture was refluxed for 6 hours, and then cooled to 0 °C. The solids were filtered off and the solvent is evaporated, leaving a crude viscous material. This was dissolved in dry THF (150 ml) under argon and cooled to 0 °C. $LiAlH_4$ (4 eq.) was added in portions. The resulting suspension is heated to reflux and stirred for 3 hours. After cooling to 0 °C, the reaction was quenced adding in sequence H_2O (1 mL/g $LiAlH_4$), NaOH 15% (0.8 mL/g $LiAlH_4$) and finally H_2O (2 mL/g $LiAlH_4$). The resulting colloid was diluted with Et_2O, treated with Na_2SO_4 and stirred for 2-4 h. The solids were filtered washing with Et_2O and the solvent is evaporated leaving a crude oil. Purification by flash chromatography yields the products as colourless oils.

[178] A. I. Meyers, G. S. Poindexter, Z. Brich, *J. Org. Chem.* **1978**, *43*, 892.

1-((*S*)-1-Benzyloxymethyl-2-methyl-propyl)-4,7-dimethyl-perhydro-1,4,7-triazonine (147a)



Starting from protected (S)-valinol **142a** (907 mg, 4.69 mmol), the product was synthesised according to the general procedure. The product was purified by flash chromatography (MeOH/NH_4OH (25%) 7:3).

237 mg; yield = 17%

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.19 (m, 5H, arom C*H*) 4.42 (d, 1H, *J* = 12.1 Hz, OCH_AH$_B$C$_6$H$_5$), 4.37 (d, *J* = 12.1 Hz, 1H, OCH$_A$$H_BC_6H_5$), 3.49 (d, *J* = 4.4 Hz, 2H, bridge CH_2), 2.87-2.79 (m, bridge 4H, CH_2), 2.70 (ddd, *J* = 2.2, 7.4, 14.0 Hz, 2H, OCH_2CH), 2.64-2.50 (m, 6H, bridge CH_2), 2.30 (s, 6H, NCH_3), 2.26-2.22 (m, 1H, NC*H*CH(CH$_3$)$_2$),1.77-1.68 (m, 1H, C*H*(CH$_3$)$_2$), 0.96 (d, 3H, *J* = 6.6 Hz, CH$_3$CHCH_3), 0.85 (d, *J* = 6.9 Hz, 3H, CH_3CHCH$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 128.5, 127.7, 127.7, 73.4, 71.4, 70.4, 58.0, 56.7, 56.7, 54.4, 29.6, 22.2, 138.8, 20.8.

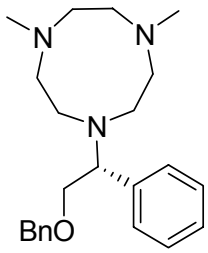
Optical rotation: $[\alpha]_D^{25}$ = –8.4 (c = 1.75, CH_2Cl_2/MeOH 10:1).

IR (capillar): ν = 700, 744; 1028; 1102; 1251; 1265; 1307; 1364; 1388; 1425; 1455; 1651; 2872; 2967.

MS (CI): *m*/*z* (%): 565 ((M+H)$^+$, (0.20)), 391 (1), 312 (9), 298 (1), 292 (2), 284 (3), 278 (2), 276 (2), 270 (7), 222 (3).

Elemental Analysis for $C_{30}H_{42}Cl_2N_2O_4$: calculated: C 63.71; H 7.48; N 4.95
found: C 63.54; H 7.45; N 5.01

1-((*R*)-2-Benzyloxy-1-phenyl-ethyl)-4,7-dimethyl-perhydro-1,4,7-triazonine (147b)



Starting from protected (*R*)-phenylglycinol **142b** (1.09 g, 4.69 mmol), the product was synthesised according to the general procedure. The product was purified by flash chromatography [MeOH/NH_4OH (25%) 9:1].

227 mg; yield = 15%

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26-7.14 (m, 10H, arom C*H*), 4.44 (s, 2H, OC$H_2C_6H_5$), 3.90 (t, *J* = 6.6 Hz, 1H, NCHC_6H_5), 3.83 (dd, *J* = 6.6, 9.6 Hz, 1H, OC$H_AH_BCHC_6H_5$), 3.69 (dd, *J* = 6.6, 9.6 Hz, 1H, OC$H_AH_BCHC_6H_5$), 2.88-2.80 (m, 2H, bridge CH_2), 2.72-2.64 (m, 8H, bridge CH_2), 2.56-2.48 (m, 2H, bridge CH_2), 2.22 (s, 6H, NCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.1, 138.3, 128.7, 128.5, 128.3, 127.8, 127.8, 127.3, 73.4, 71.1, 68.4, 56.8, 56.1, 53.4, 46.2.

Optical rotation: $[\alpha]_D^{25}$ = +2.3 (c = 1.03, CH_2Cl_2/MeOH 10:1).

IR (capillar): ν = 2922; 2837; 2785; 1452; 1366; 1318; 1105; 1029; 737; 700.

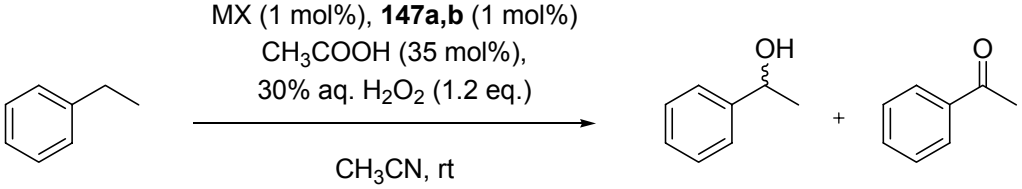
MS (CI): *m*/*z* (%): 368 ($(M+H)^+$ (41)), 260 (9).

Elemental Analysis for $C_{23}H_{33}N_3O$: calculated: C 75.16; H 9.05; N 11.43

found: C 74.04; H 9.85; N 11.96

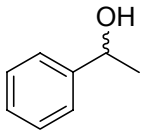
It has been impossible to date to obtain a correct elemental analysis.

5.7.1.5 General Protocol for the Enantioselective CH Oxidations Catalysed by Chiral C_1-Symmetric TACN



A solution of ethylbenzene (**5**) (1.0 mmol, 106 mg) in acetonitrile (5.0 mL) is treated with the ligand **147a** or **147b** (0.01 mmol), $Fe(ClO_4)_2 \cdot 6H_2O$ (3.66 mg, 0.01 mmol) and acetic acid (10 µL, 0.2 mmol). The mixture is stirred at rt for 15 min and H_2O_2 (74 µL, 1.2 mmol) is then added. Aliquots were taken at progressive time, quenched with MnO_2, filtered on Na_2SO_4 and analysed by GC.

1-Phenylethanol (6)



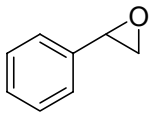
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.42 (m, 10H, arom C*H*), 4.87 (q, *J* = 6.6, 1H, C*H*OH), 3.15 (br s, 1H, O*H*), 1.52 (d, *J* = 6.6, 3H, CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.0, 128.5, 127.4, 125.5, 70.3, 25.4.
GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 140 kPa N_2; 100 °C, 40 min, 10 °C/min, 200 °C, 10 min**;** t_R = (*R*) 32.40, (S) 35.48 min.

The analytical data are in agreement with commercial compound.

5.7.1.6 General Protocol for the Enantioselective Epoxidations Catalysed by Chiral C_1-Symmetric TACN

A solution of substrate (1.0 mmol) in acetone (1.0 mL) is cooled to 0-2 °C in air and treated with the ligand (0.5 µmol in 48 µL of methanol) and $Mn(OAc)_2 \cdot 4H_2O$ (2.5 mg in 141 µL H_2O, 0.01 mmol). The mixture is stirred at 0-2 °C for 15 minutes. Oxalic buffer (0.15 M, 133 µL, 0.02 mmol) is added, followed within 1-2 minutes by H_2O_2 (30%, 0.4 mL, 4.0 mmol). After 1.5 hours stirring at 0-2 °C, another aliquot of H_2O_2 is added (0.2 mL, 2.0 mmol). After a total reaction time of 2.5-3 hours, addition of a small quantity of MnO_2 destroys the excess oxidant before the reaction mixture is diluted with 2.0 mL CH_2Cl_2 and the organic phase is separated and analysed by GC, using nitrobenzene as internal standard.

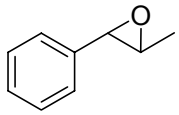
2-Phenyloxirane (149a)



Starting from styrene (**148a**) (104.2 mg, 1.0 mmol), the product was obtained according to the general protocol.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 75 kPa H_2, 110 °C, 30 min, 20 °C/min, 180 °C, 15 min; t_R = (*R*) 19.05 min; (*S*) 19.61 min.

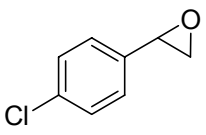
***trans*-2-Methyl-3-phenyloxirane (149b)**



Starting from *trans*-β-methylstyrene (**148b**) (118.2 mg, 1.0 mmol), the product was obtained according to the general protocol.

GC: Lipodex E (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa H_2, 80 °C, 5 min, 2010 °C/min, 120 °C, 5 min, 10 °C/min, 140 °C, 10 °C/min, 170°C; t_R = (*R*) 14.63 min; (*S*) 15.25 min.

2-(4-Chlorophenyl)oxirane (149c)

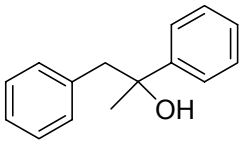


Starting from 4-chlorostyrene (**148c**) (138.6 mg, 1.0 mmol), the product was obtained according to the general protocol.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 75 kPa H_2, 110 °C, 30 min, 20 °C/min, 180 °C, 15 min; t_R = (*S*) 25.60 min; (*R*) 25.82 min.

5.7.2 Studies on the Asymmetric CH Activation Using Carboxylic Acids as Chiral Promoters

5.7.2.1 Synthesis of 1,2-diphenylpropan-2-ol (155)



A three-necked round flask, equipped with septum and condenser, is charged with Mg (136.0 mg, 5.6 mmol) under inert atmosphere. Diethyl ether is poured to completely cover the Mg and a crystal of iodine is added to the mixture. Methyl iodide (934.0 mg, 6.6 mmol) is dissolved in 5 mL diethyl ether and a small amount is added to the mixture to start the reaction. When the Mg begun reacting, the solution was slowly stirred and the methyl iodide left is added drop wise, controlling the temperature. After the consumption of the Mg, 1,2-diphenylethanone (1.01 g, 5.1 mmol), previously dissolved in 5 mL solvent, is added drop wise and the mixture is stirred for one hour. Aqueous ammonium chloride is then poured, the two phases are separated and the aqueous layer is extracted twice with diethyl ether. The collected organic phases are dried over $MgSO_4$ and the solvent is removed under vacuum. The crude is purified by flash chromatography on silica gel (pentane/diethyl ether 3:1).

585 mg; yield = 54%

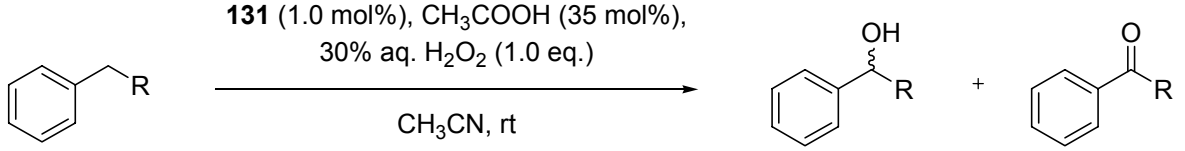
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.10-7.35 (m, 8H, arom C*H*), 6.95 (m, 2H, arom C*H*), 3.00 (dd, *J* = 13.4, 30.4 Hz, 2H, CH_2), 2.08 (s, 1H, O*H*), 1.48 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.8, 137.1, 130.8, 128.2, 126.8, 126.8, 125.3, 74.6, 50.8, 29.4.

GC: FS-Cyclodex β I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 140 kPa N_2; 40 °C, 3 min, 3 °C/min, 140 °C, 1 min, 40 °C/min, 240 °C, 1 min; t_R = 36.59 min.

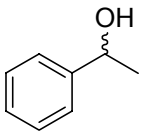
The analytical analyticaldata are in agreement with those reported in literature.[179]

5.7.2.2 General Protocol for the Asymmetric CH Activation Using Carboxylic Acids as Chiral Promoters



The substrate (2.3 mmol), carboxylic acid (1 mmol) and the complex **131** (1.58 mg, 0.002 mmol) were dissolved in acetonitrile (5 mL) and the pink solution was stirred for 10 minutes. After the addition of aqueous hydrogen peroxide (30%, 283 µL, 2.5 mmol), the reaction was stirred for one hour. The excess of oxidant is then quenched with MnO_2.

1-Phenylethanol (6)



Starting from ethylbenzene (**5**) (244.3 mg, 2.3 mmol), the product was obtained according to the general protocol. When the conversion was >60%, water was added to the solution and the organic layer was extracted twice with diethyl ether. The collected organic phase was dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel (PE/MTBE 6:4).

For analytical data, see **5.7.1.5**.

[179] S.-H. Kim, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 2320.

6. Abbreviations

Å	Angstrom
[α]	Specific Rotation Value
acac	Acetylacetonate
aq.	Aqueous
AcOEt	Ethyl Acetate
AcOH	Acetic Acid
Ar	Aryl
Arom	Aromatic
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyl-dicarbonate
calc.	Calculated
δ	Chemical Shift
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric Excess
EI	Electron Ionisation
eq.	Equivalent(s)
GC	Gaschromatography
IR	Infrared Spectroscopy
J	Coupling Constant
M	Molar
Me	Methyl
min	Minutes
MS	Mass Spectroscopy
N	Normal
NMR	Nuclear Magnetic Resonance
OAc	Acetate
Ph	Phenyl

PMB	*p*-Methoxybenzyl
ppm	Parts per Million
rac	Racemate
rt	Room Temperature
t	Retention Time
TACN	Triazacyclononane
TBS	*t*-Butylsilyl
TM-TACN	Trimethyl-triazacyclononane
THF	Tetrahydrofurane
TMS	Trimethylsilyl
TON	Turn Over Number
ν	Wave Number

7. Curriculum Vitae of Chiara Pavan

Personal Information

Name:	Chiara Pavan
Nationality:	Italian
Date and Place of Birth:	11th March 1976 in Turin, Italy

Education

October 2001 – September 2005	PhD Work under the Supervision of Prof. Dr. Bolm *Studies on Transition Metal Catalysed Oxidations with Hydrogen Peroxide as Terminal Oxidant;* RWTH-Aachen, Germany.
March 2001	Degree in Organic Chemistry at University of Turin, Italy.
March 2000 – March 2001	Master Thesis under the Supervision of Prof. Carpignano *Selection of Dyes for Dyeing of Polyethylenterephtalate using Additives with Low Environmental Impact. Application of Chemometric Techniques;* University if Turin, Italy.
September 1995 – March 2001	Chemistry Studies at the University of Turin, Italy
September 1990 – July 1995	Scientific High School "Marie Curie" Insitute In Turin, Italy

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