ASYMMETRIC EPOXIDATION OF UNFUNCTIONALISED ALKENES CATALYSED BY D-FRUCTOSE DERIVATIVES

Natalia Nieto Alonso

Dipòsit Legal: T. 62-2014

Doctoral Thesis Natalia Nieto Alonso

Asymmetric Epoxidation of Unfunctionalised Alkenes Catalysed by D-Fructose Derivatives

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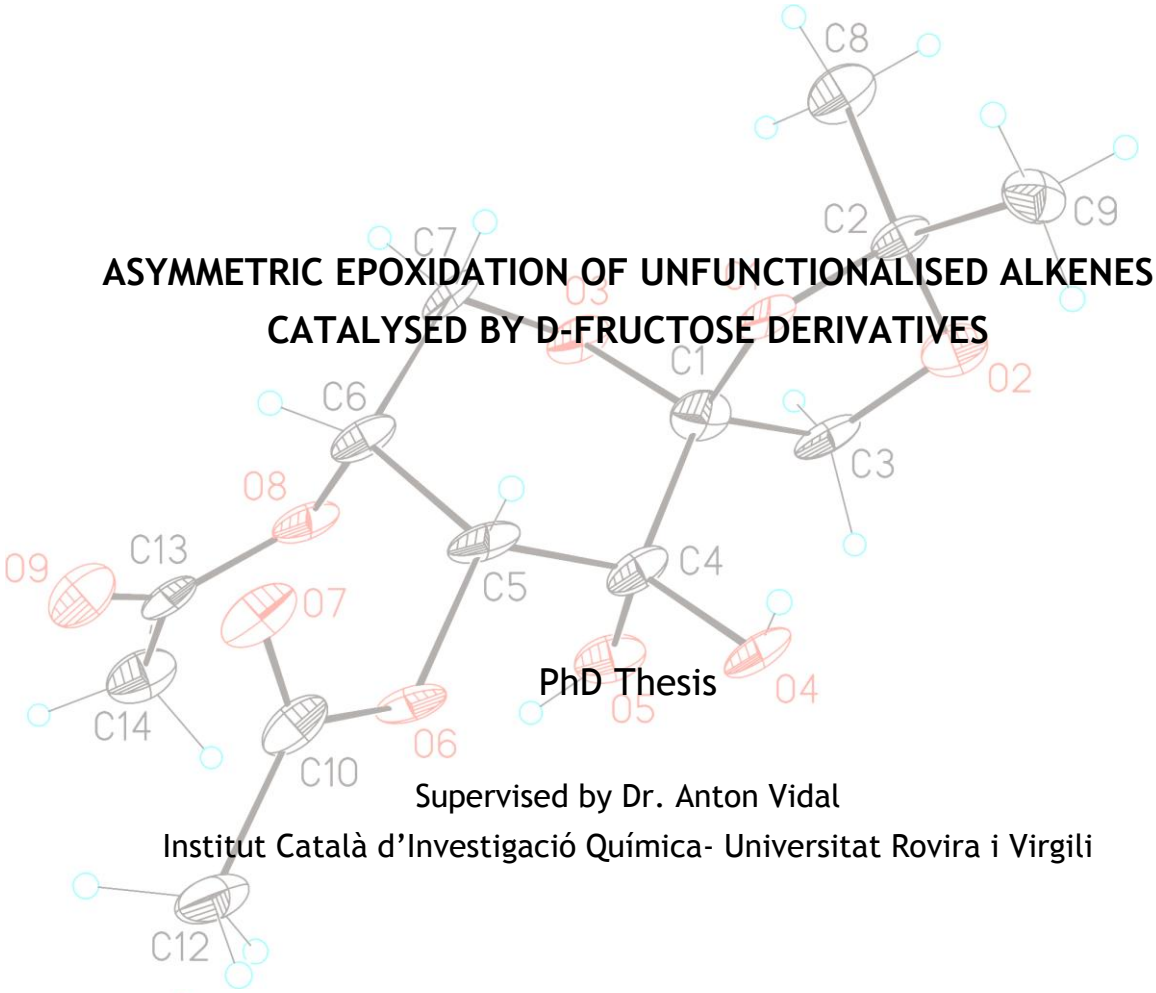

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PhD Thesis

Supervised by Dr. Anton Vidal
Institut Català d'Investigació Química- Universitat Rovira i Virgili

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Prof. Dr. Anton Vidal Ferran, Group Leader of the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor of the Catalan Institution for Research and Advanced Studies (ICREA),

CERTIFY that the present Doctoral Thesis entitled: "**ASYMMETRIC EPOXIDATION OF UNFUNCTIONALISED ALKENES CATALYSED BY D-FRUCTOSE DERIVATIVES**", presented by Natalia Nieto Alonso to receive the PhD degree in Chemistry, has been carried out under my supervision, in the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, 20 June 2013

PhD Thesis supervisor

Prof. Dr. Anton Vidal Ferran

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A mis padres

Cuanto mayor es la dificultad, mayor es la gloria

Cicerón

Publications and Patents

Upon submission of this thesis, the results contained herein have so far resulted in the following publications and patents:

i) Publications:

- Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.
- Nieto, N.; Munslow, I. J.; Barr, J.; Benet-Buchholz, J.; Vidal-Ferran, A. *Org. Biomol. Chem.* **2008**, *6*, 2276.
- Nieto, N.; Munslow, I. J.; Fernández-Pérez, H.; Vidal-Ferran, A. *Synlett* **2008**, 2856.

ii) Patents:

- Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. (Institut Català d'Investigació Química). *Efficient Synthesis of Asymmetric Epoxidation Catalyst I*. European Patent 2005, P622EP00.
- Nieto, N.; Vidal-Ferran, A. (Institut Català d'Investigació Química). *Efficient Catalyst for the Asymmetric Epoxidation of Electron Deficient as Well as Non-Electron Deficient Alkenes*. European Patent 2005, KP623EP00.

Acronyms and Abbreviations

Many of the abbreviations and acronyms commonly used in organic chemistry have been used in this Thesis, according to the "*Guidelines for authors" J. Org. Chem.* **2008**, *73*, 23A-24A.

Other acronyms and abbreviations are listed below:

Cn:	*N*,*N*',*N*''-trimethyl-1,4,7-triazacyclononane
(bmin)(PF_6):	1-Butyl-3-methylimidazolium hexafluorophosphate
n-Bu_4NHSO_5:	Tetra-*n*-butylammonium peroxomonosulfate
equiv.:	Equivalent
n-Bu_4NHSO_4 or TBAHS:	Tetra-*n*-butylammonium hydrogen sulfate
ee:	Enantiomeric excess
TBA-Ox:	Tetra-*n*-butylammonium peroxymonosulfate
DMD:	Dimethyldioxirane
MTFD:	Methyl(trifluoromethyl)dioxirane
MCPBA:	*m*-chloroperoxybenzoic acid
DMM:	Dimethoxymethane
PPTs:	Pyridinium *p*-toluenesulfonate

Contents Summary

Introduction and Aims

In the field of chemistry the concept of chirality is extremely important. Chirality is the property of an object of not being superimposable on its mirror image, *i.e.* any structure that has no rotation-reflexion axes (S_n)[1] can exist as two mirror-images, which are called enantiomers.[2]

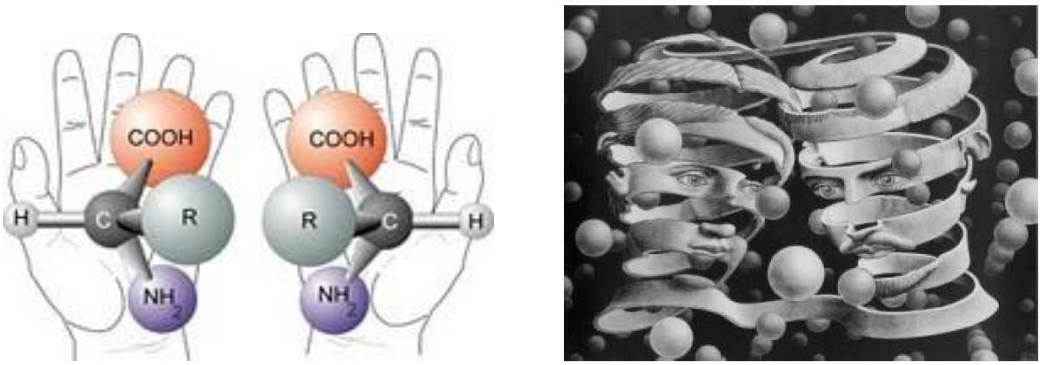


Figure 1. Some examples of chirality: Two enantiomers of a generic amino acid superimposed on images of a left and right hand[3], and Chirality and Art, M. C. Escher's "Bond of Union" in which the woman's head is a left-handed helix whilst the man's head is a right-handed helix.[4]

Chirality is extremely prevalent in the natural world; all living systems exist in a chiral environment. Nature has chosen to create all of its living structures from chiral molecules (*e.g.* amino acids, sugars, etc.) and has selected a single enantiomeric form of each. For instance, the DNA and RNA of all living organisms are based exclusively on D-sugars, and a consequence of this is the chiral double helix architecture of DNA. On the other hand, most proteins consist of linear polymers built from a series of L-amino acids. The general structures of L- and D-amino acids are depicted in Figure 2.

[1] Rotation-reflection axis is also called *n*-fold improper rotation axis, with the angle of rotation being 360°/*n*. A plane mirror (σ) and an inversion centre (i) can be considered a S_1 and S_2 rotation-reflexion axis, respectively.
[2] a) Kelvin, L. *Baltimore lectures* **1884**. b) Whyle, L. L. *Nature* **1958**, *182*, 198.
[3] Taken from http://en.wikipedia.org/wiki/Chirality.
[4] Taken from http://www.mpilkington.comLecture_6.

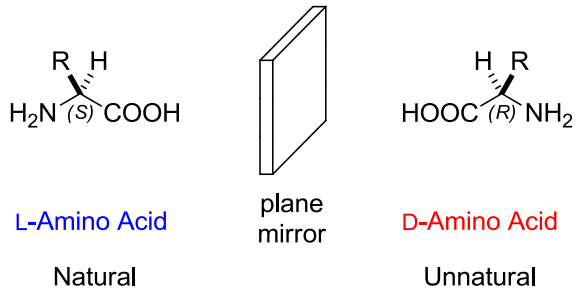


Figure 2. Natural and unnatural amino acids.

Chirality is omnipresent in nature, and not surprisingly, chiral compounds are of tremendous importance to various sectors of the chemical industry (*e.g.* drug development, agrochemical research, fragrances, advanced material sciences, etc.). High enantiomeric purities are widely sought after, since the biological properties of these products are normally restricted to only one of the enantiomers. The other enantiomer may show no or different activity, including positive or, in the worst case, undesirable effects.[5] This was demonstrated by the incident involving thalidomide: whilst the (*R*)-isomer is a sedative, the (*S*)-isomer produces birth defects including malformations.[6]

In order to ensure the regulated preparation, use and sale of active pharmaceutical ingredients (APIs), agencies like the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA) now outline and enforce guidelines requesting optical purity in chiral molecules.[7] For instance, 94% of the approved chiral drugs by the FDA in 2006 were commercialised in enantiomerically pure form.[8] Furthermore, seven of the ten top-selling drugs in the U.S. for the year 2010 were all single enantiomers.[9] According to the Global Industry Analysts Inc. report,[10] the direct and

[5] For instance, see: a) Tumlison, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L. *Science* **1977**, *197*, 789. b) Drayer, D. E. *Clin. Pharmacol. Ther*. **1986**, *40*, 125. c) Wainer, I. W. *Am. J. Hosp. Pharm.* **1992**, *46*, S4.

[6] For example, see: a) Fabro, S.; Smith, R. L.; Williams, R. T. *Nature* **1967**, *215*, 296. b) Höglund, P; Eriksson, T; Björkman, S. *J. Pharmacokinet. Biopharm.* **1998**, *4*, 363.

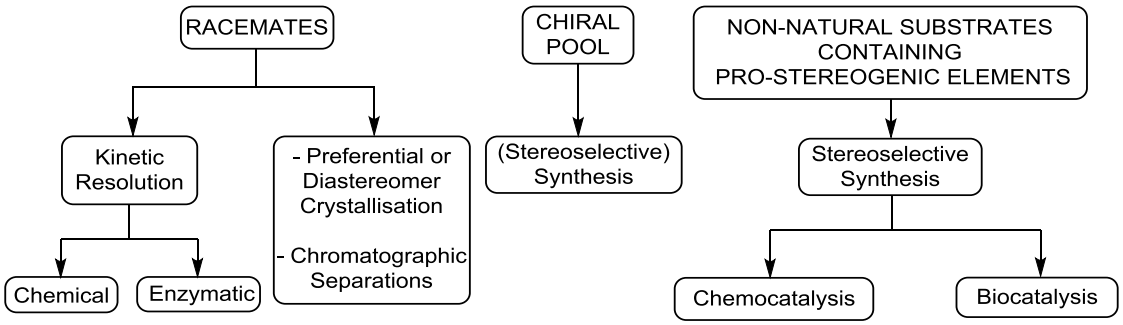
[7] For example see: a) Investigation of Chiral Active Substance: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002816.pdf. b) FDA Policy Statement for the Development of New Stereoisomeric Drugs, Washington DC, **1992**: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.httm.

[8] a) Thayer, A. M. *Chem. Eng. News* **2007**, *85 (32)*, 11. b) Thayer, A. M. *Chem. Eng. News* **2008**, *86 (31)*, 12.

[9] These drugs are Lipitor®, Nexium®, Plavix®, Advair®, Singulair®, Crestor® and Actos® representing $35.8 billion in sales in 2010. Source IMS Health, Pharmacy Times, see: http://www.pharmacytimes.com/publications/issue/2011/May2011/Top-200-Drugs-of-2010.

global market for Chiral Technology products is forecast to reach $4.9 billion by the year 2015. Apart from pharmaceutical products, agrochemicals (*i.e.* chiral pesticides, fungicides, herbicides, and insecticides) are another class of compound that will probably have to meet increased demands regarding enantiopurity in the near future.[11]

Consequently, obtaining the different classes of life-science products in high enantiopurity, ideally by controlling their stereochemistry during preparation, has been and still is a big challenge for the chemical industry. Strategies to prepare enantiopure compounds can be divided into three groups depending on the kind of starting material used.[12]



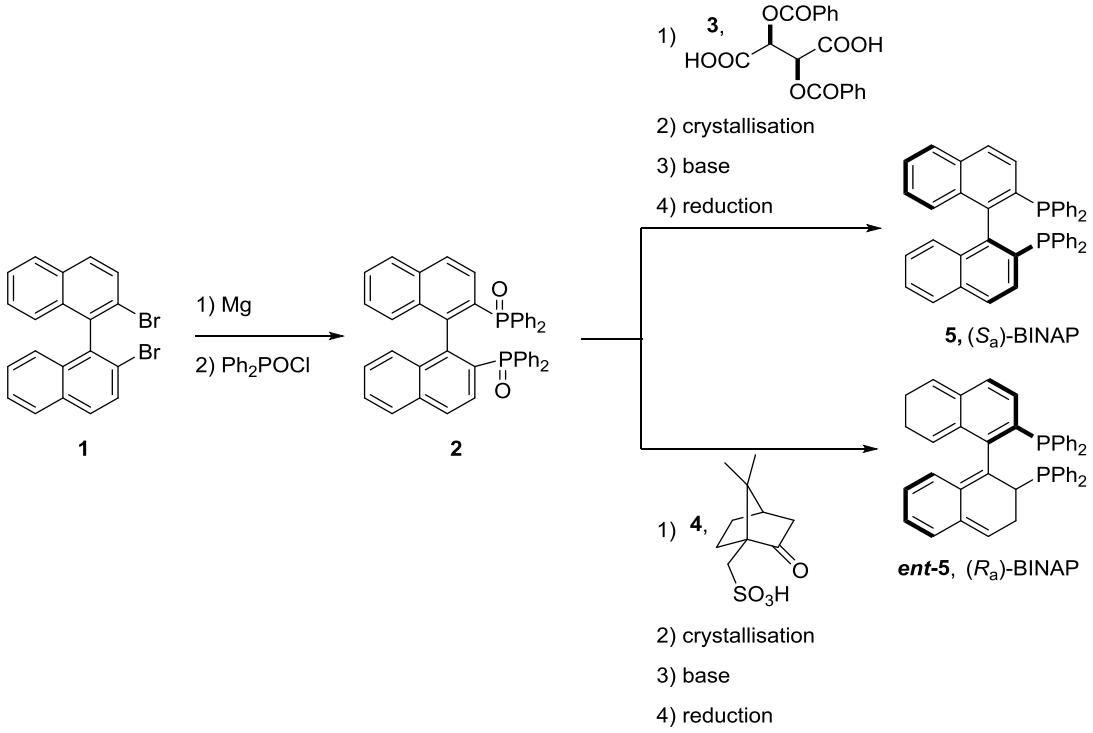
Scheme 1. Strategies to prepare enantiopure compounds.

The resolution of racemates into their enantiomers by preferential or diastereomer crystallisation was one of the first methods to be used and it still is probably the most important method for the industrial preparation of pure enantiomers.[12]

Theoretical yields of 100% of pure enantiomers are achievable for both crystallisation types under certain conditions, such as spontaneous *in situ* racemisation (for preferential crystallisation) and spontaneous diastereomer interconversion (for diastereomer crystallisation). However, the more common cases result in theoretical yields of only 50%, which represents a drawback unless the undesired enantiomer can be racemised

[10] Global Industry Analysts, Inc. (GIA) is a publisher of off-the-shelf market research. An abstract of the chiral technology report can be found on the following web link: http://www.prweb.com/releases/chiral_technology/separation_stereogenic/prweb8145406.htm.
[11] a) Kurihara, N.; Miyamoto, J.; Paulson, G. D.; Zeeh, B.; Skidmore, M. W.; Hollingworth, R. M.; Kuiper, H. A. *Pure Appl. Chem.* **1997**, *69*, 2007. b) Sekhon, B. S. J. *J. Pestic. Sci.* **2009**, *34*, 1.
[12] Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optically Active Compounds*, Marcel Dekker, New York, 1993.

and recycled, or there is a demand for both enantiomers. This is the case for the enantioselective catalyst BINAP that is produced in enantiomerically pure form by resolution.[13]



Scheme 2. Synthesis of (S_a)- and (R_a)-BINAP (**5** and ***ent*-5**) by resolution.

Large-scale chromatographic separation techniques (*e.g. simulated moving bed (SMB) chromatography*)[14] are emerging and are becoming important preparation methods for APIs, especially at the early phases of product development or even for the whole production process.

The success of kinetic resolutions on the other hand depends on the fact that the two enantiomers of a given starting material react at different rates with a chiral reagent or interact differently with a chiral catalyst. Ideally, one of the enantiomers is transformed whereas the other remains unreacted.[15]

[13] a) Miyashita, A.; Yasuda, H.; Takaya, K.; S.; Toriumi, T.; Ito T.; Souchi, R.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. b) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629. c) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth*. **1989**, *67*, 20.
[14] For instance, see: Rajendran A.; Paredes, G.; Mazzotti, M. *J. Chromatogr. A.* **2009**, *1216*, 709.
[15] Koskinen, A. *Asymmetric synthesis of natural products*, Wiley-VCH, Chichester, 1993.

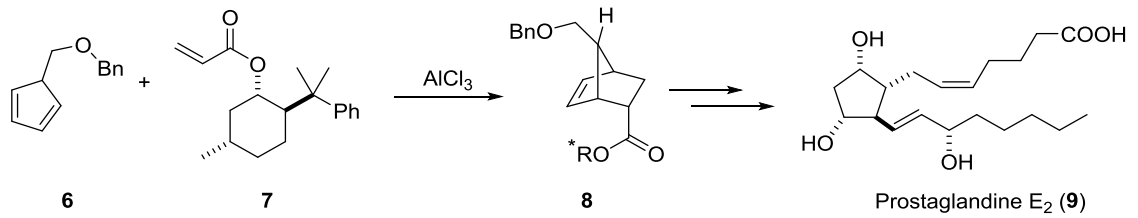
Some of these preparation methods (*e.g.* diastereomer crystallisation and non-catalytic kinetic resolution) require stoichiometric amounts of a chiral reagent or resolving agent, which in industrial processes calls for recycling of the enantiomerically pure derivative with the corresponding operative expenses involved.

The chiral pool approach relies on inexpensive and readily available enantiomerically pure natural products or their derivatives that can be transformed into the desired products by chemical means. One inherent weakness of this method results from the limited starting materials of the chiral pool that cannot hope to cover all of the desired target molecules. The second major disadvantage of this strategy is the unavailability of both enantiomers of most natural products, which restricts the accessibility to just one enantiomer of a given target molecule.

Organic synthesis, that introduces in a controlled manner one or more new and desired stereogenic elements in a molecule, is referred to as stereoselective synthesis, which implies transformation of a substrate's prostereogenic element into a stereogenic centre, plane, helix or axis in the resulting molecule.

The use of chiral reagents or chiral auxiliaries (an enantiomerically pure compound that is reversibly incorporated into an organic substrate so that the required reaction can be carried out stereoselectively under selective formation of one diastereoisomer) has proven to be revolutionary as these reagents allowed the preparation of complex enantiopure organic molecules. The seminal work of Cram,[16] Prelog[17] and Felkin[18] illustrate this strategy, which has been commonly used by the synthetic community. For instance, Corey used this strategy in his famous synthesis of prostaglandine E_2 (**9**), in which a derivative from (*S*)-pulegone (**7**) was used as a chiral auxiliary.[19]

[16] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
[17] Chan, R. S.; Ingold, C.; Prelog, V. *Angew.Chem., Int. Ed. Engl.***1966**, *5*, 385.
[18] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199.
[19] Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.



Scheme 3. Synthesis of prostaglandine E_2 (**9**) using the (*S*)-pulegone derivative (**7**) as a chiral auxiliary.

However, both approaches (the use of chiral reagents and chiral auxiliaries) come with substantial drawbacks. Chiral reagents must be applied in stoichiometric amounts whereas chiral auxiliaries require additional synthetic steps (attachment and removal of the chiral auxiliary followed by its recycling). Furthermore, the availability of these chiral entities is again limited.

Asymmetric catalysis, in which each equivalent of chiral catalyst, by virtue of being continually regenerated, yields many molecules of enantioenriched product is *a priori* the more elegant approach compared to the ones mentioned above. During the past few decades, asymmetric transformations catalysed by different classes of artificial catalysts have become highly versatile tools in asymmetric organic synthesis, thus providing efficient solutions for a growing number of asymmetric transformations.[20] The Nobel Prize in Chemistry in 2001 was awarded to William S. Knowles and Ryoji Noyori for their achievements in catalytic asymmetric hydrogenations, and to K. Barry Sharpless for his work on catalytic asymmetric oxidations, and for the impact of their contributions to the field of organic synthesis.[21]

Until recently, two main categories of enantioselective catalysts were used. Much of the work in the area of catalytic asymmetric synthesis focused on the design and synthesis of organometallic complexes that are able to induce asymmetry into organic transformations. First of all, the chiral catalyst provides a low energy path, and

[20] For example, see the following general textbooks on asymmetric catalysis: a) *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Eds., Springer, Berlin, 2004. b) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*, John Wiley & Sons, Inc., Hoboken, 2007. c) Blaser, H. U.; Schmidt, E., *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, 2007. d) Ojima, I., *Catalytic Asymmetric Synthesis*, John Wiley & Sons, Inc., New Jork, 2010. e) *Comprehensive Chirality*, Carreira, E. M.; Yamamoto, H.; Eds., Elsevier Science, Oxford, 2012.
[21] a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. c) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

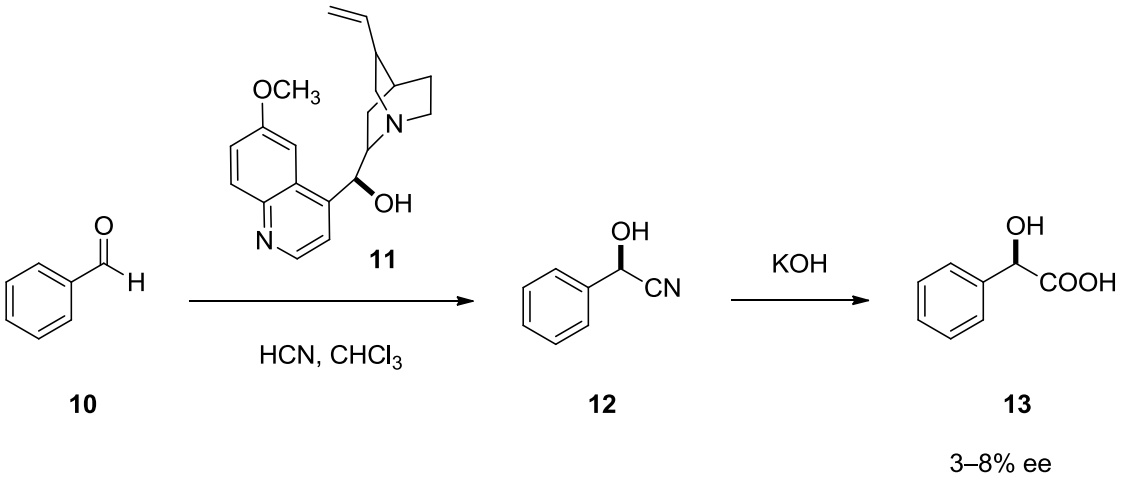
secondly, it governs the stereochemistry of the final products. The key step is usually the formation of a supramolecular system around the metallic centre with the participation of the substrate, the reagent(s), and an enantiomerically pure chiral molecule (ligand) bound to the metal. The stereogenic elements of the catalyst (understood as the set of the chiral ligand and the catalytically active metallic centre) have a stereodirective effect in the course of the reaction.

Enzymes constitute the second general category of enantioselective catalysts that have been used to efficiently prepare pharmaceutical products, agrochemicals, fine chemicals or synthetic intermediates.[22] In nature, most catalysts are based on proteins (*i.e.* enzymes), which catalyse different metabolic and catabolic processes.

Organocatalysis has been defined as the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound that is composed of (mainly) carbon, hydrogen, nitrogen, oxygen, sulphur and phosphorus.[20,23]

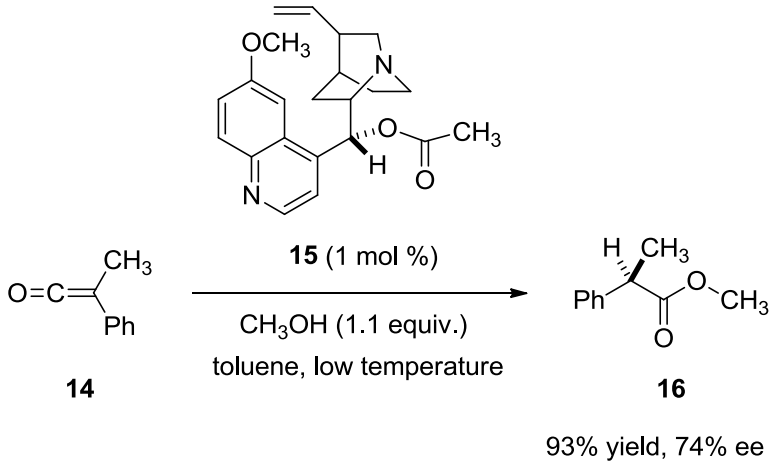
The first example of an asymmetric organocatalytic reaction was reported by Bredig and Fiske as early as 1913.[24] This work showed that the addition of HCN to benzaldehyde, if mediated by the alkaloids quinine and/or quinidine, afforded optically active cyanohydrins (**10**), although in low optical yield (Scheme 4).

[22] Drauz, K.; Waldmann H. *Enzyme Catalysis in Organic Synthesis*, Wiley-VCH, Weinheim, 2002.
[23] For selected book reviews and review articles on asymmetric organocatalysis, see: a) Dalko, P. I.; Moisan, L. *Angew.Chem., Int. Ed.* **2004**, *43*, 5138. b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005. c) Seayad, J.; List, *B. Org. Biomol. Chem*. **2005**, *3*, 719. d) Dalko, P. I. *Enantioselective Organocatalysis*, Wiley-VCH, Paris, 2007. e) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. f) Pellisier, H. *Tetrahedron* **2007**, *63*, 9267. g) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065. h) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2. i) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. j) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. k) Pellisier, H. *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry, Cambridge, 2010. l) Valero, G.; Companyó, X.; Bravo, N.; Alba, A.-N. R.; Moyano, A.; Rios, R. *Synlett* **2010**, 1883. m) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *17*, 1138. n) List, B. *Asymmetric Organocatalysis*, Springer, Berlin, 2010. o) Ma, S. *Top. Organomet. Chem.*, Springer, Berlin, 2011, Vol. 36. p) Gruttadauria, M.; Giacalone, F. *Catalytic Methods in Asymmetric Synthesis*, Wiley, New Jersey, 2011. q) Carreira., E. M. *Organocatalysis*, Thieme, 2011. r) Buckley, B. R.; Kimber, M. C.; Slater, N. H. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2012**, *108*, 98. s) *Comprehensive Chirality*, Carreira, E. M.; Yamamoto, H.; Eds., Elsevier Science, Oxford, 2012, Vol. 6.
[24] Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7.



Scheme 4. The first example of an organocatalytic enantioselective reaction reported by Bredig and Fiske.[24]

The enantioselectivity in an organocatalysed transformation was enhanced by Pracejus in 1960 using *O*-acetylquinine (**15**) in the addition of methanol to methyl phenyl ketene (**14**) (Scheme 5).[25]

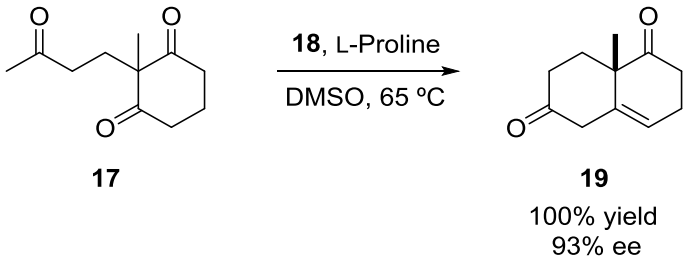


Scheme 5. Addition of methanol to methyl phenyl ketene catalysed by a quinine derivative.

Before the turn of the century, only a limited number of preparatively useful applications of organocatalysts were reported. In 1971, a ground-breaking study by Eder, Sauer and Wiechert demonstrated for the first time that asymmetry could be

[25] a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. b) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195.

induced in a Robinson-type annulation using triketone (**17**) by simply adding catalytic amounts of D- or L-Proline (Scheme 6).[26]



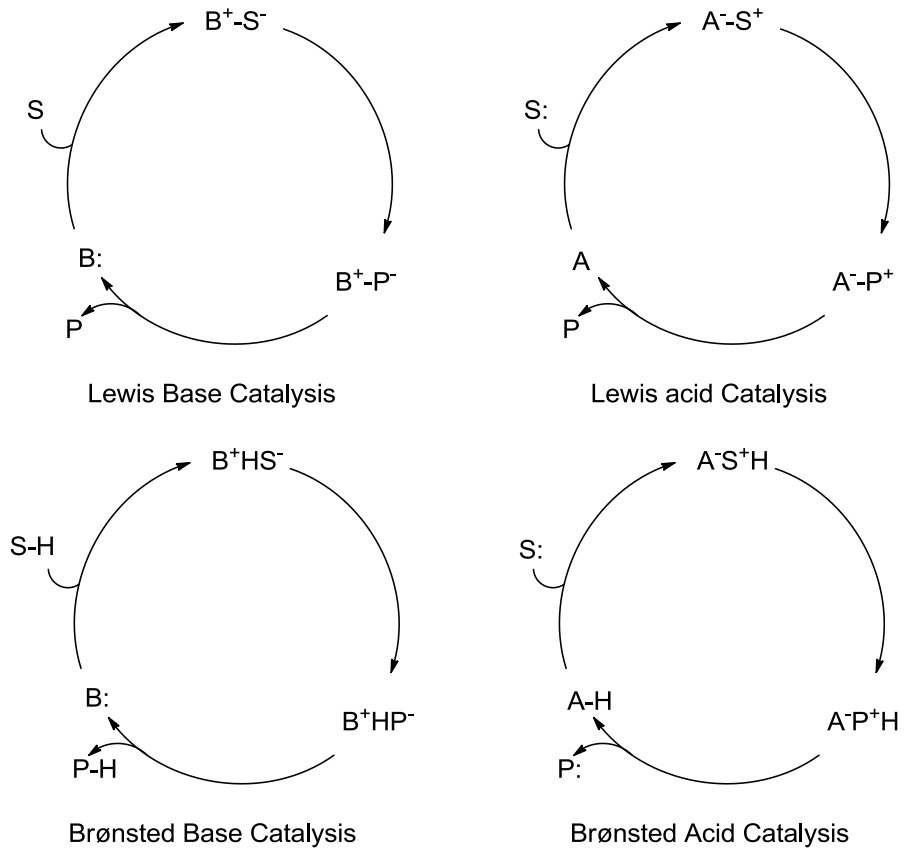
Scheme 6. An example of an organocatalysed asymmetric Robinson annulation.

This approach, which is now commonly known as asymmetric organocatalysis, was almost completely ignored for three decades. Developments in this field in recent years have proven that organic molecules alone, in addition to metal complexes and biocatalysts, can be highly selective and efficient catalysts. As a consequence, asymmetric organocatalysis[23] has gained importance in this area, complementing both asymmetric biocatalysis and organometallic catalysis.

Organocatalysts offer new and attractive perspectives and advantages to synthetic chemists. This type of catalyst is usually robust, inexpensive, readily available and non-toxic. Moreover, inert atmospheres, low temperatures, anhydrous solvents, etc. are in many instances not required.

Most, but not all organocatalysts, can be broadly classified as Lewis bases, Lewis acids, Brønsted bases or Brønsted acids. If we consider **B** as an organic compound with a basic functional group and **A** an organic compound with an acidic functional group, general catalytic cycles for organocatalysed reactions are shown in the following scheme:

[26] a) Eder, U.; Suer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. b) Hajos, Z.G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.



Scheme 7. General catalytic cycles in organocatalysis.

Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction, then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base- and acid-mediated catalytic cycles are initiated *via* deprotonation and protonation of the substrate, respectively.[23c]

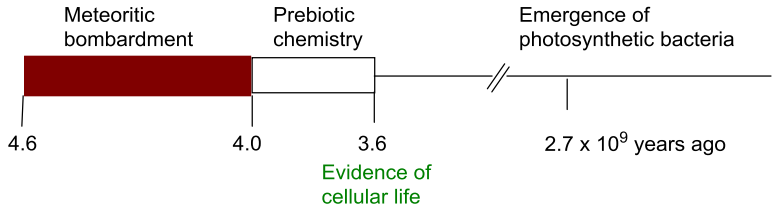
Carbohydrates are an important class of chiral compounds that perform numerous roles in living organisms. Along with serving as the energy reservoir (*e.g.* starch and glycogen) and as the structural components in plants and animals (*e.g* cellulose and chitin), they have a pivotal role in life as key constituents of nucleic acids.

The idea that organic compounds, and carbohydrates included amongst them, served as the basis of life was already suggested by Oparin some decades ago.[27]

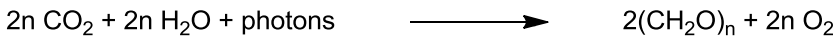
Miller's studies on the generation of molecular complexity from basic building blocks (mainly ammonia, water, hydrogen, methane, formaldehyde and hydrogen cyanide) revealed that these elemental chemical compounds combined to form simple molecules (such as formic acid and urea) and more complex molecules containing carbon-carbon bonds (such as amino acids glycine and alanine) under laboratory conditions similar to those believed to be present in the Earth's early atmosphere.[28] In similar experiments performed later by other scientists, more than 30 different carbon compounds were identified.[29] Butlerow performed in 1861 what has become known as the "formose reaction", in which a mixture of branched and linear aldoses and ketoses (*i.e.* triose, tetrose, pentose, hexose and heptose sugars) were formed under laboratory conditions similar to those believed to be present in the Earth's early atmosphere.[30]

Photosynthesis[31] could also explain the origin of carbohydrates. A basic chemical equation is presented in Scheme 8, where $(CH_2O)_n$ stands for the general formula of a carbohydrate.

[27] Oparin, A. I.; Morgulis, S. *The Origin of life*, The Macmillan Co., New York, 1938.
[28] Prebiotic chemistry refers to the sources and formation paths of complex molecules on early Earth. The timescale for the emergence of the primitive forms of life is represented in the figure below. For Miller's work, see: a) Miller, S. L. *Science* **1953**, *117*, 528. b) Miller, S. L. *J. Am. Chem. Soc.* **1955**, *77*, 2351.



[29] For instance, see: a) Oró, J. *Nature* **1961**, *191*, 1193. b) Oehlenschläger, F.; Manfred, E. *Origins of Life and Evolution of Biospheres*, Springer, Göttingen, 1997, Vol. 27, p 437. c) Lazcano, A.; Bada, J. L. *Origins of Life and Evolution of Biosphere*, Kluwer Academic Publishers, Netherlands, 2003. d) Menor-Salván, C.; Ruiz-Bermejo, D. M.; Guzmán, M. I.; Osuna-Esteban, S.; Veintemillas-Verdaguer, S. *Chem. Eur. J.* **2007**, *15*, 4411.
[30] a) Butlerow, A. *Justus Liebigs Ann. Chem.* **1861**, *120*, 295. b) John D.; Sutherland, J. D.; Whitfield, J. N. *Tetrahedron* **1997**, *53*, 11493.
[31] For example, see: a) Stryer, L. *Bioquímica*, Reverté, Barcelona, 1995, Vol. II. b) Gunatilaka, A. L. *Plant Natural Products, in Natural Products in Chemical Biology*, Civjan, N.; Ed., John Wiley & Sons, Inc., Hoboken, 2012. c) Chow, W. S. *Advances in Photosynthesis and Respiration* **2012,** *34*, 607.

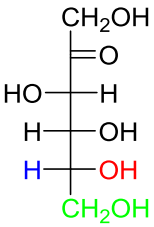


Scheme 8. Photosynthetic process.

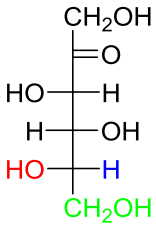
Since the early involvement of carbohydrates in the diverse chemical processes associated with life, Nature has provided us with a huge number of enantiopure[32] and structurally diverse carbohydrates. A full description of all carbohydrates falls beyond the scope of this introduction. Figure 3 and Figure 4 illustrate the structural diversity of basic carbohydrates (aldoses and ketoses). Chemical structures of more complex carbohydrates can be found in general references in the literature.[33]

The wide repertoire of carbohydrates with well-defined three-dimensional structures has been extensively used in many fields of chemistry. Their ready availability, high functionalisation, the multiple spatial disposition of their substituents, and solubility in water have made them particularly attractive for many applications in fields such as molecular recognition,[34] chemical biology,[35] material sciences[36] and stereoselective synthesis.[37]

[32] Almost all carbohydrates contain stereogenic carbons. Monomeric sugars (*i.e.* monosaccharides) of natural origin belong to the D-series: the stereogenic carbon furthest from the carbonyl group has the same absolute configuration as the one in D-(+)-glyceraldehyde ((*R*)-(+)-2,3-dihydroxypropanal). This implies that in a standard Fischer projection of a D-carbohydrate, the hydroxyl group of the furthest carbon from the C=O group is on the right of the molecule. On the other hand, L-carbohydrates present the same hydroxyl group on the left side (see below for an example of D- and L-fructose).



20, D-Fructose



21, L-Fructose

[33] a) Vollhardt, P. C., *Química Orgánica*, Freeman, W.H. and Company, Omega, S.A, Barcelona, 1994. b) Bols, M. *Carbohydrate building blocks*, J. Wiley and Sons, Inc., New York, 1996. c) Ernst, B.; Hart, G. W.; Sinaý, P. *Carbohydrates in Chemistry and Biology*, Wiley-VCH, Weinheim, 2000. d) Boons, G-J.; Hale, K. J. *Organic Synthesis with Carbohydrates*, Blackwell Publishing, England, 2000.

[34] For representative examples on the use of carbohydrates in molecular recognition, see: a) Revell, D. J.; Knight, J. R.; Blyth, D. J.; Haines, A. H.; Russell, D. A. *Langmuir* **1998**, *14*, 4517. b) Mazik, M.; Radunz, W.; Sicking, W. *Org. Lett.* **2002**, *4*, 4579. c) Mazik, M.; Radunz, W.; Sicking, W. *J. Org. Chem.* **2004**, *69*, 7448. d) Mazik, M. *Chem. Soc. Rev.* **2009**, *38*, 935. e) Asensio, J. L.; Arda, A.; Canada, F. J.; Jiménez-Barbero, *J. Acc. Chem. Res.* **2012**, *15*, 1.

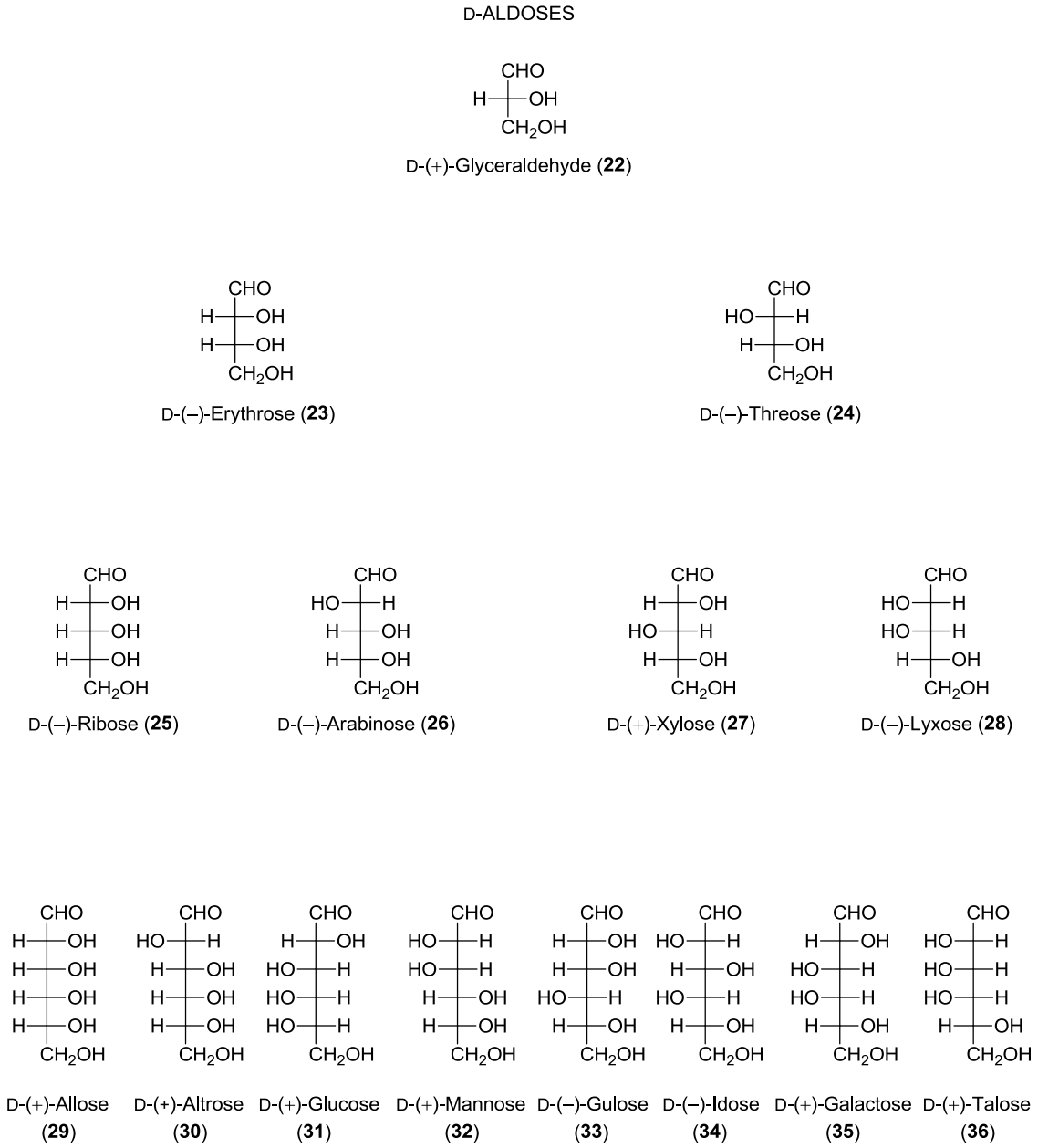


Figure 3. Fischer projection forms of D-aldoses.

[35] For representative examples on the use of carbohydrates in chemical biology, see: a) Nicolaou, K. C.; Mitchell, H. J., *Angew. Chem., Int. Ed.* **2001**, *40*, 1576. b) Gabius, H. J.; Siebert, H. C.; André, S.; Jiménez-Barbero, J.; Rüdiger, H. A. *ChemBioChem*. **2004**, *5*, 740. c) Lepenies, B.; Yin, J.; Seeberger, P. H. *Curr. Opin. Chem. Biol.* **2010**, *14*, 404.

[36] For representative examples on the use of carbohydrates in material sciences, see: a) De la Fuente, J. M.; Penadés, S. *Biophys. Acta* **2006**, *1760*, 636. b) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Comm.* **2007**, *28*, 15.

[37] Literature references for stereoselective synthesis employing carbohydrates has been included in this Thesis.

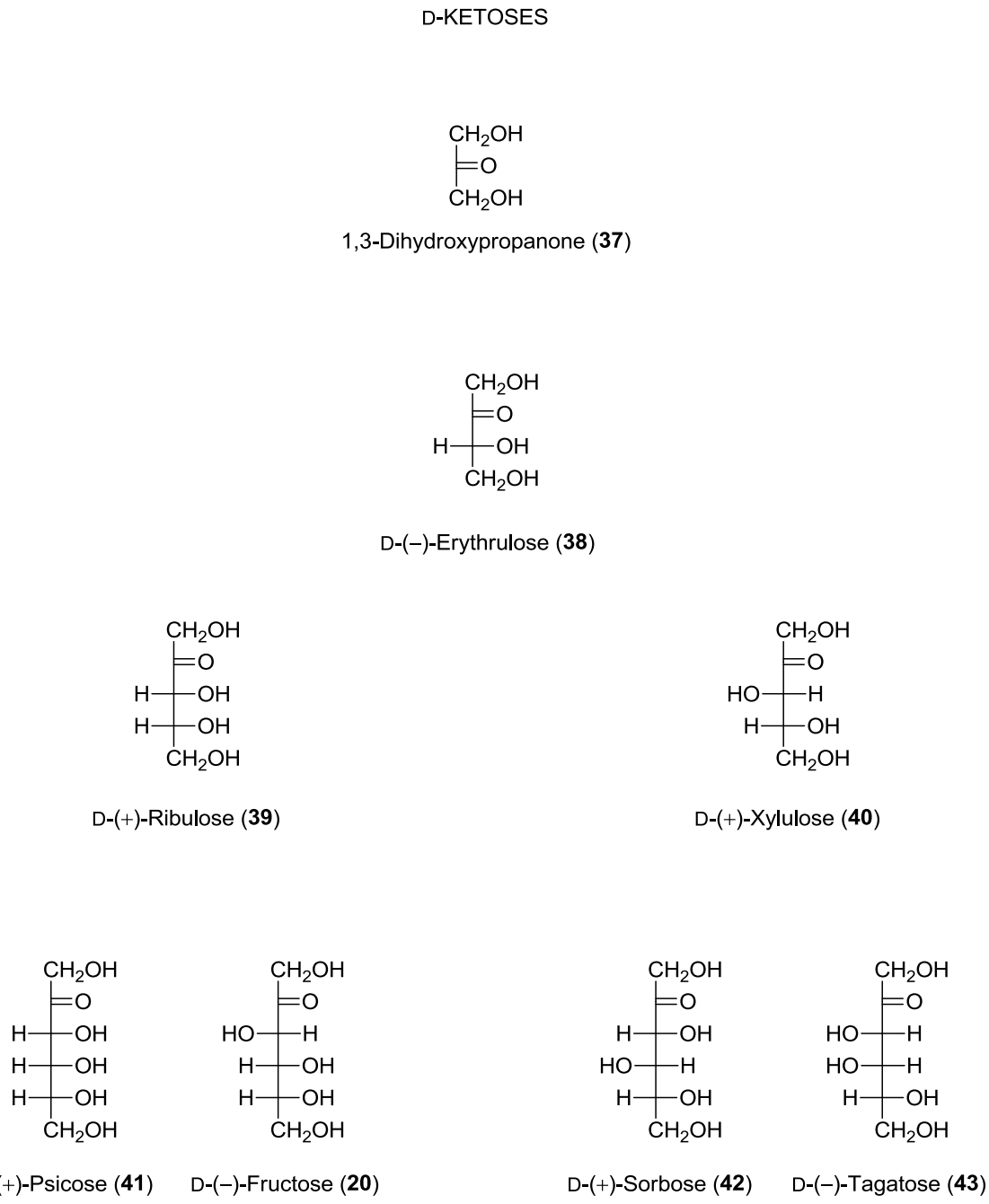
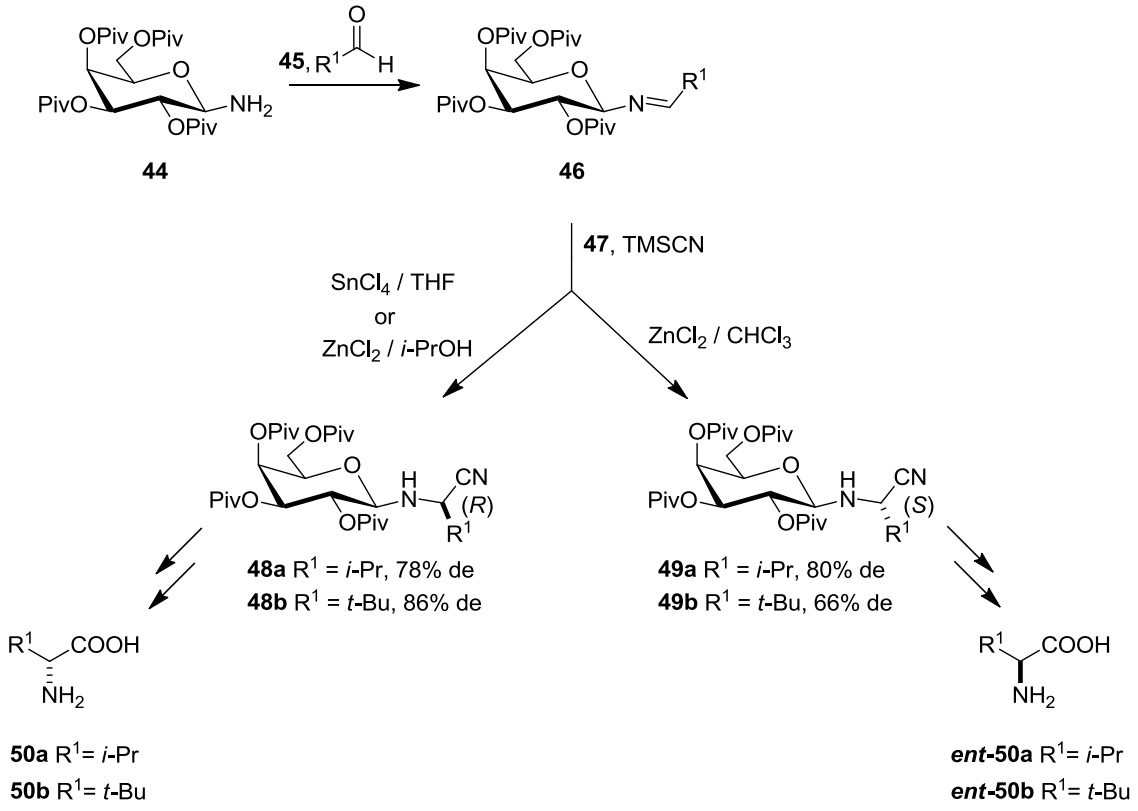


Figure 4. Fischer projection forms of D-ketoses.

As mentioned, carbohydrates have been extensively used in many fields of chemistry, the most relevant in terms of this Thesis are the applications studied in the field of stereoselective synthesis. These compounds have been widely used as chiral auxiliaries, chiral reagents or as scaffolds for chiral ligands (the different strategies in stereoselective synthesis are summarised in Scheme 1).

The use of pivalolyl protected D-galactosyl amines for the synthesis of unnatural amino acids developed by Kunz and co-workers deserves mention.[38]

Condensation of D-galactosyl derivative (**44)** with an aldehyde (**45**) yielded the corresponding aldimine (**46)**, which underwent highly diastereoselective Strecker reactions with trimethylsilyl cyanide (**47**) in the presence of Lewis acids.[39]

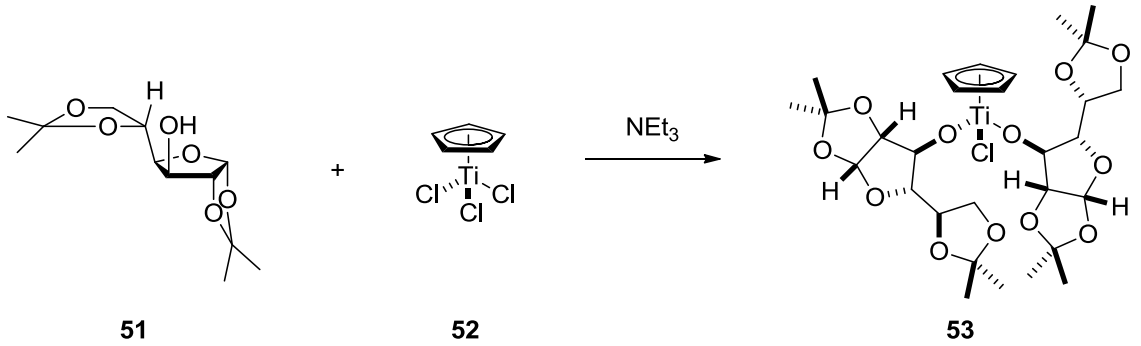


Scheme 9. Diastereoselective Strecker reaction using a D-galactosyl derivative as chiral auxiliary.

The solvent and Lewis acid had a crucial influence on the stereochemical outcome of the reaction. Whilst zinc chloride in chloroform yielded diastereomerically enriched adducts (**49a** and **49b**) that could be further transformed into L-amino acids (***ent*-50a** and ***ent*-50b**), $SnCl_4$ in THF or $ZnCl_2$ in *i*-PrOH gave access to several examples of amino acids belonging to the unnatural D-series (**50a** and **50b**).

[38] a) Kunz, H.; Sager, W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 557. b) Kunz, H.; Sager, W.; Pfrengle, W. *Tetrahedron Lett.* **1988**, *29*, 4397.
[39] Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648.

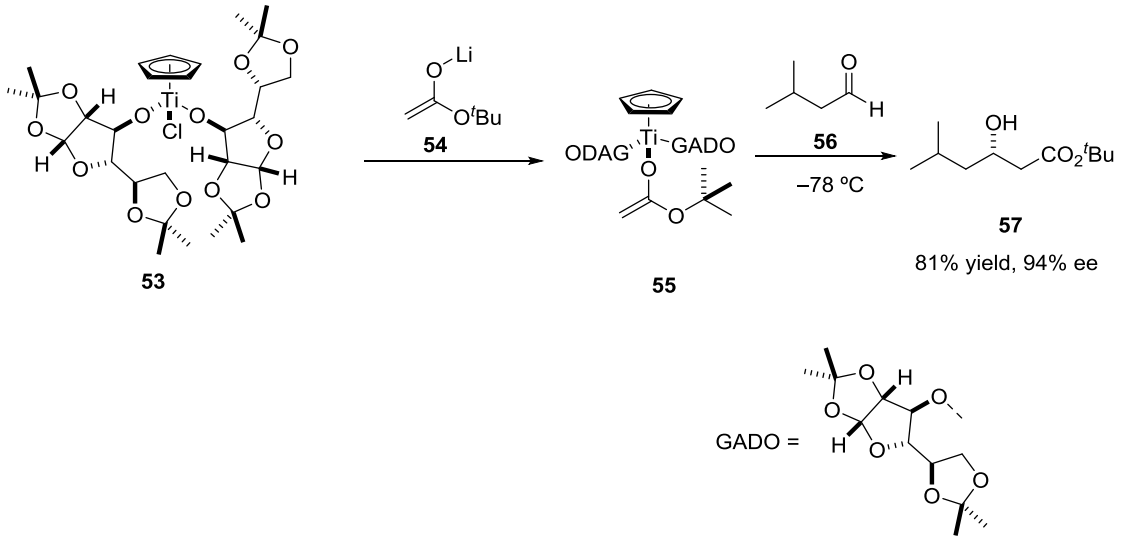
The application of carbohydrate-derived chiral titanium reagents developed by Duthaler *et al.* constitutes another important example of carbohydrate-based stereoselective synthesis. Duthaler's chiral reagents could be easily prepared from half-sandwich titanium precursors $CpTiCl_3$ (**52**) and 1,2:5,6-di-*O*-isopropylidene-D-glucose (DAG, **51**) in the presence of a base (Scheme 10).



Scheme 10. Chiral titanium complex **53** used for stereoselective synthesis.

This chiral reagent was efficiently used in diastereoselective aldol reactions. Transmetallation of the lithium enolate of *t*-butyl acetate with glucose-derived chiral titanium reagent **53** afforded titanium enolate **55**, which reacted with a number of aldehydes in high *Re*-face preference. Enantioselectivities ranged from 90% to 96% ee were obtained. Scheme 11 shows the stereoselective preparation of the aldol product **57**, which derives from isovaleraldehyde (**56)**, with 94% ee. Titanium enolate **55** depicted in Scheme 11 represents one of the most useful chiral enolates reported in the literature up to now.[40]

[40] Duthaler, R. O.; Andreas, H. *Chem. Rev.* **1992**, *92*, 807.



Scheme 11. Glucose-derived chiral titanium enolates used in diastereoselective aldol reactions.

The design and preparation of ligands for enantioselective catalysis have also benefited from employing carbohydrates as scaffolds. The first chiral ligands derived from carbohydrates were reported in the late 70's by Sinou and Descotes, who synthesised monophosphines **58** and **59** from D-xylose (**27**) and diphosphine **60** from D-glucose (**31**) (Figure 5).[41]

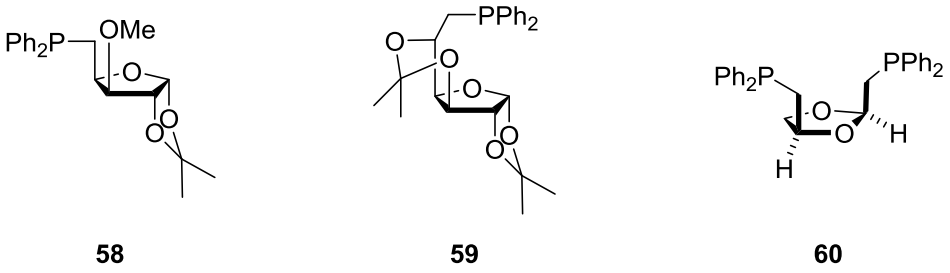
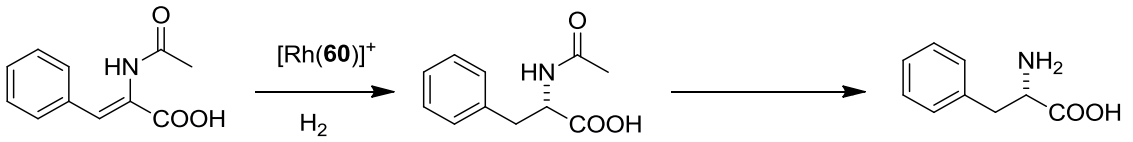


Figure 5. The first chiral ligands prepared from carbohydrates.

They were all tested in the Rh-mediated asymmetric hydrogenation of α-(acylamino)acrylic acid derivatives, yielding the corresponding amino acids in high enantioselectivities (85% ee, Scheme 12).

[41] Descotes, G.; Lafont, D.; Sinou, D. *J. Organomet. Chem.* **1978**, *150*, C14.



61 **62** 85% ee **63** (*S*)-Phenylalanine

Scheme 12. Rh-Mediated asymmetric hydrogenation using carbohydrate-derived diphosphine **60** as chiral ligand.

A full description of all of the ligands that have been synthesised from carbohydrates falls beyond the scope of this section.[42] Carbohydrate-based ligands developed independently by the groups of Claver and Castillón and Shi are briefly summarised below as representative and outstanding examples within this area.

Claver, Castillón and co-workers have developed a series of highly efficient modular C_1-diphosphite ligands with a furano backbone for the Rh-mediated asymmetric hydrogenation of functionalised olefins with excellent enantioselectivities (up to >99% ee) in the hydrogenation of dimethyl itaconate (**64**).[43] These particular ligands derived from D-(+)-xylose (**27**) and D-(+)-glucose (**31**) and their structures are shown in Scheme 13. Other carbohydrate-based ligands for Rh-mediated hydroformylation,[44] Pd- or Cu-mediated allylic alkylation,[45] Ir-mediated hydrogenation,[46] and Cu-mediated

[42] For representative examples on the preparation of chiral ligands for asymmetric catalysis from carbohydrates, see: a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 410. b) Yang, W. K.; Cho, B. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2947. c) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 693. d) Yang, W. K.; Cho, B. T. *Bull. Korean Chem. Soc.* **2005**, *26*, 1101. e) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207. f) Irmak, M.; Groschner, A.; Boysen, M. M. K. *Chem. Commun.* **2007**, 177. g) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. h) Lehnert, T.; Ozuduru, G.; Grugel, H.; Albrecht, F.; Telligmann, S. M.; Boysen, M. M. K. *Synthesis* **2011**, *17*, 2685. i) Grugel, H.; Albrecht, F.; Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2012**, *14*, 3780.

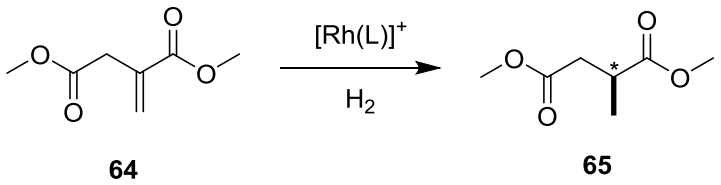
[43] a) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Eur. J. Inorg. Chem.* **2000**, *2*, 1287. b) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 1097 c) Diéguez, M.; Ruiz, A.; Claver, C. *J. Org. Chem.* **2002**, *67*, 3796. d) Castillón, S.; Claver, C.; Díaz, Y. *Chem. Soc. Rev.* **2005**, *34*, 702.

[44] a) Axet, M. R.; Benet-Buchholz, J.; Claver, C.; Castillón, S. *Adv. Synth. Catal.* **2007**, *349*, 1983. b) Gual, A.; Godard, C.; Claver, C.; Castillón, S. *Eur. J. Org. Chem.* **2009**, *8*, 1191.

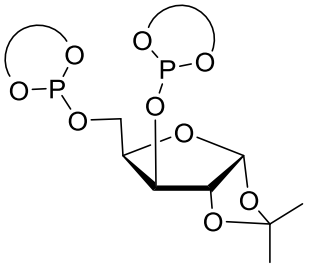
[45] a) Gual, A.; Castillón, S.; Pàmies, O.; Diéguez, M.; Claver, C. *Dalton Trans.* **2011**, *40*, 2852**.** b) Favier, I.; Castillo, A. B.; Godard, C.; Castillón, S.; Claver, C.; Gómez, M.; Teuma, E. *Chem. Commun.* **2011**, *47*, 7869. c) Magre, M.; Mazuela, J.; Diéguez, M.; Pàmies, O.; Alexakis, A. *Tetrahedron: Asymmetry* **2012**, *23*, 67.

[46] For instance, see: Margalef, J.; Lega, M.; Ruffo, F.; Pàmies, O; Diéguez, M. *Tetrahedron: Asymmetry* **2012**, *23*, 945.

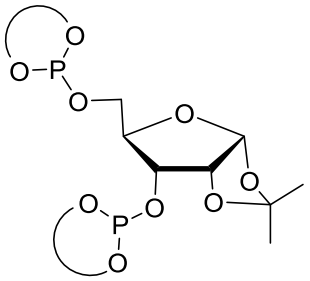
conjugate addition[47] amongst other applications have also been reported by the research groups located at the *URV* (Tarragona, Spain).



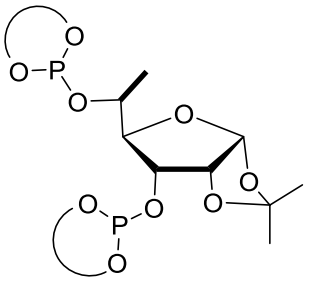
64 **65**



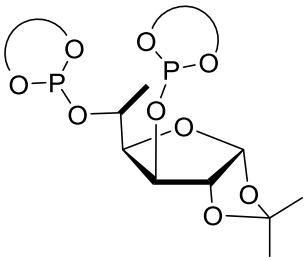
66a, 12% yield, 22% ee



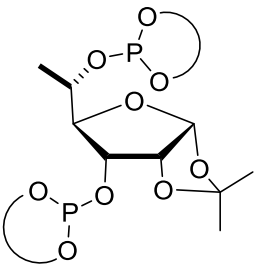
67a, 28% yield, 64% ee



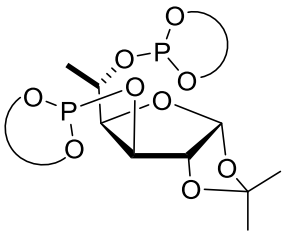
68a, 90% yield, 90% ee
68b, 100% yield, 99% ee



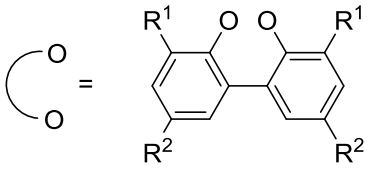
69a, 100% yield, 2% ee



70a, 87% yield, 67% ee



71a, 73% yield, 29% ee

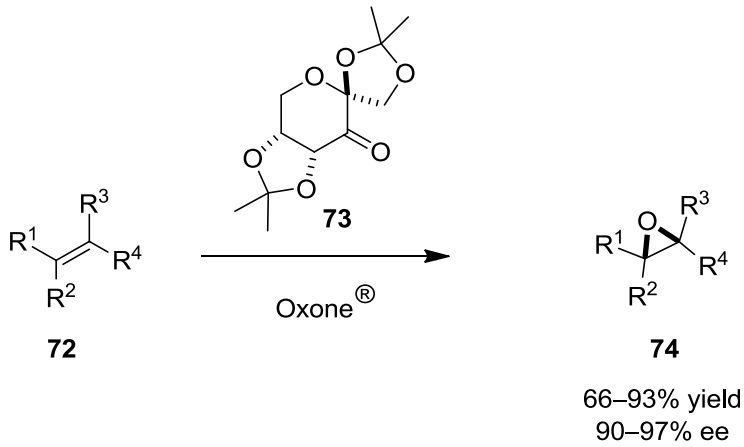


a, $R^1 = R^2 =$ *t*-Bu
b, $R^1 = Si(CH_3)_3$, $R^2 = H$

Scheme 13. Rh-Mediated asymmetric hydrogenation of dimethyl itaconate (**64**) using carbohydrate-derived diphosphites.

[47] For instance, see: Raluy, E.; Pàmies, O.; Diéguez, M.; Rosset, S.; Alexakis, A. *Tetrahedron: Asymmetry* **2009**, *20*, 2167.

Carbohydrate-based chiral ligands developed by Shi and co-workers found application in the field of asymmetric organocatalysis. D-Fructose-derived ketone **73** constitutes a prominent example of an organocatalyst in the epoxidation of unfunctionalised alkenes with Oxone®.[48] *(E)*-Di- and trisubstituted alkenes were epoxidised in good to excellent enantioselectivities using this catalyst and Oxone® as the oxidising agent.[49]



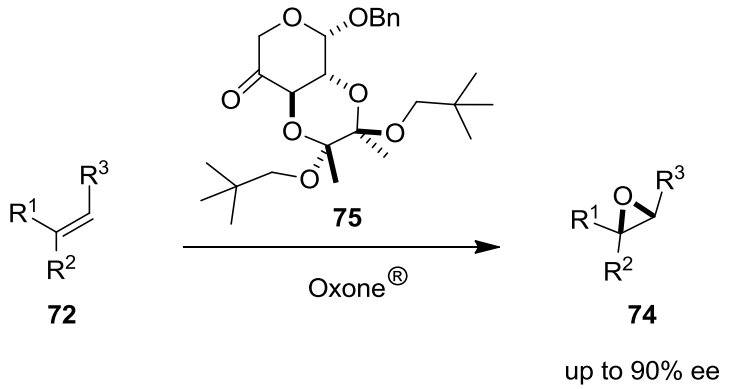
Scheme 14. D-fructose-based ketone-organocatalysed epoxidation of unfunctionalised alkenes with Oxone®.

Shi also considered other carbohydrate–derivatives for this epoxidation chemistry, as carbohydrates are readily available, have rigid conformations and are highly substituted with oxygen functional groups. A summary of the other carbohydrate derivatives used as epoxidation organocatalysts developed by Shi and co-workers will be presented in the next section.[50]

On the other hand, Shing and co-workers also developed carbohydrate-based chiral ligands for enantioselective epoxidation, such as enantiomerically pure ketone **75** derived from L-arabinose (diastereoisomer of **26**), which was reported to mediate the

[48] Oxone® = Potassium peroxomonosulfate together with other salts ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).
[49] a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. b) Shi, Y. *Acc. Chem. Res*. **2004,** *37*, 488. c) Roberts, S. M.; Whittal, J. *Catalysts for Fine Chemical Synthesis, Regio- and Stereo-Controlled*, Wiley-VCH, Hoboken, 2007. d) Wong, O. A.; Shi, Y. *Chem Rev*. **2008**, *108*, 3958. e) Bäckvall, J. E. *Modern Oxidation Methods*, Wiley-VCH, Wenheim, 2010. f) Wong, O. A, Shi, Y. *Curr. Chem*. **2010**, 201.
[50] Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224.

epoxidation of *(E)*-di- and trisubstituted olefins with ee's of up to 90% (Scheme 15).[49c, 51]



Scheme 15. L-Arabinose-based ketone-organocatalysed epoxidation of *(E)*-di- and trisubstituted alkenes.

In the same year, Zhao and co-workers reported the use of D-fructose-derived ketone **76** and aldehydes **77** and **78** (Figure 6) for enantioselective epoxidations of unfunctionalised alkenes. For example, *trans*-stilbene oxide was obtained in 94% ee, when hydroxyaldehyde **78** was used as the chiral organocatalyst.[52]

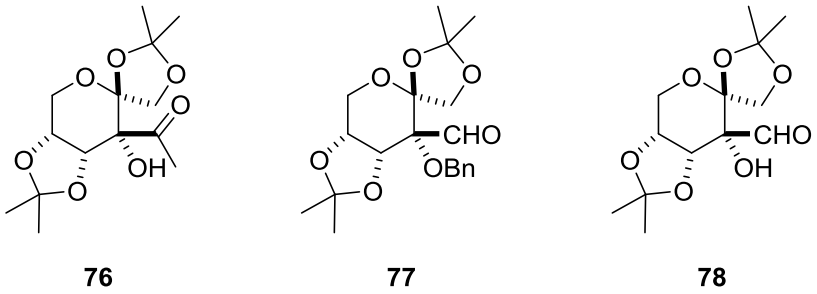
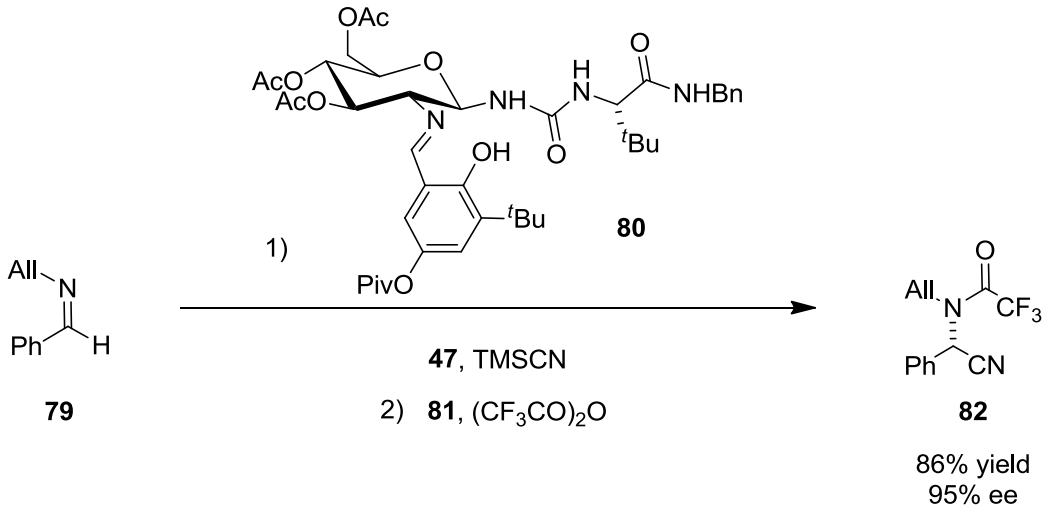


Figure 6. Organocatalysts designed by Zhao and co-workers.

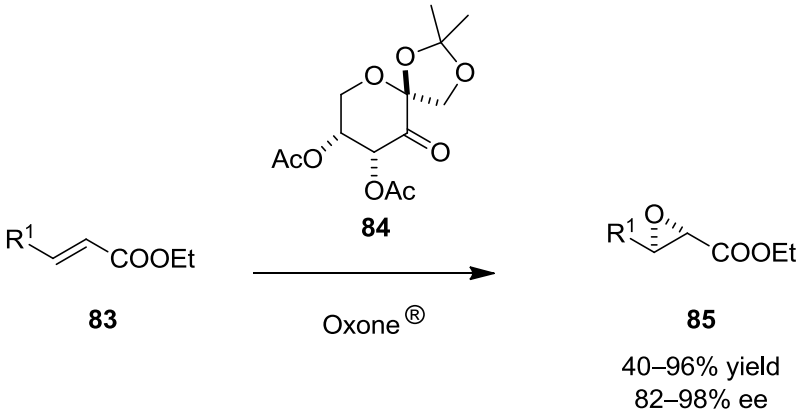
Carbohydrate-derived ligands have also been used in catalytic asymmetric Strecker reactions. Kunz and co-workers recently reported the use of a derivative of D-glucosamine **80** as an efficient mediator of the addition of trimethylsilyl cyanide (**47**) to aldimines derived from aromatic aldehydes (ee's up to 95%, Scheme 16).[53]

[51] a) Shing, T. K. M.; Leung, Y. C.; Yeung, K. W. *Tetrahedron* **2003**, *59*, 2159. b) Shing, T. K. M.; Leung, Y. C.; Luck, T. *J. Org. Chem.* **2005**, *70*, 7279.
[52] Bez, G.; Zhao, C. G. *Tetrahedron Lett.* **2003**, *44*, 7403.
[53] Becker, C.; Hoben, C. Kunz, H. *Adv. Synth. Catal.* **2007**, *349*, 417.



Scheme 16. Organocatalysed asymmetric Strecker reactions.

Shi's diester fructose derivative **84**, which also derives from D-fructose, has been described as an outstanding catalyst for the enantioselective epoxidation of α,β-unsaturated esters.[54]



Scheme 17. Shi's diester fructose derivative-organocatalysed epoxidation of α,β-unsaturated esters.

This catalyst has not only led to excellent enantioselectivities in the epoxidation of α,β-unsaturated carbonyl compounds (up to 98% ee), but also proved to be more robust towards the usual reaction conditions in this chemistry (aqueous-organic basic solutions at pH values ranging from 9 to 10 and in the presence of strong oxidants such a Oxone®).

[54] a) Wu, X. Y.; She, X.; Xu, J.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. b) Wang, B.; Wu, X. Y.; Wong, O. A.; Nettles, B.; Zhao, M. X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986. c) Peng, X.; Li, P.; Shi, Y. *J. Org. Chem.* **2012**, *77*, 701.

No reports on the catalytic activity of this highly interesting fructose-derived ketone **84** towards unfunctionalised electron rich alkenes had been published prior to the commencement of the research work presented in this Thesis. Furthermore, its described preparation method implied the use of inconvenient, non-efficient and toxic reagents.

Therefore, the objectives of this thesis are the following:

- Development of a practical synthesis of diester fructose derivative **84** (4,5-*O*-di-acetyl-1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose) and of related analogues, which might present improved activity in epoxidation reactions (Chapter I).

- Study of the catalytic properties of these fructose-derived organocatalysts in the epoxidation of electron rich unfunctionalised alkenes (Chapter II).

- Studies towards the rationalisation of the stereochemical outcome of these reactions (Chapter III).

CHAPTER I

Preparation of Catalysts Based on D-Fructose for the Asymmetric Organocatalytic Epoxidation of Unfunctionalised Alkenes

1. Background

The synthesis and production of enantiopure compounds using catalytic methods is a core topic in current organic synthesis research. The broad utility of synthetic enantiopure chiral molecules as life-science products,[55] components for electronic and optical devices,[56] probes of biological function[57] and building blocks of new polymers in material chemistry[58] has made asymmetric catalysis a prominent area of investigation.

Organocatalysts have several important advantages over organometallic catalysts (metal complexes) and biocatalysts (enzymes), since they are usually robust, inexpensive, and readily available. Because of their inertness towards moisture and oxygen, demanding reaction conditions (such as inert atmospheres, low temperatures, anhydrous solvents, etc.) are in many instances not required.

The use of small molecules as chiral catalysts (organocatalysis) has blossomed notably over the past decade and has expanded from a structurally reduced set of catalysts

[55] For enantiopure chiral molecules as life-science products, see for example: a) Fox, M. A.; Whitesell, J. K. *Organic Chemistry*, Oxford, 2004. b) Bruice, P. Y. *Organic Chemistry*, Oxford, 2005. c) Cintas, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4016. d) Meierhenrich, U. J. *Amino acids and the asymmetry of life*, Springer, Berlin, 2008. e) Solomons, T. W. G.; Fryhle, G. B. *Organic Chemistry*, John Wiley & Sons, Inc., New York, 2011.

[56] For enantiopure chiral molecules as components for electronic and optical devices, see for example: a) Lindell, V. I.; Shivola, A.; Tretyakov, S. A.; Viitanen, A. J. *Electromagnetic waves in Chiral and Bi-Isotropic Media*, Artech House, 1994. b) Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Top. Curr. Chem.* **1998**, *197*, 125. c) Kopp, V. I.; Zhang, Z. Q.; Genack, A. Z. *Prog. Quant. Elect.* **2003**, *27*, 369. d) Papakostas, A.; Potts, A.; Bagnall, D. L.; Prosvirnin, S. L.; Coles, H. J.; Zheludev, N. I. *Phys. Rev. Lett.* **2003**, *90*, 107404.

[57] For enantiopure chiral molecules as probes of biological function, see for example: a) Yashima, E.; Maeda, K.; Nishimura, T. *Chem. Eur. J.* **2004**, *10*, 42. b) Yashima, E.; Maeda, K.; Nishimura, T. *Chem. Eur. J.* **2004**, *10*, 42. c) Gottarelli, G.; Lena, S.; Masiero, S.; Pieraccini, S.; Spada, G. P. *Chirality* **2008**, *20*, 471. d) Carroll, V. M.; Jeyakumar, M.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **2012**, *55*, 528. e) Gingras, M. *Chem. Soc. Rev.* **2013**, *42*, 1051.

[58] For enantiopure chiral molecules as building blocks of new polymers in material chemistry, see for example: a) Miyasaka, M.; Rajca, A. *Synlett* **2004**, *1*, 177. b) Miyasaka, M.; Rajca, A.; Pink, M.; Rajca, S. *J. Am. Chem. Soc.*, **2005**, *127*, 13806. c) Wang, Z.; Masson, G.; Peiris, F. C.; Ozin, G. A.; Manners, I. *Chem. Eur. J.* **2007**, *13*, 9372. d) Hu, T.; Hu, C. L.; Kong, F.; Mao, J. G.; Mak, T. C. W. *Inorg. Chem.* **2012**, *51*, 8810. e) Rivera-Fuentes, P.; Diederich, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818.

including L–proline (studied by Hajos, Wiechert and co-workers, amongst others),[59] pyrrolidines and L–proline analogues (studied by Jørgensen, List, Barbas III, Palomo and co-workers, amongst others),[60] chiral imidazolidinones (developed by MacMillan and co-workers),[61] and sugar derivatives (developed by Shi and co-workers)[62] to a rich array of structurally diverse organocatalysts. Some selected examples of other types of organocatalysts are indicated in the following: alkaloids (studied by Jew, Park and co-workers, amongst others),[63] chiral phosphoric acids (studied by List, Akiyama and co-workers, amongst others),[64] diols and thioureas (studied by Jacobsen and co-workers, amongst others),[65,66] quaternary ammonium salts (studied by Maruoka and co-workers, amongst others),[67] triazolium salts which act as N-heterocyclic carbenes (studied by

[59] See for example: a) Eder, U.; Sauer, G.; Wiechert, R., *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[60] See for example: a) List, B.; Lerner, R. A.; Barbas III, C. F. *Org. Lett.* **1999**, *1*, 59. b) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. c) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. d) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. e) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. f) List, B.; Hoang, L.; Martin, H. *J. Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 5839. g) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. h) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. i) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. j) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. k) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

[61] See for example: a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4379. d) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. e) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. f) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327.

[62] See for example: a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. b) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. c) Shi, Y. *Acc. Chem. Res.* **2004,** *37*, 488. d) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

[63] See for example: a) Jew, S. S.; Jeong, B. S.; Yoo, M. S.; Huh, H.; Park, H. G. *Chem. Commun.* **2001**, 1244. b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. c) Lygo, B.; Andrews, B. J. *Acc. Chem. Res.* **2004**, *37*, 518.

[64] See for example refs. 23c and 23f, and: a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. c) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 612. d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. e) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227.

[65] See for example: a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. d) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

[66] For example, see the following general book reviews and review articles on asymmetric organocatalysis cited as refs. 23a–d, and: a) Ed. Yudin, A. K., *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, 2006. b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. c) References cited in: *Organocatalysis*, ChemFiles (Sigma-Aldrich™), Aldrich Chemical Co., Inc. Eds, **2007**, vol. 7, issue 9.

[67] See for example: a) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549. b) Ooi, T Arimura, Y.; Hiraiwa, Y.; Yuan, L. M.; Kano, T.; Inoue, T.; Matsumoto, J.; Maruoka, K.

Rovis, Nolan, Enders, and co-workers, amongst others),[68] chiral *N*,*N*'-dioxides (studied by Feng *et al.*),[69] amongst others.[66] The structures of the mentioned examples of organocatalysts are depicted in Figure I. 1.

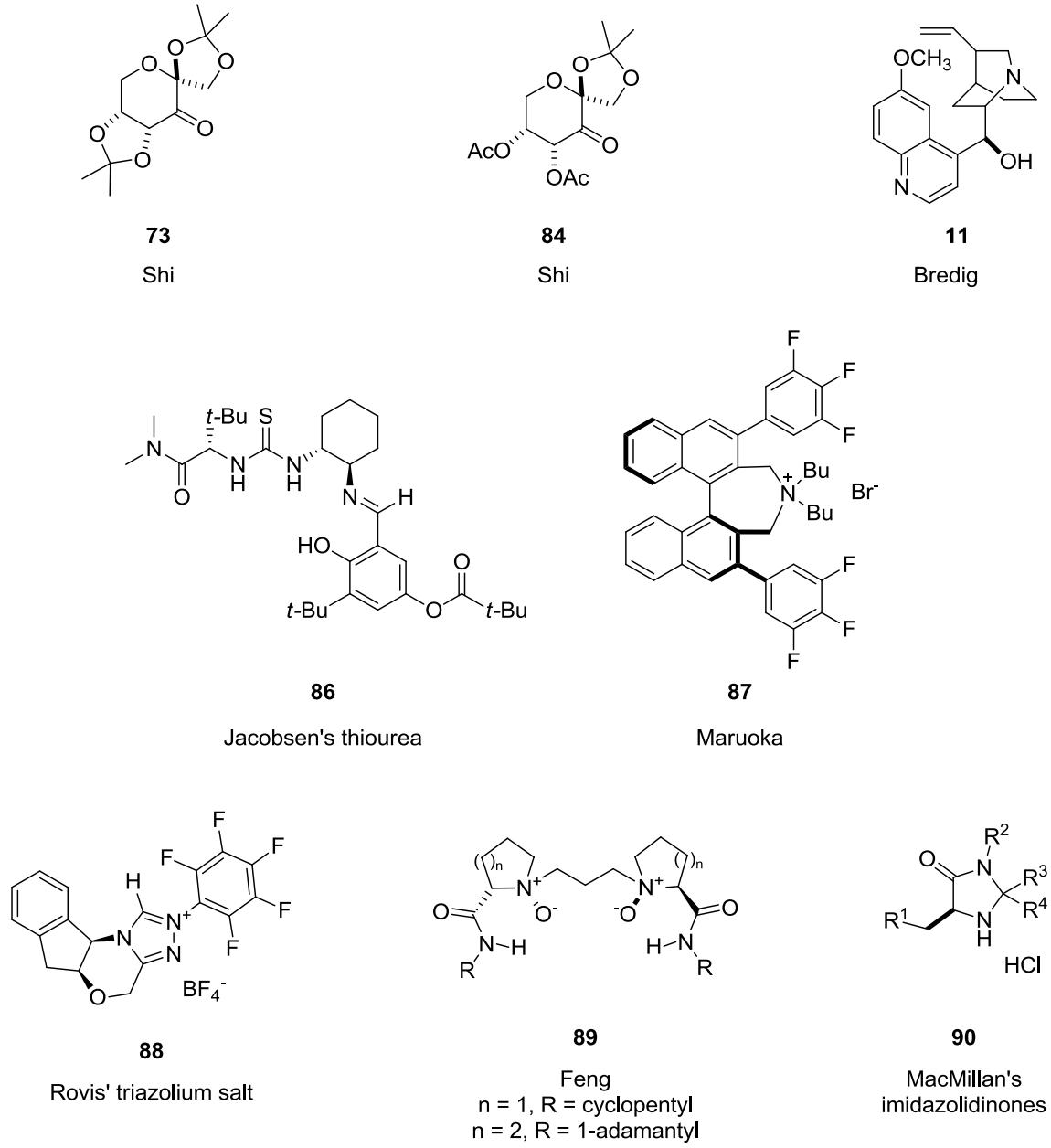


Figure I. 1. Some examples of structurally diverse organocatalysts.

Tetrahedron: Asymmetry **2006**, *17*, 603. c) Ooi, T.; Kato, D.; Inamura, K.; Ohmatsu, K.; Maruoka,K. *Org. Lett.* **2007**, *9*, 3945. d) Nakayama, K.; Maruoka, K. *Tetrahedron Lett.* **2008**, *49*, 5461. e) Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. *Org. Biomol. Chem.* **2012**, *10*, 5753. f) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312.

[68] For instance, see: a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

[69] Hua, X.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574.

These types of catalysts have also been immobilised onto different solid supports, facilitating their recovery and recycling.[70]

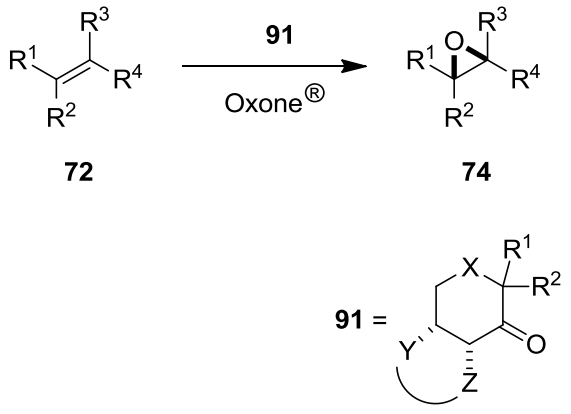
Our research group is interested in enantioselective organocatalytic epoxidation, which is an extremely useful methodology to generate chiral epoxides. We have for some time been using enantiomerically pure epoxides for the synthesis of efficient modular ligands for asymmetric catalysis.[71] In addition, many biologically active compounds and natural products contain epoxide functionalities.[72]

As has already been mentioned in the introductory chapter, one of the most prominent classes of asymmetric catalysts for the organocatalysed epoxidation of unfunctionalised alkenes are sugar-derived compounds with general structure **91**, which were developed in 1996 by Shi and co-workers (Scheme I. 1).[62a]

[70] For example, see: a) Kondo, K.; Takemoto, K. *Makromol. Chem.* **1985**, *186*, 1781. b) Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal.* **2001**, *343*, 171. c) Calderón, F.; Fernández, R.; Sánchez, F.; Fernández-Mayoralas A. *Adv. Synth. Catal.* **2005**, *347*, 1395. d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734. e) Chandrasekhar, S.; Reddy, R. N.; Sultana, S. S.; Narsihmulu, Ch.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338. f) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653. g) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007** *9*, 1943. h) Wang, L.; Liu, J.; Miao, T.; Zhou, W.; Li, P.; Ren, K.; Zhang, X. *Adv. Synth. Catal.* **2010**, *352*, 2571. i) Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 3668.

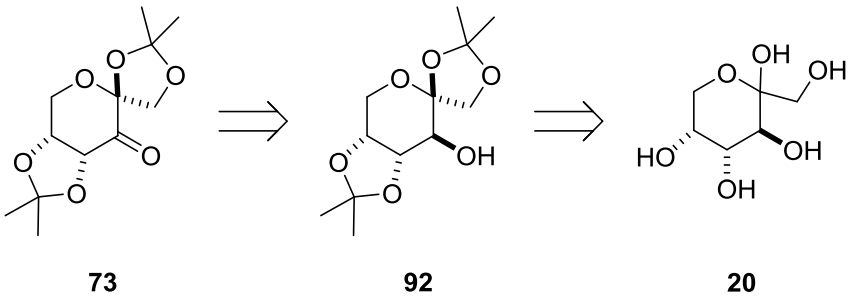
[71] See for example the following references: a) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gomez, M.; Jimenez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164. b) Popa, D.; Puigjaner, C.; Gómez, M.; Benet-Buchholz, J.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal*, **2007**, *14*, 2265. c) Fernández-Pérez, H.; Pericàs, M. A.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2008**, *350*, 1984. d) Fernández-Pérez, H.; Etayo, P.; Núñez-Rico, J. L.; Vidal-Ferran, A. *Chim. Oggi* **2010**, *28*, XXVI. e) Núñez-Rico, J. L.; Fernández-Pérez, H.; Benet-Buchholz, J.; Vidal-Ferran, A. *Organometallics* **2010**, *29*, 6627. f) Fernández-Pérez, H.; Donald, S. M. A.; Munslow, I. J.; Benet-Buchholz J.; Maseras, F.; Vidal-Ferran, A. *Chem. Eur. J.* **2010**, *16*, 6495. g) Panossian, A.; Fernández-Pérez, H.; Popa, D.; Vidal-Ferran, A. *Tetrahedron: Asymmetry* **2010**, *21*, 2281. h) Etayo, P.; Núñez-Rico, J. L.; Fernández-Pérez, H.; Vidal-Ferran, A. *Chem. Eur. J.* **2011**, *17*, 13978. i) Etayo, P.; Núñez-Rico, J. L.; Vidal-Ferran, A. *Organometallics* **2011**, *30*, 6718. j) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119. k) Núñez-Rico, J. L.; Etayo, P.; Fernández-Pérez, H.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2012**, *354*, 3025. l) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728. m) Núnez-Rico, J. L.; Vidal-Ferran, A. *Org. Lett.* **2013**, *15*, 2066. n) Fernández-Pérez, H.; Benet-Buchholz, J.; Vidal-Ferran, A. *Org. Lett.* **2013**, *15*, 3634.

[72] See for instance: a) Nicolau, K. C.; Sorensen, E. J. *Classic in Total Synthesis*, Wiley, New York, 1996. b) Nicolau, K. C.; Synder, S. A. *Classics in Total Synthesis II*, Wiley, New York, 2003. c) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857.



Scheme I. 1. General catalyst structure for the asymmetric organocatalytic epoxidation of olefins.

Fructose-derivative **73**, which is commercially available, is the most well-known chiral organocatalyst from this series. This compound, also known as Shi's ketone, can be readily obtained *via* a two-step synthesis from D-fructose (double ketalisation followed by oxidation of the free hydroxyl group in the intermediate compound **92**; see Scheme I. 2).[62a,73]

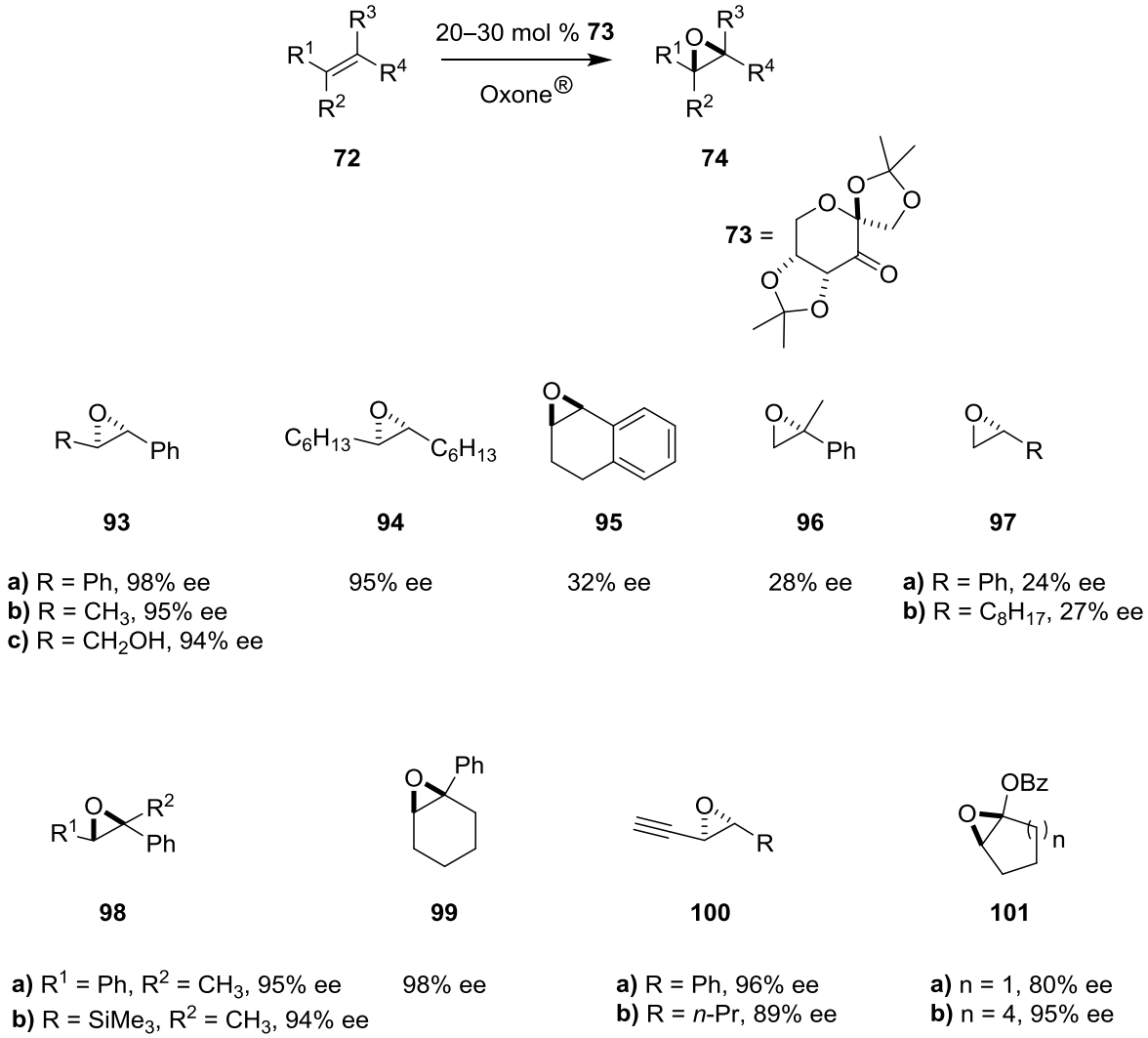


Scheme I. 2. Retrosynthetic sequence for the synthesis of organocatalyst **73**.

The scope and the different factors that govern this transformation have been well studied, rendering this transformation very valuable with wide-ranging applications. High enantioselectivity has been obtained with its use in the epoxidation of a wide variety of *(E)*-di- and trisubstituted alkenes. However, moderate results have been obtained in the epoxidation of a wide variety of *(Z)*- and terminal olefins (Scheme I.

[73] a) Tu, Y.; Frohn, M.; Wang, Z. X.; Shi, Y.; Diffendal. J. M.; Danheiser, R. L. *Org. Synth.* **2003**, *80*, 1. b) Ager, D. J.; Anderson, K.; Oblinger, E.; Shi, Y.; VanderRoest, J. *Org. Process Res. Dev*. **2007**, *11*, 44.

3).[74] One of the major disadvantages of fructose-derived organocatalyst **73** is the high catalyst loading (20–30 mol %), which is required to achieve high conversions.

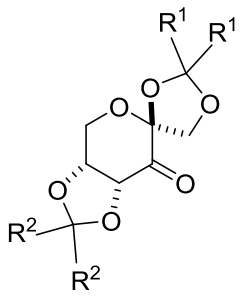


Scheme I. 3. The scope of Shi's epoxidation of unfunctionalised alkenes using ketone **73**.

[74] For instance, see: a) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.*, **1997**, *62*, 2328. b) Cao, G. A.; Wang, Z. X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. c) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. d) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. e) Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. f) Wang, Z. X.; Cao, G. A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646. g) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675. h) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721. i) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807. j) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818. k) Shu, L.; Shi, Y. *Tetrahedron*, **2001** *57*, 5213. l) Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J. R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2008**, *70*, 2904. m) Bin Wang, O.; Wong, A.; Zhao, M. X.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 9539. For general reviews on the topic, see: n) Frohn, M.; Shi, Y. *Synthesis*, **2000**, 1979. o) See refs. 62c and 62d.

The discovery of Shi's catalyst **73** cannot be considered as merely serendipitous. The structural requirements of the optimal catalyst **73** arose from an optimisation process, in which Shi and co-workers prepared many analogues of **73**, derived from D-Fructose (Figure I. 2) and other monosaccharides (Figure I. 3).[75]

[75] a) Tu, Y.; Wang, Z. X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475. b) Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715. c) Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521.



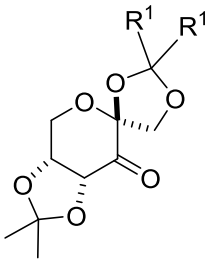
102

a) $R^1 = R^2 = CH_2CH_3$

b) $R^1 = R^2 = -(CH_2)_4-$

c) $R^1 = R^2 = -(CH_2)_5-$

d) $R^1 = R^2 = -(CH_2)_6-$

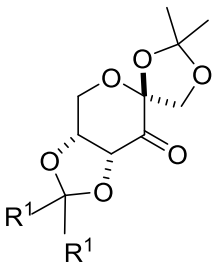


103

a) $R^1 = CH_2CH_3$

b) $R^1 = -(CH_2)_4-$

c) $R^1 = -(CH_2)_5-$



104

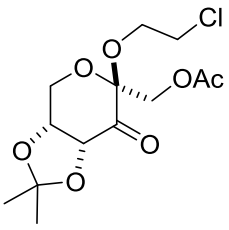
a) $R^1 = CH_2CH_3$

b) $R^1 = -(CH_2)_4-$

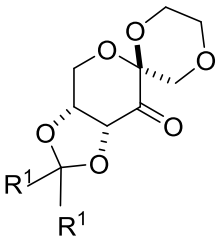
c) $R^1 = -(CH_2)_5-$

d) $R^1 = -(CH_2)_6-$

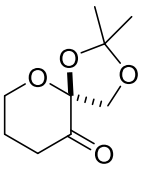
e) $R^1 = Bn$



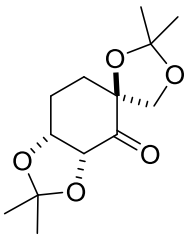
105



106



107



108

a) $R^1 = CH_3$

b) $R^1 = CH_2CH_3$

c) $R^1 = -(CH_2)_4-$

d) $R^1 = -(CH_2)_5-$

e) $R^1 = Bn$

f) $R^1 = Ph$

Figure I. 2. Structural diversity of other organocatalysts derived from D-Fructose (**20**) for the asymmetric epoxidation of olefins.

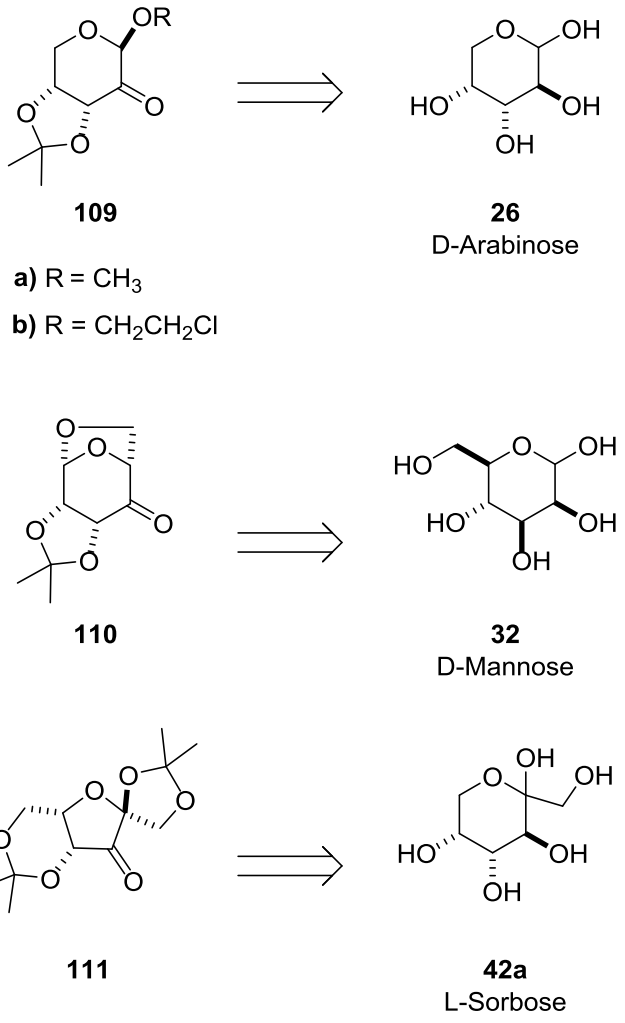
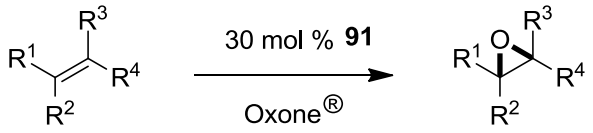


Figure I. 3. Structural diversity of other organocatalysts derived from D-arabinose (**26**), D-mannose (**32**) and L-sorbose (diastereoisomer of **42**), respectively, for the asymmetric epoxidation of olefins.

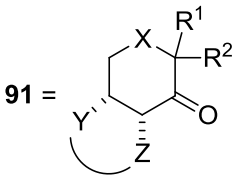
Shi *et al.* found that these ketones, analogues of fructose-derived ketone **73**, gave lower enantioselectivity and reactivity than **73** for the asymmetric epoxidation of *(E)*-olefins. Table I. 1 shows the results obtained by Shi *et al.* in the asymmetric organocatalytic epoxidation of (*E*)-1,2-diphenylethene (**112a**) and styrene (**113a**), using 30 mol % of the catalysts indicated in Figure I. 2 and Figure I. 3.

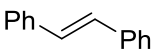
Optimal catalyst **73** contains the following key structural features for highly enantioselective epoxidation of unfunctionalised alkenes:

- A stereogenic element placed in close proximity to the reactive carbonyl.
- The presence of a fused ring and a quaternary centre α to the carbonyl group which minimizes potential epimerisation of the sterogenic centres.
- The olefin approach to the reacting dioxiranes is controlled by sterically blocking one of the catalyst's and one of the olefin's faces.
- Electron-withdrawing substituents are introduced to activate the carbonyl.



72 **74**

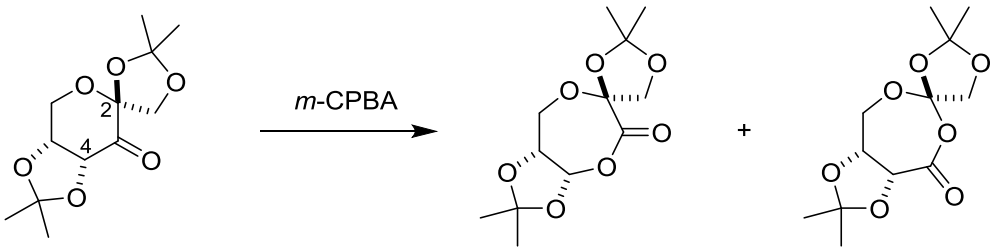


		 **112a**		 **113a**	
Entry	Ketone	Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[c]
1	**73**	75	98	64	13
2	**102 (a–d)**	16–57	96–98	43–100	12–30
3	**103 (a–c)**	36–59	92–94	77–93	12–27
4	**104 (a–e)**	7–59	92–94	6–100	17–30
5	**105**	6	96	5	23
6	**106 (a–f)**	3–35	11–90	6–42	20–43
7	**107**	25	77	–	–
8	**108**	10	88	88	15
9	**109 (a, b)**	10	74–90	15–40	10–29
10	**110**	27	74	40	10
15	**111**	14	75	41	15

[a] All results were carried out at 0 ºC, ketone (30 mol %), Oxone® (1.38 equiv.), and K_2CO_3 (5.8 equiv.) at pH ~ 10.5. [b] The epoxide has the (*R*,*R*) configuration. [c] The epoxide has the (*R*) configuration unless otherwise noted.

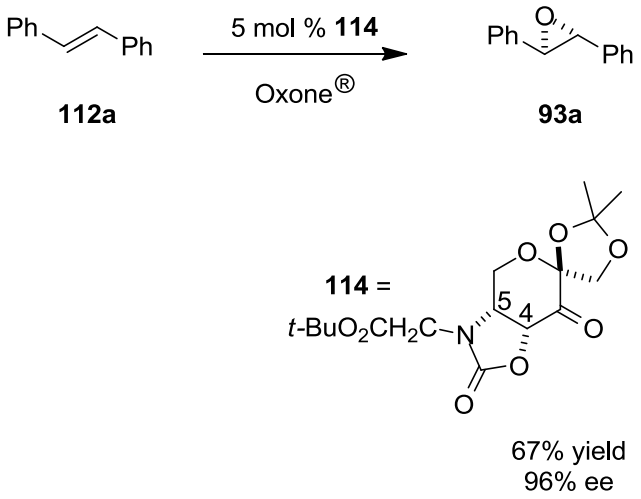
Table I. 1. Asymmetric epoxidation of (*E*)-1,2-diphenylethene and styrene by ketone **73** and its analogues.

Even if ketone **73** appears to be the best catalyst for asymmetric organocatalytic epoxidation, one drawback of this ketone is its low stability under the oxidative reaction conditions, thus requiring high catalyst loadings (typically 20–30 mol %). It has been postulated that a Baeyer-Villiger reaction is the likely decomposition pathway, although the corresponding lactones (**73a** or **73b**) have not been isolated or detected from the reaction mixture by Shi, presumably as a result of the facile hydrolysis of these lactones under the aqueous reaction conditions. By reaction of ketone **73** with *m*-CPBA under anhydrous conditions, Shi *et al.* observed that the lactone **73a** was detected as the major product, indicating that, during the Baeyer-Villiger reaction, C_4 in ketone **73** is more prone to migrate than C_2 (Scheme I. 4).[75b]



Scheme I. 4. Baeyer-Villiger reaction involving Shi's ketone **73**

Since the migratory tendency of the carbonyl substituents during a Baeyer-Villiger oxidation can in principle be influenced by electronic factors, ketone **114** incorporating a more electron-withdrawing substituent at the α-carbonyl position (*i.e.* oxazolidinone ring) than in **73** (*i.e.* a ketal group) was designed by Shi *et al.* to determine the electronic effects of new ring substituents on the catalyst stability. According to Shi *et al.*, an increase in the electron deficiency of the α-carbon, by decreasing the electron density of the oxygen attached to it, should provide more stable ketone catalysts and inhibit the Baeyer-Villiger decomposition pathway (Scheme I. 5).[62c,d,75b]

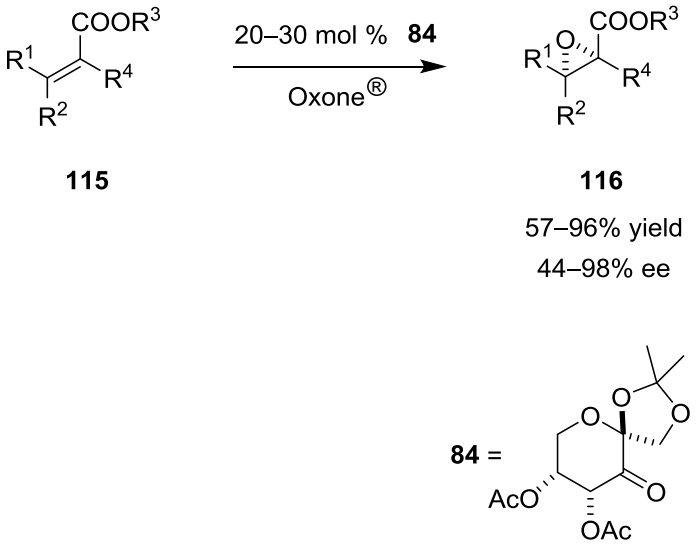


Scheme I. 5. Asymmetric epoxidation of unfunctionalised olefins catalysed by ketone **114**.

By adjusting the electron nature of the α-carbonyl carbon, the catalyst loading could be lowered from 20–30 mol % for ketone **73** to 1–5 mol % for ketone **114**. The enantioselectivity obtained by Shi *et al.* using ketone **114** was very similar to that of ketone **73**. Whilst the similarity in the observed enantioselectivities for both catalysts indicate that the steric environment around the carbonyl group was not greatly changed by replacing a ketal by an oxazolidinone ring at C_4 and C_5, the required lower catalyst amount for **114** (1–5 mol % instead of 20–30 mol %) clearly indicates the influence of the electronic nature of the substituent at C_4 on the catalyst stability.

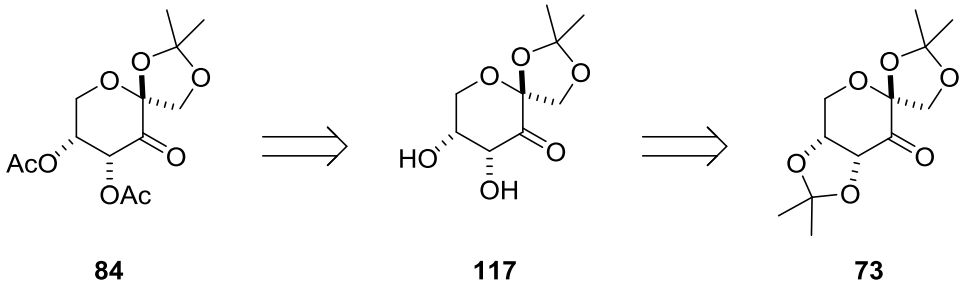
Along these lines, Shi and co-workers also found that fructose-derived ketone **73** was not effective in the epoxidation of α,β-unsaturated esters due to its decomposition under the basic reaction conditions for this type of epoxidation. Ketone **84**, in which the fused ketal of derivative **73** was replaced by two acetate groups that have a more electron-withdrawing character, was found to be very efficient and highly enantioselective for the epoxidation of α,β-unsaturated esters (Scheme I. 6).[76] Much to our surprise, no reports on the catalytic activity of **84** in the epoxidation of unfunctionalised electron-rich alkenes were known at the time the research contained in this Thesis commenced.

[76] a) Wu, X. Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. b) Wang, B.; Wu, X. Y.; Wong, O. A.; Nettles, B.; Zhao, M. X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986. c) Peng, X.; Li, P.; Shi, Y. *J. Org. Chem.* **2012**, *77*, 701.



Scheme I. 6. Asymmetric epoxidation of α,β-unsaturated esters catalysed by ketone **84**.

This more elaborate organocatalyst **84** could be obtained in two synthetic steps (selective deketalisation and diacetylation) from its predecessor **73**, which in turn was obtained in two synthetic steps from D-Fructose (**20**) by double ketalisation and oxidation of this monosaccharide (see Scheme I. 2 and Scheme I. 7).[76, 77]

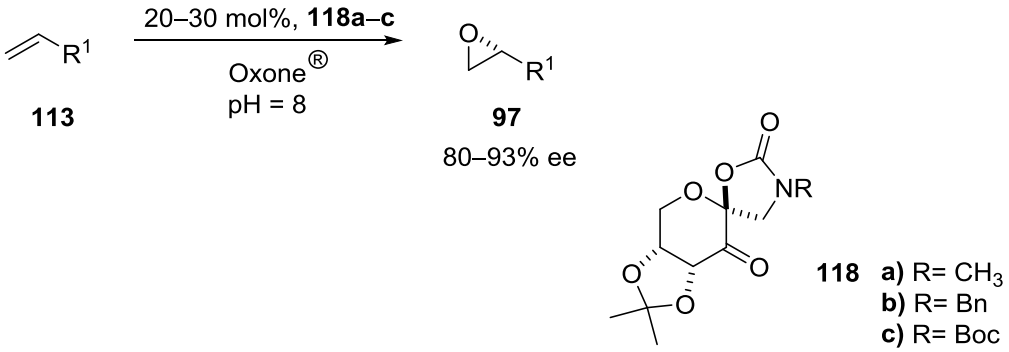


Scheme I. 7. Retrosynthesis sequence for the synthesis of the organocatalyst **84**.

As catalyst **73** only mediated the epoxidation of *(E)*-di- and trisubstituted olefins with high ee's (Scheme I. 3), Shi and co-workers further pursued the design and development of new organocatalysts for the epoxidation of terminal and *(Z)*-disubstituted olefins. Ketones **118a–c** were synthesised and investigated by Shi and co-workers in the enantioselective epoxidation of the aforementioned types of alkenes. The spiroketal moiety placed α to the carbonyl group in the original catalyst **73** was replaced by an

[77] a) Shi, Y. U.S. Patent 003147, 2003. b) Shi, Y. International Patent WO 066614, 2003.

oxazolidinone ring in this new generation of catalysts (Scheme I. 8). Catalyst **118c**, incorporating an *N*-Boc substituent at the oxazolidinone ring, provided the highest ee's in the epoxidation of these kinds of alkenes.[74m,78]

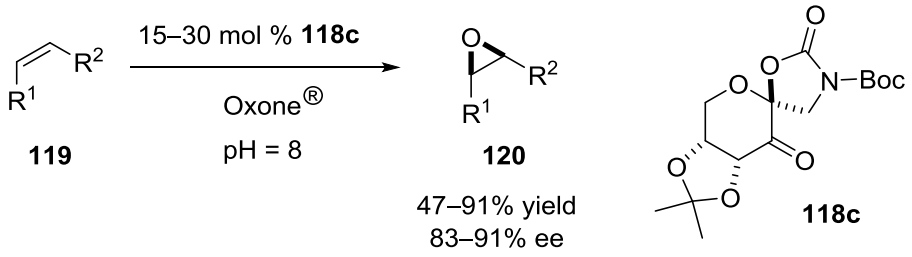


Scheme I. 8. Asymmetric epoxidation of terminal olefins catalysed by ketones **118a–c**.

Glucose-derived ketone **118c** was also reported as a very efficient asymmetric catalyst for the epoxidation of *(Z)*-disubstituted olefins, as indicated in Scheme I. 9.[79]

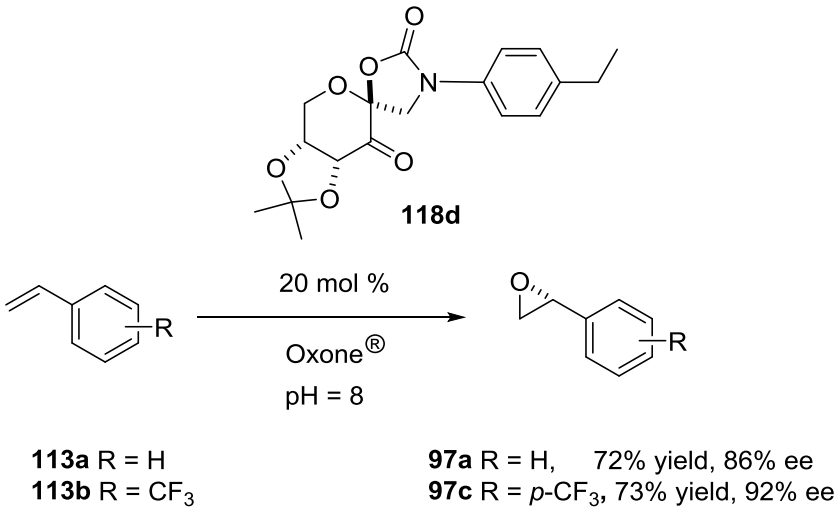
[78] See for example: a) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. b) Shu, L.; Shen, Y. M.; Burke, C.; Goeddel, D.; Shi, Y. *J. Org. Chem.* **2003**, *68*, 4963. c) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115. d) Hicky, M.; Goeddel, D.; Shi, Y. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5794. e) Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409. f) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715. g) Wang, B.; Shen, Y. M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519. h) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093. i) Boysen, M. M. K. *Carbohydrates-Tools for stereoselective synthesis*, Wiley-VCH, Hannover, 2013.

[79] For leading references on this transformation, see: a) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem.* **2000**, *122*, 11551. b) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435.



Scheme I. 9. Asymmetric organocatalytic epoxidation of *(Z)*-disubstituted olefins with ketone **118c**.

High enantioselectivity (80–92% ee) was also obtained for the epoxidation of various substituted styrenes using fructose derivative **118d**, which contains an aryl substituent at the nitrogen of the oxazolidinone ring (Scheme I. 10).[78f]



Scheme I. 10. Asymmetric organocatalytic epoxidation of styrene derivatives with ketone **118d**.

The epoxidation results indicated that there is a strong π–π interaction between the aryl substituent of the alkene and the aryl group of the oxazolidinone in the transition state, possibly facilitating the correct orientation of the substrate and mediating the epoxidation with high enantioselectivity (Figure I. 4).[80]

[80] a) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. b) Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973, and references cited therein.

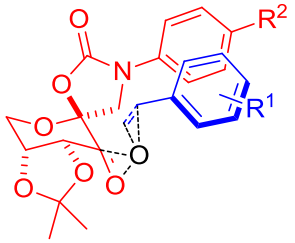
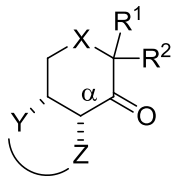


Figure I. 4. Favoured transition state for the asymmetric epoxidation of styrene derivatives mediated by ketone **118d**.

To conclude, Shi and co-workers have synthesised a variety of chiral organocatalysts whose general structure is depicted in Figure I. 5.



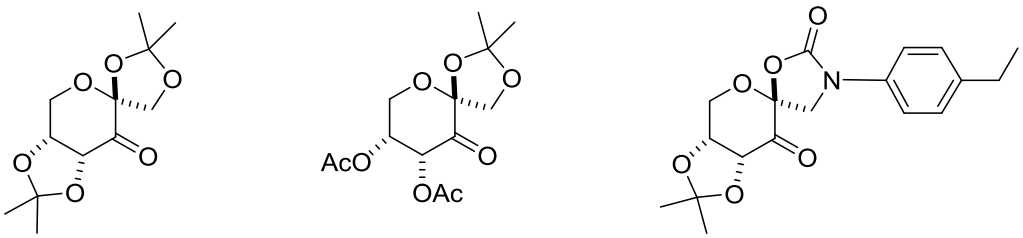
91

General structure of Shi's catalysts

Figure I. 5. Shi's ketone catalyst **91** derived from D-Fructose for the asymmetric epoxidation of olefins.

Shi's fructose-derivative **73** is the most well-known chiral organocatalyst for the asymmetric epoxidation of *(E)*-di- and tri-substituted olefins but requires relatively high catalyst loadings (typically 20–30 mol %), and fructose-derivative **84** is the most effective for the enantioselective epoxidation of α,β-unsaturated esters (see Figure I. 6 for the catalyst structures).

Finally, Shi and co-workers have designed new catalysts in which the original spirodioxo unit was replaced with an N-substituted oxazolidinone. Catalyst **118d** gave outstanding enantioselectivities in the asymmetric epoxidation of styrene and other terminal olefins (see Figure I. 6 for the catalyst structure).



73 **84** **118d**

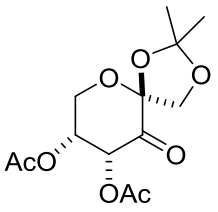
Figure I. 6. Highest-performing Shi's carbohydrate derivatives for the asymmetric organocatalytic epoxidation of unfunctionalised olefins.

2. Preparation of catalysts for the asymmetric organocatalytic epoxidation of unfunctionalised alkenes

Our research group is particularly interested in asymmetric catalysis and utilises optically pure epoxides as starting materials for the preparation of phosphorus-containing enantiopure ligands for asymmetric transformations of interest.[71c–m]

We considered it very interesting to use Shi's epoxidation catalysts for the preparation of optically pure epoxides that could be further used in the research program of our group as starting materials for the preparation of other ligands for asymmetric catalysis.

For this reason, we decided to dedicate research efforts to the development of a practical and efficient synthesis of 4,5-di-*O*-acetyl-1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose, **84** (Figure I. 7).



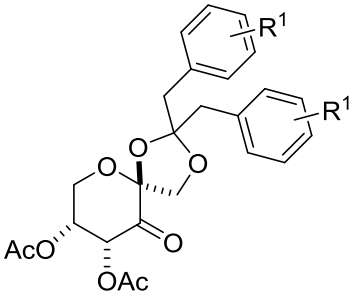
84

Figure I. 7. 4,5-Di-*O*-acetyl-1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose, **84**.

We turned our attention to Shi's diester fructose derivate **84** as the epoxidation catalyst instead of **73** (Figure I. 6) as **84** is even more attractive than **73** as far as the scope of alkene substrates which it can convert (it can be further used for α,β- unsaturated esters) and its catalytic robustness (it is not so easily degraded in the reaction media by the undesired Baeyer-Villiger degradation pathway) are concerned.

We also considered that catalyst **121a** (Figure I. 8**)**, which should retain the stability properties of catalyst **84** (acetyl substituents disfavour Baeyer-Villiger catalyst degradation pathways) and substrate orientation potential of catalyst **118d**, could be an

interesting target. Synthetic attempts towards its preparation will also be described in this section.

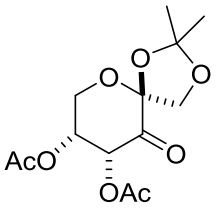


121a

Figure I. 8. General structure of a new organocatalyst (**121a**) for the epoxidation of styrene-type substrates and other terminal olefins.

2. 1 Development of a practical synthesis of 4,5-di-*O*-acetyl-1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose (84)

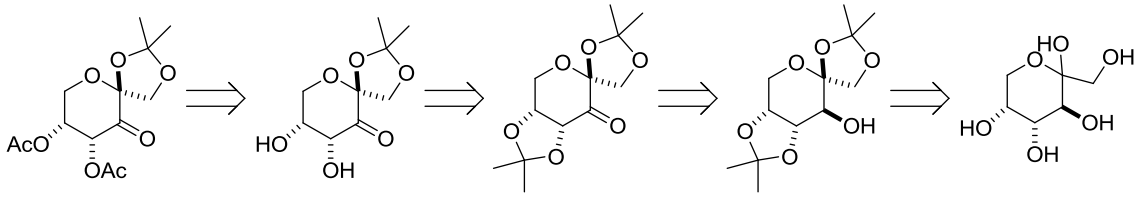
In the first instance, we aimed to reproduce, and wherever possible optimise, the preparation method for diester **84** that had been reported in the literature by Shi and co-workers[75,77] at the time this Ph.D. Thesis work started. It should be again remembered at this point that **84** had *a priori* a more advantageous catalytic profile than **73** towards epoxidation of unfunctionalised alkenes, and whilst the latter was affordable from usual suppliers and had been studied in epoxidation reactions previously,[76] the catalytic properties of **84** in this chemistry remained unexplored and the catalyst itself had to be prepared by everyone willing to use it.



84

Figure I. 9. Shi's diester **84**.

Diacetate catalyst **84** was prepared by Shi in four steps:[75,77,81] Protection of D-fructose (**20)**, oxidation of **92**, selective deprotection of **73**, and the final diacetylation of **117** afforded the desired derivative **84** (Scheme I. 11).

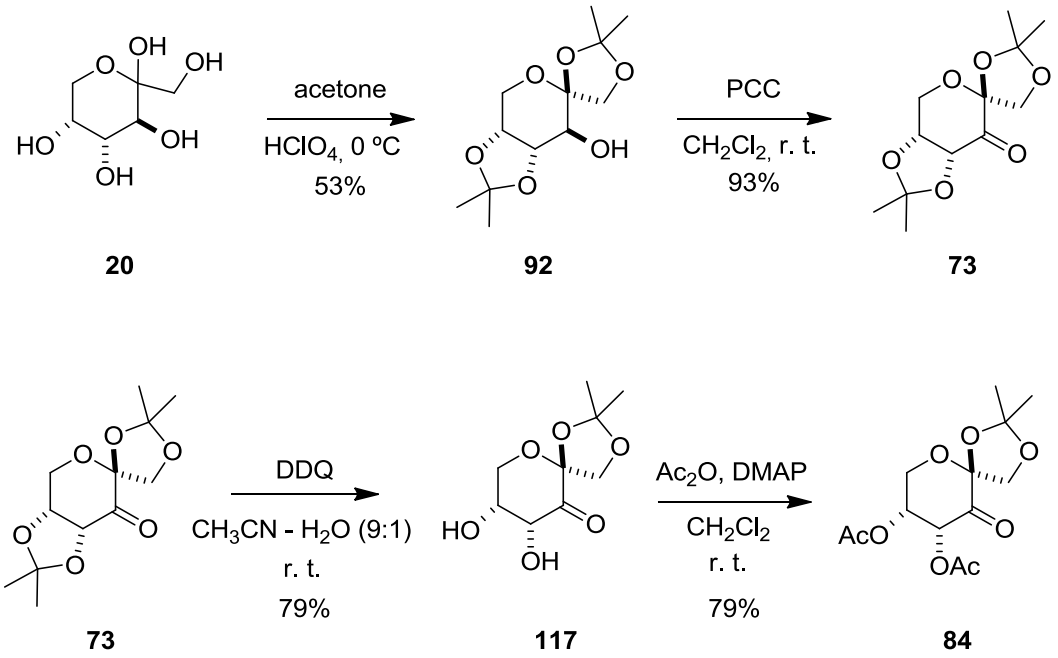


84 **117** **73** **92** **20**

Scheme I. 11. Shi's retrosynthetic analysis for **84**.

[81] Ager, D. *Handbook of Chiral Chemicals*, Taylor & Francis, New York, 2006.

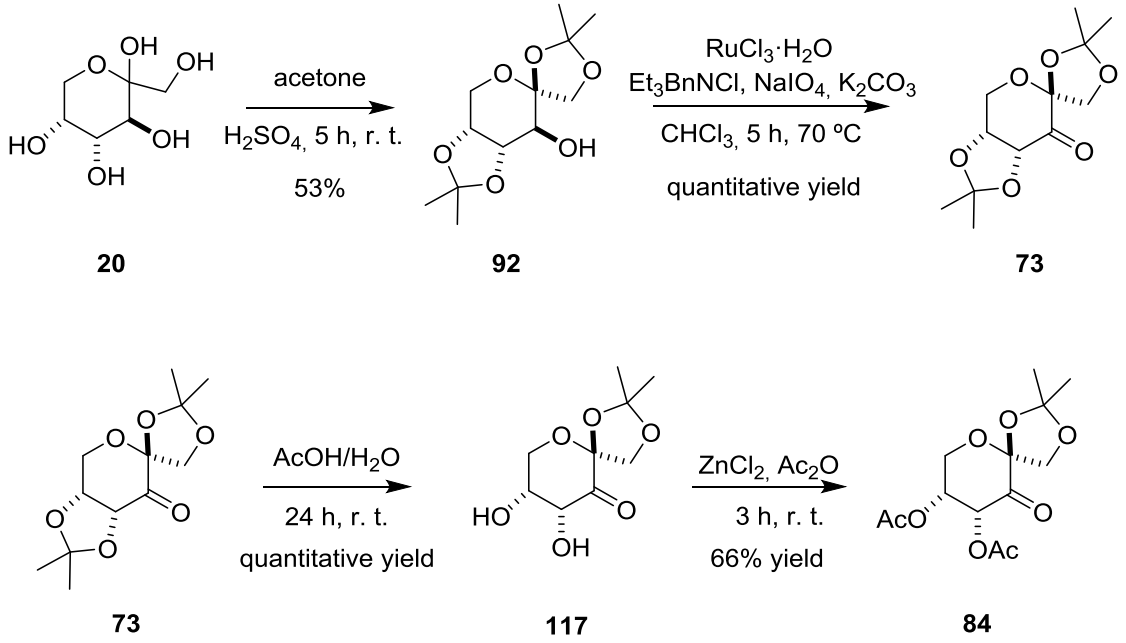
In the original synthetic procedure described by Shi, D-fructose was transformed into **92** by reaction with acetone, which acted both as reagent and solvent at room temperature using perchloric acid as catalyst.[62a-b,73,75,81] The desired product **92** was isolated in 53% yield. The diacetonide **92** was converted into ketone **73** using pyridinium chlorochromate (PCC) as oxidant (93% yield).[62a,74] Finally, selective deketalisation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), followed by acetylation with acetic anhydride using DMAP as catalyst afforded the desired compound **84** (Scheme I. 12).[76,77]



Scheme I. 12. Reaction sequences for the synthesis of Shi's diester **84**.

This synthesis suffered, at least from our point of view, from one important drawback: the use of environmentally unfriendly reagents (mainly PCC and DDQ) in stoichiometric amounts. According to literature precedents and from our own expertise, we considered that milder oxidation and deprotection methods involving environmentally friendlier reagents were in fact available. Thus, efficiency, cost, selectivity and environmental aspects of the reagents involved during the preparation of **84** were all accounted for. We prepared the diester derivative **84** in multigram quantities from D-fructose (**20**) in four steps with 35 % overall yield. Scheme I. 13 summarises the

optimised synthesis that was developed within this Ph.D. Thesis and that will be detailed in this section.



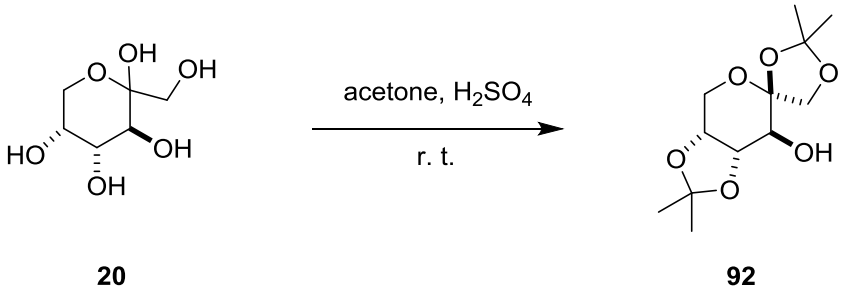
Scheme I. 13. Optimised reaction sequence for the synthesis of diester **84**.

2.1.1 Protection of D-fructose as diacetonide, 92 (1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose).

We decided to transform D-Fructose (**20**) into **92** following the procedure described by Kang and co-workers[82] (Scheme I. 14) using sulfuric acid as catalyst, instead of the method reported by Shi involving the use of perchloric acid. The reaction was performed in acetone, which acted both as reagent and solvent. Different conditions were assayed and the best yield was obtained when sulfuric acid was used as catalyst (30 mol %) in combination with 50-fold excess of anhydrous acetone per mol of D-fructose at room temperature for 5 hours. The product could be easily isolated (53% yield) after recrystallisation (entry 2, Table I. 2). Attempts to reduce the acetone amount led to lower yields (compare entries 2 and 3 in Table I. 2). Overall, the substitution of perchloric acid by sulfuric acid had no detrimental effect on the final yield of

[82] Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564.

diacetonide **92**, and we consider this procedure to be safer, as the potential risk of explosion related to the use perchloric acid is ruled out.



20 **92**

Scheme I. 14.

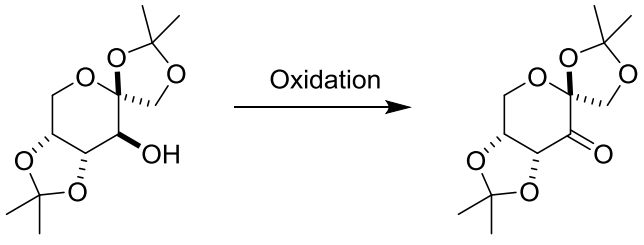
Entry	**20** (mmol)	Acetone (equiv.)	t (h)	Yield (%)[a]
1	500	50	3	46
2	**500**	**50**	**5**	**53**
3	1000	50	5	37

[a] Isolated compound, after recrystallisation.

Table I. 2. D-Fructose protection in acetone catalysed by sulfuric acid.

2.1.2 Oxidation of 1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (92)

The oxidation of **92** into ketone **73** is a particularly interesting reaction. Selective oxidation of primary alcohols to aldehydes and secondary alcohols to ketones has been a highly desired transformation in industry and academia. From the economic and environmental points of view, there is a need for catalytic systems able to perform this transformation working at low concentration of transition metals and releasing the lowest possible amounts of by-products and waste.



92 **73**

Scheme I. 15. Oxidation of derivative **92**.

Several efficient methods were already reported for the oxidation of derivative **92** into the desired ketone **73**. As was mentioned before, Shi and co-workers obtained ketone **73** in 93% yield by reaction of **92** with an excess of pyridinium chlorochromate.[83,84] Following this, moderate selectivity to **73** was obtained by Fung *et al.* by using $[Ru(CF_3CO_2)_3(Cn^*)(H_2O)_x]$ (1 mol %; Cn*= *N*,*N*',*N*''-trimethyl-1,4,7-triazacyclononane) and *t*-BuOOH in CH_2Cl_2 under reflux.[62a,b] Alternatively, the ruthenium-promoted oxidation of secondary alcohols developed by Morris and Kiely[85] and further improved by Mio *et al*. was considered as a possibility to oxidise **92**.[86] Mio and co-workers reported the successful oxidation of **92** using $RuCl_3 \cdot nH_2O/NaIO_4$ as catalyst under phase transfer conditions at reflux in quantitative yield. Finally, Sheldon *et al.* transformed compound **92** into **73** using a recyclable ruthenium-catalysed hypochlorite oxidation protocol under biphasic conditions (MTBE/water) in the presence of an alkaline buffer (pH 9.5) with excellent yields. They also reported some experiments using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical) as an alternative oxidising agent but with unsuccessful results.[87]

TEMPO oxidation is a well-known alternative as a metal-free oxidation system for the catalytic synthesis of aldehydes and ketones, and is desirable from an environmental and economic point of view.[87–92] For this reason, oxidation conditions using catalytic amounts of TEMPO were also assayed in this Thesis.

Oxidising agents such as $NaClO_2$,[88] $NaNO_2/Br_2$,[89] Oxone®[90]/*n*-Bu_4NBr[91] and CuCl/ionic liquid[92] in combination with TEMPO as catalyst were studied (Table I. 3). Unfortunately, none of these oxidation conditions proved to be effective, as the starting material remained unchanged.

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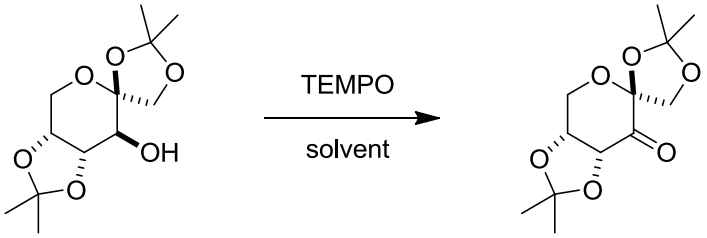
[83] Fayet, C.; Gelas, J. *Carbohydr. Res*. **1986**, *155*, 99.
[84] See refs. 62a and 74.
[85] Morris, P. E., Jr.; Kiely, D. E. *J. Org. Chem.* **1987**, *52*, 1149.
[86] Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133.
[87] Gonsalvi, L.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Lett.* **2002**, *4*, 1659.
[88] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reide, P. J. *J. Org. Chem.*, **1999**, *64*, 2564.
[89] Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *1126*, 4112.
[90] The composition of the oxidising agent Oxone® is $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The active component potassium monopersulfate ($KHSO_5$, potassium peroxomonosulfate) is a salt from Caro's acid (H_2SO_5).
[91] Bolm, C.; Magnus, S.; Hildebrand, P. *Org. Lett.* **2000**, *2*, 1173.
[92] Ansari, I. A.;. Gree, R. *Org. Lett.* **2002**, *4*, 1507.



92 **73**

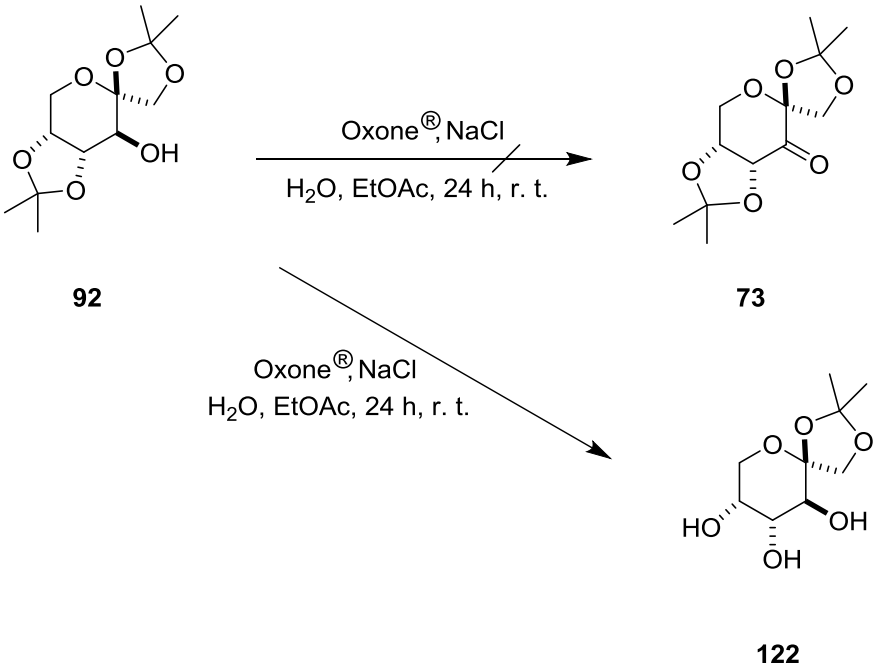
Entry	TEMPO (mol %)	Reagents (equiv.)	Solvent	T (ºC)	t (h)	Conv. (%)
1	7	$NaClO_2$ (2.0)	CH_3CN/pH 6 buffer[a]	80	24	n. c.[d]
2	1	$NaNO_2/Br_2$ (0.08/0.04), O_2	H_2O	Reflux	24	n. c.
3	5	CuCl (0.05), O_2	(bmin)(PF_6)[b]	65	65	n. c.
4	1	Oxone®/*n*-Bu_4NBr (2.2/0.04)	CH_2Cl_2	r. t.	48	n. c.

[a] Sodium phosphate buffer. [b] (bmin)(PF_6)= 1-Butyl-3-methylimidazolium hexafluorophosphate. [c] Conversion determined by ^1H NMR. [d] n. c.: no conversion (starting material was recovered).

Table I. 3. Attempted oxidation reactions with TEMPO as catalyst.

On the other hand, Oxone® has been applied for several oxidations. The combination of Oxone®/NaCl was reported to oxidise benzylic alcohols to aldehydes and secondary alcohols to ketones.[93] These reaction conditions represented a fast, low-cost, effective and environmentally benign method. In fact, only catalytic amounts of sodium chloride were used, whereas the stoichiometric oxidant, *i.e*. Oxone®, is inexpensive, stable, easy to transport, and non-toxic. Unfortunately, when Oxone®/NaCl was used to oxidise derivative **92** to **73**, we only observed selective deprotection of the ketal substituting C_4–C_5 in **92** affording compound **122** in quantitative conversion (Scheme I. 16).

[93] Schulze, A.; Pagona, G.; Giannis, A. *Synth. Commun.* **2006**, *36*, 1147.

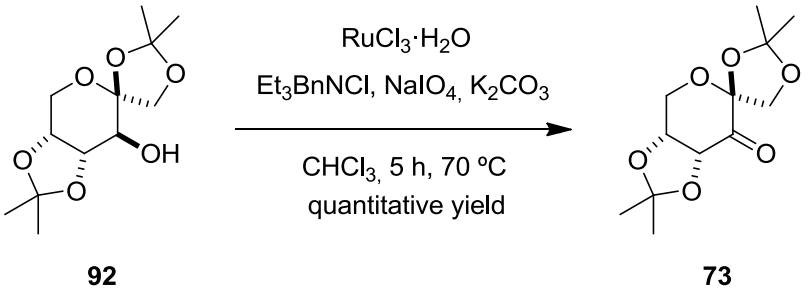


Scheme I. 16. Oxidation attempts using Oxone® as the oxidising agent.

Oxidation of **92** was also attempted using tetra-*n*-butylammonium peroxomonosulfate (*n*-Bu_4NHSO_5), which is also known to be an effective, cheap, environmentally benign and metal-free oxidation method of alcohols using water as the solvent.[94] However, after forty eight hours at reflux, the starting material was recovered.

Finally, as we were unable to develop alternative and more efficient oxidation conditions to the ones developed by Mio and co-workers, we used their method to convert compound **92** to **73**.[86] This transformation, which uses catalytic amounts of a ruthenium precursor and sodium (meta)periodate as the stoichiometric oxidant, affords, after removing solvents and drying, compound **73** in quantitative yield as a solid. No further purification was required (Scheme I. 17).

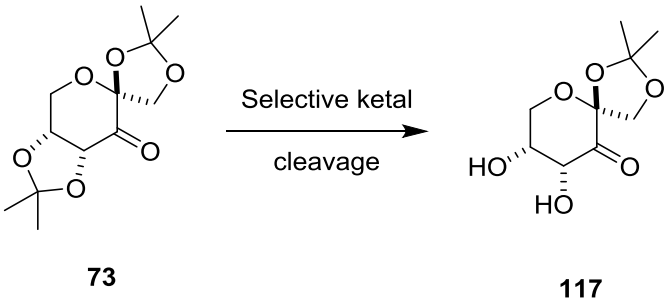
[94] Lei, Z.; Yang, Y.; Bai, S. *Adv. Synth. Catal*. **2006**, *348*, 877.



Scheme I. 17. Oxidation of **92** using ruthenium as catalyst (Mio's procedure).

2.1.3 Selective 4,5-deketalisation of the ketone 73 towards 1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose, 117

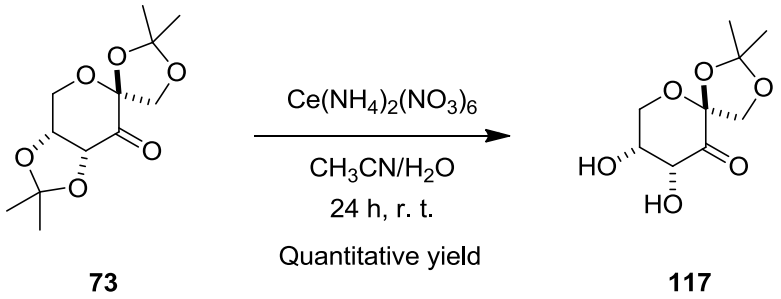
The selective C_4–C_5-deketalisation of **73** has been described by Shi *et al.* using water and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ).[76a] Alternative deprotection methods that avoided the use of DDQ were studied in our group (Scheme I. 18).



Scheme I. 18. Selective deketalisation of ketone **73** yielding **117**.

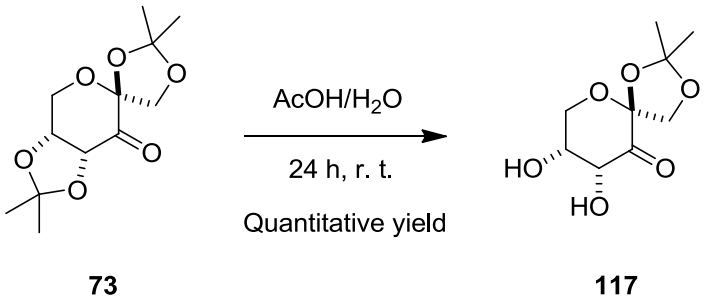
The ketal ring substituting C_4–C_5 in derivative **73** was selectively deprotected using the methodology described by Markó for other acetonides, in which cerium(IV) ammonium nitrate (CAN) was used as catalyst and water as solvent. Compound **117** was obtained in quantitative yield (Scheme I. 19).[95]

[95] Ates, A.; Gautier, A.; Leroy, B.; Plancher, J. M.; Quesnel, Y.; Vanherck, J. C.; Markó, I. E. *Tetrahedron* **2003**, *59*, 8989.



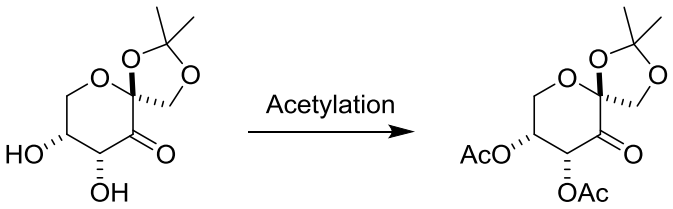
Scheme I. 19. Selective deketalisation of compound **73**.

Additionally, excellent results were also obtained following the method reported by Kang for analogous compounds.[82] Compound **73** was allowed to react at room temperature in a mixture of acetic acid and water (80:20 v/v). After the removal of solvent under vacuum, deprotected compound **117** was obtained in high purity and quantitative yield. The easy workup together with overcoming the toxicity and purification problems associated with DDQ or Ce(IV) renders this deprotection method highly practical. Most conveniently, the crude mixture containing diol **117** could be directly used in the acetylation step without any further purification.



Scheme I. 20. Selective deketalisation of compound **73**.

2.1.4 Diacetylation of 1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose, 117

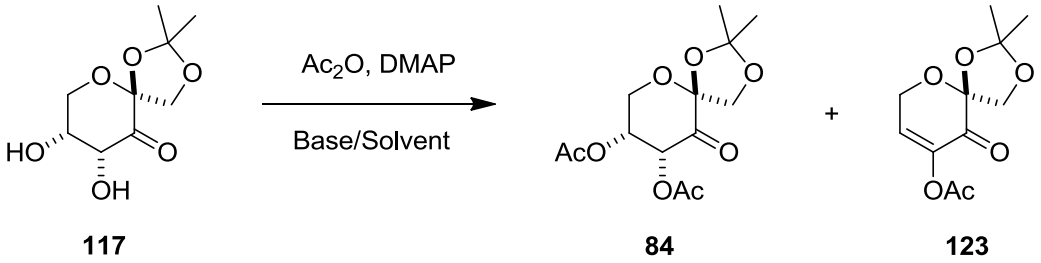


117 **84**

Scheme I. 21.

Shi *et al.* reported[76a,b] that the desired diester derivative **84** (4,5-di-*O*-acetyl-1,2-*O*-isopropylidene-*β*-D-*erytro*-2,3-hexadiulo-2,6-pyranose) could be isolated in good yield (79%) after treating substrate **117** with Ac_2O as acetylating reagent in the presence of catalytic amounts of 4-(dimethylamino)pyridine (DMAP; 20 mol %) and subsequent chromatographic purification.[96] However, when we reproduced Shi's conditions, we observed that elimination product **123** was also formed together with the desired compound **84**, (see Scheme I. 22, and entry 2 in Table I. 4).

[96] It has to be mentioned that there is an error in the synthetic recipe originally described by Shi and co-workers (Wu, X. Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792) for the preparation of compound **84**: the amount of DMAP that the authors indicate to use for 16.1 mmol of compound **117** does not correspond with the number of moles that the authors calculate (0.4 g, 0.32 mmol of DMAP for 16.1 mmol of compound **117**). Whilst 0.4 g of DMAP implies a molar ratio of 20 mol % of DMAP with respect to **117**, 0.32 mmol of DMAP implies a 2 mol % excess with respect to compound **117**. We studied the two catalyst amounts (see entries 1 and 2 in Table I. 4 for 20 and 2 mol % of DMAP, respectively) and we could not reproduce the results reported. Subsequent to our publication with the results presented in this section (Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143), Shi and co-workers published again the synthetic procedure for **84** (Wang, B.; Wu, X. Y.; Wong, O. A.; Nettles, B.; Zhao, M. X.; Chen, D.; Shi, Y. *J. Org. Chem* **2009**, *74*, 3986, ref 76b), which implied the use of 2 mol % of DMAP with respect to **117**. In this later publication, Shi reports again that compound **84** is obtained in 79% yield after chromatographic purification. Shi *et al.* neither make mention in this case of the formation or isolation of the elimination product **123**.



117 **84** **123**

Scheme I. 22. Acetylation using DMAP as catalyst.

Entry	Ac_2O (equiv.)	DMAP (mol %)	Base	Solvent	T (ºC)	t (h)	Ratio **84**/**123**[a]	Yield (%)[b]
1	3.0	20.0	–	CH_2Cl_2	r. t.	24	1/99	[c]
2	3.0	2.0	–	CH_2Cl_2	0 → r. t.	24	65/35	36
3	7.0	1.0	–	–	r. t.	24	81/19	57
4	3.0	0.2	–	CH_2Cl_2	0 → r. t.	24	–/–	s. m.[d]
5	3.0	10.0	py	CH_2Cl_2	r. t.	24	3/97	-
6	3.0	10.0	py	–	r. t.	24	14/86	-

[a] Relation between derivative **84**/**123** has been determined by ^{1}H NMR, [b] The crude has been purified by flash chromatography (1:0 to 7:3 hexanes/EtOAc) to give an oil (derivative **84**). [c] Compound **123** was isolated with 43% overall yield from compound **92** after chromatographic purification. [d] s. m. = starting material, compound **117**.

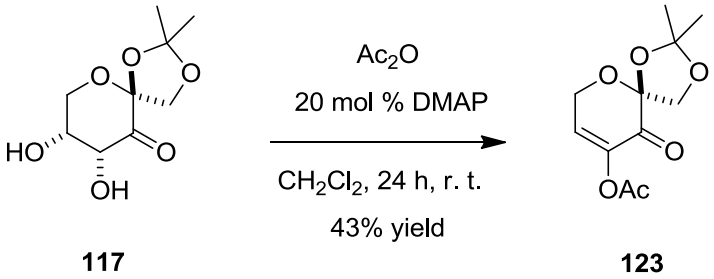
Table I. 4. Acetylation assays on **117** using DMAP as catalyst.

We observed that a first reaction parameter that favoured the formation of this by-product (compound **123**; see Scheme I. 22) was the amount of DMAP: whilst the use of 2 mol % of the catalyst (entry 2) afforded a *ca.* 2:1 mixture of diacetate **84** and elimination product **123**, the use of 20 mol % of DMAP (entry 1) afforded exclusively the elimination product **123** (compare entries 1 and 2 in Table I. 4). The structure of the new compound **123** could be proved by X-Ray analysis (Figure I. 10). When the acetylation agent was increased and the amount of catalyst was decreased, an improvement in the formation of diacetate **84** was observed but still considerable amounts of compound **123** (*ca.* 20%) were formed (entry 3). When 0.2 mol % of DMAP was added as catalyst, no reaction was observed (entry 4). Finally, in entries 5 and 6, the use of DMAP as catalyst together with a base (pyridine) was assayed. Despite using such an auxiliary base, no better selectivity in the acetylation was observed.

On the other hand, we observed that the work-up procedure affected as well the selectivity of the reaction: Washing compound **84** during the work-up with basic

aqueous solutions (*i.e.* 5% $NaHCO_3$) should be avoided as the ratio of elimination of compound **123** increases. Heating the acetylation crude mixture for long periods of time increased the ratio of elimination product also.

As far as the preparation of the elimination product **123** is concerned, this compound was prepared from **117** using the original recipe reported by Shi *et al.*[76a,b] in 43% yield from **92** after chromatographic purification (Scheme I. 23).



Scheme I. 23. Synthesis of (5*S*)-9-acetoxy-2,2-dimethyl-1,3,6-trioxaspiro[4.5]dec-8-en-10-one, **123**.

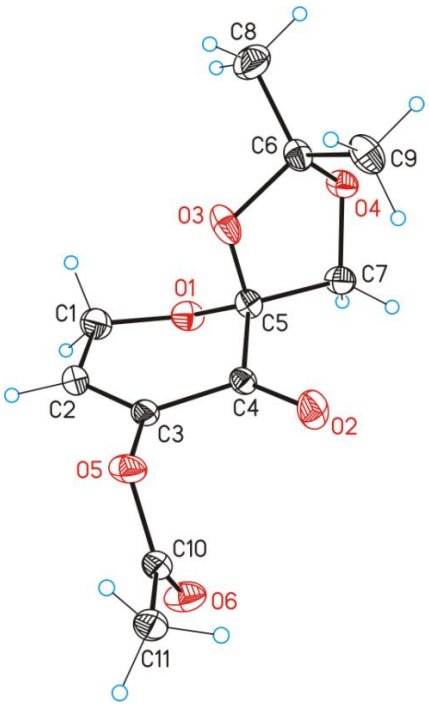


Figure I. 10. Ortep plot (ellipsoids drawn at 50% probability level) of compound **123**.

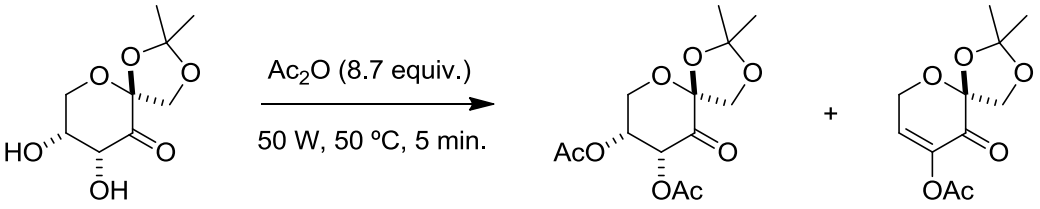
As the previously mentioned acetylation conditions involving basic catalysis were not optimal, we decided to study milder and more selective acetylating conditions.

Several methods have been described for fast and high yielding microwave-assisted protection of carbohydrate hydroxyl functionalities with acetic anhydride together with a catalyst. For example, Limousing *et al.* performed peracetylation of D-glucose by using a small excess of acetic anhydride under catalysis of either anhydrous potassium acetate, sodium acetate, or zinc(II) chloride with microwave heating.[97,98]

Acetylation of derivative **117** with sodium acetate under microwave irradiation turned out to be unselective (see entries 1–3 in Table I. 5). The use of this acetylating catalyst, even in a 1 mol % amount, gave a 63:37 mixture of the desired compound **84** and its elimination product (**123**).

On the contrary, we found that catalytic amounts of $ZnCl_2$, a very convenient and cheap Lewis acid, with an excess of acetic anhydride gave high selectivity in the acetylation reaction (entries 4, 5, Table I. 5). We proved that the acetylation took place in a very short period of time (five minutes to transform *ca.* 1 g of **117** into the bisacetylated compound **84**) and in quantitative conversion. The final crude mixture contained *ca.* 1% of the elimination product and bisacetylated compound **84** was isolated in 44% overall yield (entry 5, Table I. 5). This preparation method for **84** could not be further scaled-up as the maximal capacity of the microwave reactor was used for the acetylation of this amount of starting material.

[97] Corsaro, A.; Chiacchio, U.; Pistarà, V.; Romeo, G. *Curr. Org. Chem.* **2004**, *8*, 511.
[98] Limousin, C.; Cleophax, J.; Petit, A.; Loupy, A.; Lukacs, G. *J. Carbohydr. Chem.* **1997**, *16*, 327.



117 **84** **123**

Entry	Catalyst (mol %)	Ratio **84/123**[a]
1	NaOAc (50.0)	43/57
2	NaOAc (10.0)	42/58
3	NaOAc (1.0)	63/37
4	$ZnCl_2$ (10.0)	99/1
5	$ZnCl_2$ (1.0)	99/1

[a] Measured by ^{1}H NMR.

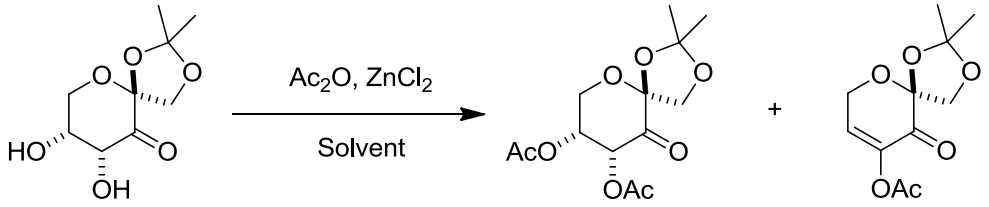
Table I. 5. Testing of different catalysts under microwave irradiation.

Subsequent studies on the preparation of **84** dealt with the development of an adequate procedure for higher amounts of the target compound. When $ZnCl_2$ was used as acetylating catalyst of multigram amounts of **117**, the reaction was highly selective (Table I. 6, entries 1–5). In order to minimise the formation of the elimination side product **123**, the following work-up was used: the reaction mixture was diluted with EtOAc, and the solution was passed through a neutral silica gel pad. SiO_2 was washed with EtOAc, the combined organic solutions were combined, EtOAc was removed *in vacuo* at room temperature, and the resulting oil was chromatographed through a short SiO_2 pad eluting with mixtures of hexanes/EtOAc of increasing polarity. When the solvents from the combined extracts were removed, the temperature was carefully controlled.

The importance of a work-up carried out under controlled conditions was evidenced within this series of experiments. Removal of solvents after filtering the solution through a neutral silica gel pad was carried out in one case at 40 ºC (see entry 4 in Table I. 6) and higher amounts of elimination product (**123**) (*ca.* 4%) were observed.

A considerable excess of acetylating agent is required when 1 mol % of catalyst is used in order to achieve full conversion (Table I. 6, entries 1–4). A further reduction of the

acetylating agent was possible at the expense of increasing the catalyst amount up to 2.5 mol % (Table I. 6, entry 5).



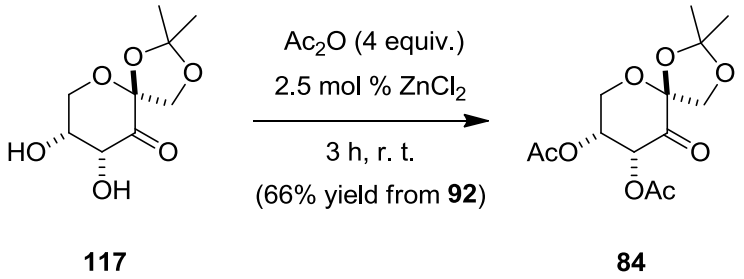
117 **84** **123**

Entry	Ac_2O (equiv.)	$ZnCl_2$ (mol %)	Solvent	T (ºC)	t (h)	Ratio **84**/**123**[a]	Yield (%)[b]
1	8.7	1.0	–	50	0.16	99/1[b]	66
2	8.7	1.0	–	0 → r. t.	3	99/1[b]	76
3	6.0	1.0	–	r. t.	3	99/2[b]	93
4	6.0	1.0	–	r. t.	3	96/4[b,c]	67
5	4.0	2.5	–	r. t.	3	99/1[b]	66
6	2.1	1.0	CH_2Cl_2	r. t.	3	s. m.[d]	–

[a] Determined by ^1H NMR. [b] Determined after purifying by flash chromatography (1:0 to 7:3 hexanes/EtOAc) to give an oil (derivative **84**). [c] In the work-up the solvent was removed under pressure at 40 ºC. [d] s. m. = compound **117**.

Table I. 6. Optimisation of the acetylation reaction conditions using $ZnCl_2$ as catalyst.

Finally, the acetylation reaction conditions from entry 5 were chosen as the most convenient option for large-scale preparation of the target organocatalyst **84**. We have performed the acetylation of **117** using Ac_2O both as solvent and reagent, with 2.5 mol % of $ZnCl_2$ as catalyst and an excess of acetic anhydride, at room temperature and in a short period of time (3 h; see Scheme I. 24). Analytically pure Shi diester (compound **84**) could be isolated with 66% overall yield from compound **92** (*ca.* eight grams) after chromatographic filtration.

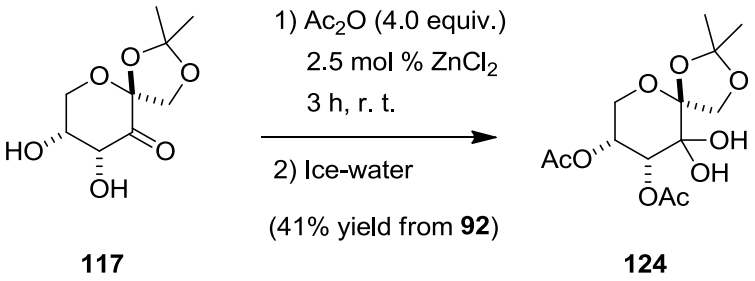


Scheme I. 24. Synthesis of derivative **84** using $ZnCl_2$ as catalyst.

Here we have described a practical synthesis of diester **84**. However, our method suffered from a minor drawback: a chromatographic purification of the reaction crude was required. Therefore, we decided to assess an aqueous work-up directly after the bisacetylation was complete.

Once the acetylation was completed, ice-water was added to the reaction mixture (Scheme I.25). Rather interestingly, a white precipitate was formed, which was filtered and dried. Surprisingly, the isolated product proved to be the hydrate **124**, which had not been described in the literature previously. The structure of this newly isolated material could be unambiguously proven by X-Ray analysis (the Ortep plot of the structure obtained using small crystal needles grown in 1,1,1- trichloroethane is shown in Figure I. 11) and proved to be the hydrate of ketone **84**. This new compound was isolated with a 41% overall yield from **92** (3 steps).

In summary, we have developed a practical synthesis of diester **84** and the new derivative **124**, in which efficiency, cost, selectivity and environmental aspects of the reagents involved for its preparation have been considered. Diester **84** and hydrate **124** were prepared in four steps, using easy work-up procedures and with no purification steps until the very end.



Scheme I. 25. Acetylation reaction using an aqueous work-up.

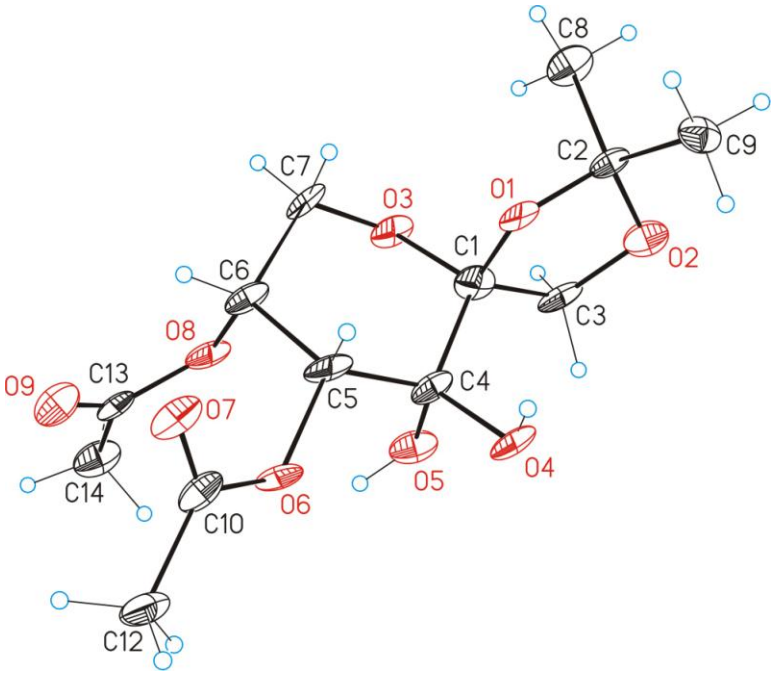
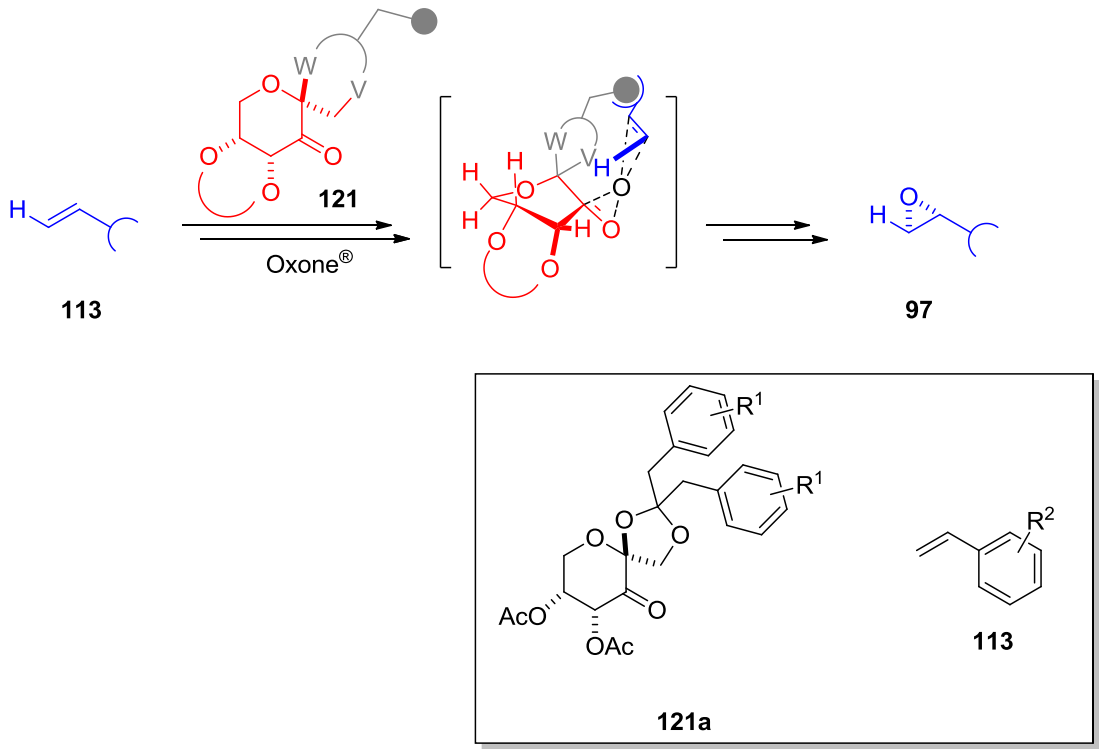


Figure I. 11. Ortep plot (ellipsoids drawn at 50% probability level) of the molecular structure of **124**.

2. 2 Synthetic attempts of new catalysts for the epoxidation of styrene or terminal olefins

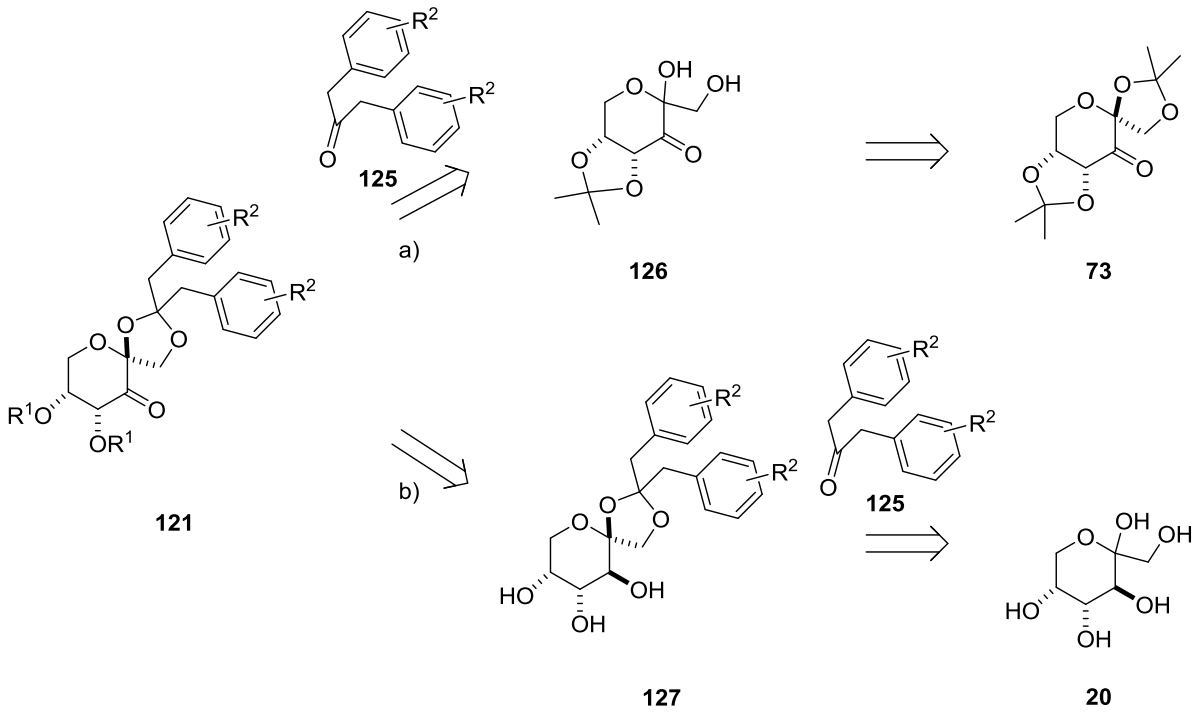
As has been mentioned at the beginning of Section 2 of this chapter, preliminary attempts towards the development of a synthetic strategy for a new chiral organocatalysts (for instance **121a**) for the asymmetric epoxidation of styrene or terminal olefins were carried out. The underlying design principle of these new catalysts retains most of the structural characteristics of Shi's initial catalyst **73** and diester **84**, but also incorporates complementary binding groups in the catalyst and substrate (see Scheme I. 26).



Scheme I. 26. Modifications of the standard Shi's catalyst.

We believe that these new classes of catalysts should retain the stability properties of catalyst **84** and favour adequate substrate orientation for highly enantioselective epoxidation of suitably designed substrates. In this way, we believe that styrene derivatives capable of interacting through strong π–π interactions with the catalyst could be epoxidised by **121** in high enantioselectivities.

Two synthetic strategies were envisaged for the preparation of the first type of substrate-selective catalysts **121** as indicated in Scheme I. 27.



Scheme I. 27. Retrosynthetic analysis of the new catalysts for the epoxidation of styrene derivatives.

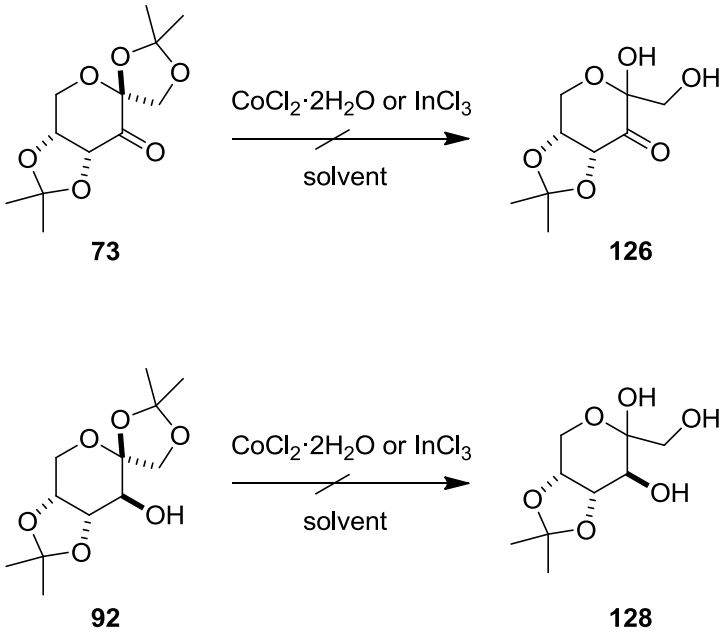
The first one (path a) relies on selective deketalysation of the spirodioxo moiety in **73**, which would give access to compound **126**. Subsequent reaction with the required ketone followed by transformation of the remaining acetonide in the diacetate could afford the target catalyst.

In the second synthetic strategy (path b), the key transformation involves formation of the spirocyclic ketal **127** from D-fructose (**20**) and the required 1,3-diarylpropan-2-one, followed by further selective transformation of the hydroxyl groups into oxo and acetoxy substituents.

The selective deprotection of the spirocyclic ketal in compounds **73** and **92** using several Lewis acids has been reported.[99] The authors stated that indium(III) chloride or

[99] Mahalingam, S. M.; Aidhen, I. S. *Z. Naturfosrch*. **2005**, 962.

cobalt(II) chloride mediated this selective deketalisation. Unfortunately, we were unable to reproduce these results despite many attempts: we did not observe any conversion under any of the assayed conditions (CH_3CN, CH_3CN/H_2O or MeOH as solvents in temperatures ranging from 55 to 95 ºC).



Scheme I. 28. Deprotection attempts of the spirocyclic ketal groups in **73** and **92** using Lewis acids.

Entry	Comp.	Lewis acid (mol %)	Solvent	T (ºC)	Conv. (%)[a]
1	**73**	$CoCl_2·2H_2O$ (1)	CH_3CN	55	n. c.[b]
2	**92**	$CoCl_2·2H_2O$ (1)	CH_3CN	95	n. c.
3	**92**	$CoCl_2·2H_2O$ (10)	CH_3CN	55	n. c.
4	**73**	$CoCl_2·2H_2O$ (10)	CH_3CN/H_2O	55	n. c.
5	**92**	$CoCl_2·2H_2O$ (10)	CH_3CN/H_2O	55	n. c.
6	**92**	$InCl_3$ (10)	MeOH	60	n. c.

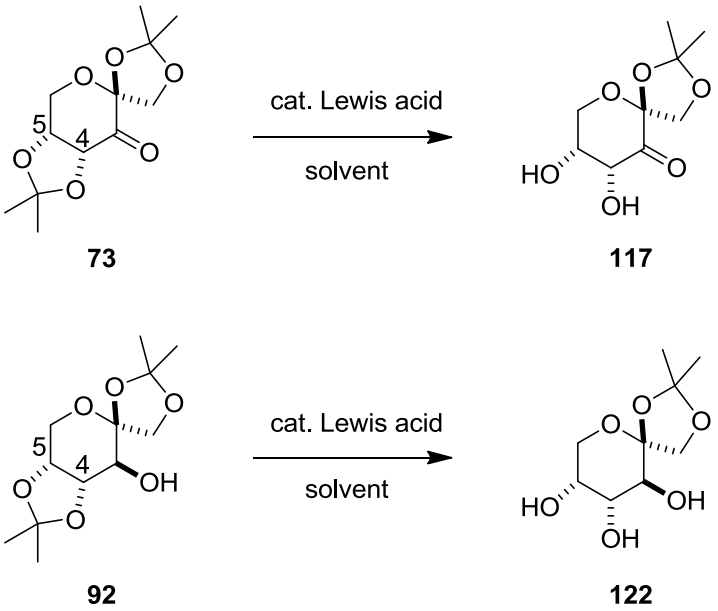
[a] Determined by ^1H NMR. [b] n. c.: no conversion (starting material was recovered).

Table I. 7. Testing deprotection of the spirocyclic ketal groups in **73** and **92** using Lewis acids as catalysts.

The use of $CoCl_2·2H_2O$ in acidic conditions or the use of other Lewis acids ($CeCl_3·7H_2O$,[100] $Ce(NH_4)(NO_3)_6$[95] and $FeCl_3/SiO_2$[101]) was also studied in the selective deketalisation of the spirodioxo moiety in compounds **73** and **92**. The target compounds **126** and **128** were not observed in any case and, unfortunately, these reaction conditions

[100] Sabitha, G.; Babu, R. S.; Rajkumar, M.; Srividya R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149.
[101] a) Kim, K. S.; Song, Y. H.; lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404. b) Vankar, D. Y.; Agarwal, A. *Carbohydr. Res.* **2005**, *340*, 1661.

led in most cases to the cleavage of the ketal unit bridging C4 and C5 (see Scheme I. 29 and Table I. 8).



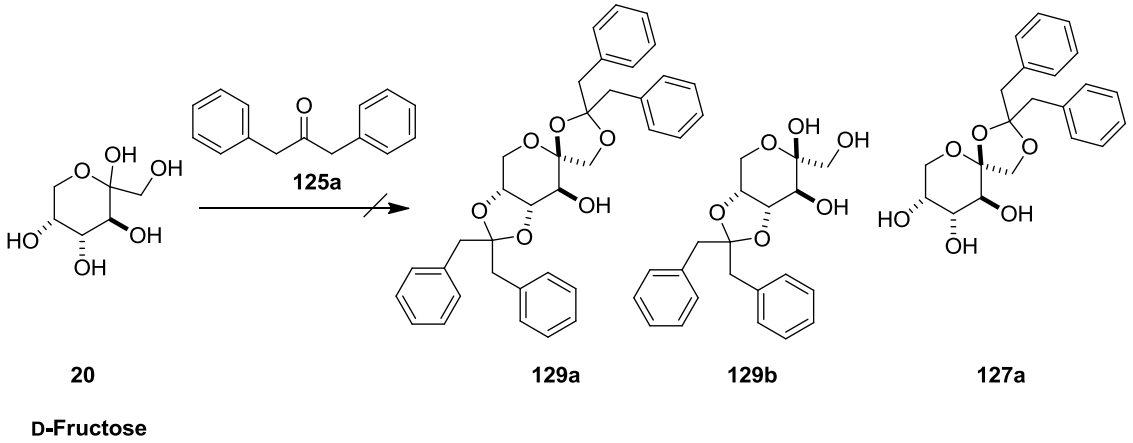
Scheme I. 29. Deprotection attempts of spirocyclic ketal groups in **73** and **92** using Lewis acid catalysts.

Entry	Comp.	Lewis acid (mol %)	Solvents/Co-catalyst	T (ºC)	Conv. (%)[a]
1	**73**	$CoCl_2 \cdot 2H_2O$ (10)	CH_3CN/HCl 0.1M	r. t.	99
2	**92**	$CoCl_2 \cdot 2H_2O$ (10)	CH_3CN/HCl 0.1M	r. t.	99
3	**92**	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN	95	n. c.[b]
4	**73**	$Ce(NH_4)_2(NO_3)_6$ (1.5)	CH_3CN/H_2O	r. t.	99
5	**92**	$Ce(NH_4)_2(NO_3)_6$ (1.5)	CH_3CN/H_2O	r. t.	99
6	**92**	$FeCl_3/SiO_2$ (10)	$CHCl_3$	r. t.	n. c.

[a] Determined by ^1H NMR. [b] n. c: no conversion.

Table I. 8. Testing of the deprotection of spirocyclic ketal groups in **73** and **92** using Lewis acids.

As far as the second strategy towards the target catalyst **121** is concerned (path b, Scheme I. 27), acid-catalysed ketalisation of D-fructose with **125a** did not proceed at all (see Scheme I. 30 and Table I. 9 for the assayed reaction conditions).



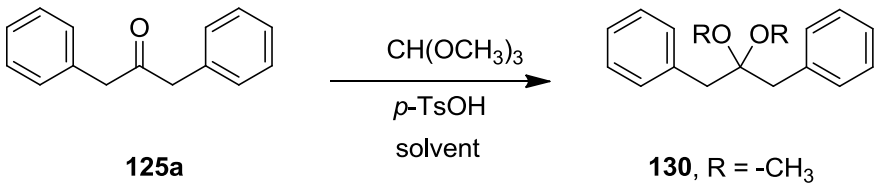
Scheme I. 30. Attempted ketalisation reactions of D-fructose with ketone **125a**.

Entry	Comp. **125a** (equiv.)	Cat. (mol %)	Solvent	Conv. (%)
1	7.5	H_2SO_4 (1 drop)	CH_3CN	d. p.[a]
2	8	$HClO_4$ (1 drop)	1,4-dioxane	n. r.[b]
3	8	$ZnCl_2$ (10)	1,4-dioxane	n. r.
4	2	$ZnCl_2$ (10)	DMF	n. r.

[a] d. p.: degradation products. [b] n. r.: no reaction.

Table I. 9. Testing protection of the D-fructose using **125a**.

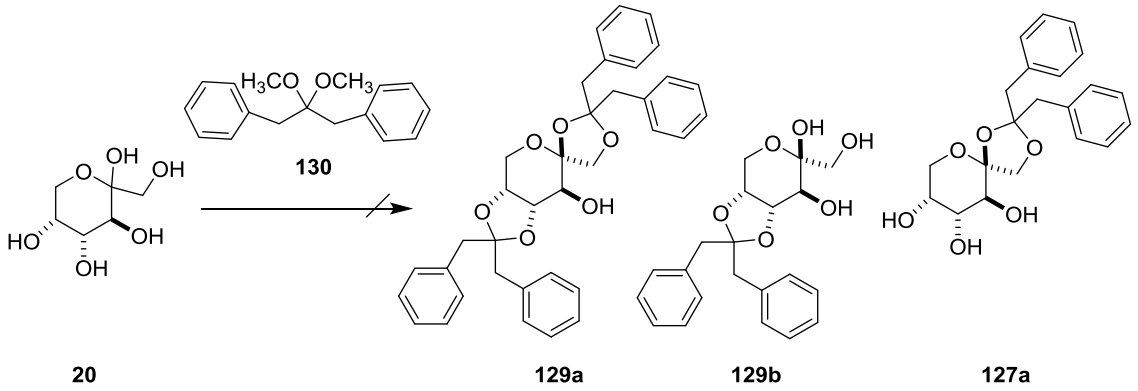
The preparation of target compound **121** was also tackled by transketalisation reaction between D-fructose and compound **130**. The required ketal **130** was prepared in 96% yield following a reported procedure from ketone **125a** and trimethyl orthoformate under acid catalysis (*p*-TsOH) and using montmorillonite K10 as additive.[102]



Scheme I. 31. Synthesis of ketal **130**.

Acid catalysed transketalisation of D-fructose (**20**) with **130** did not proceed at all (see Scheme I. 32 and Table I. 10 for the assayed reaction conditions).

[102] a) Lipshutz, B. H.; Morey, M. C. *J. Org. Chem.* **1981**, *46*, 2419. b) Mansilla, H.; Rega´s, D. *Synth. Commun.* **2006**, *36*, 2195.



Scheme I. 32. Attempted transketalisation assays between D-fructose and **130** under acid catalysis.

Entry	Comp. **130** (equiv.)	Cat. (mol %)	Solvent	Conv.(%)
1	2.6	*p*-TsOH (1)	CH_3CN	n. c.[a]
2	2.6	*p*-TsOH, $HClO_4$ (1/1drop)	THF	n. c.
3	4	PPTs[b] (2)	THF	n. c.
4	4	PPTs (2)	CH_3CN	n. c.
5	2.6	PPTs (4)	DMF	n. c.
6	4	PPTs (2)	1,4-dioxane	n. c.
7	4	$CuSO_4$, PPTs (130/1)	1,4-dioxane	n. c.
8	4	$CuSO_4$, H_2SO_4 (130/1 drop)	1,4-dioxane	n. c.
9	4	$ZnCl_2$ (10)	1,4-dioxane	n. c.
10	2.6	$ZnCl_2$ (10)	DMF	n. c.

[a] n. c.: no conversion. [b] PPTs: Pyridinium *p*-toluenesulfonate.

Table I. 10. Testing of the D-fructose ketalisation.

In conclusion, functionalisation of the 1,2-diol units in D-fructose by ketalisation (or transketalisation) did not proceed. The lack of solubility of D-fructose in most organic solvents was the main limitation. Higher reaction temperatures certainly increased the solubility of the starting materials (D-fructose and compound **130**)[75a,102a,103] but did not bring any improvement given their instability in polar solvents in the presence of acids. Thus, no further work in this direction was carried out.

[103] a) Arasappan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 177.

3. Experimental section

A. Experimental section organisation

The different compounds synthesised in this section are not presented strictly in the same order of appearance as they are in the discussion. Instead, they have been organised according to reaction types.

B. Instrumentation

Polarimetry ($[\alpha]_D$):

Specific rotation was determined by using a Jasco P-1030 polarimeter equipped with a sodium lamp, and a photomultiplier tube detector with a 589 nm filter, in a polarimetry cell of 100 mm length. The measurement accuracy is of ± 0.002º. All measurements were performed at room temperature. Concentration is given in g/100 mL and solvent used is indicated in brackets.

Melting points (m.p.):

Uncorrected melting points have been determined in an open capillary tube in a Büchi B-540 melting point instrument, which covers a range of temperatures from room temperature up to 400 ºC, and allows for three simultaneous sample determinations.

Infrared Spectroscopy (IR).

Off-line IR spectra were recorded in a FTIR (Fourier Transform InfraRed) Thermo Nicolet 6700 spectrometer. The most characteristic absorption IR bands (υ_{max} in cm^{-1}) are indicated.

Nuclear Magnetic Resonance (NMR):

NMR spectra were recorded in a Bruker Advance 400 or 500 Ultrashield NMR spectrometer for ^{1}H NMR at 400 or 500 MHz, and ^{13}C NMR at 100 MHz or 125 MHz.

The solvent employed in each case is indicated in brackets ($CDCl_3$, DMSO-d_6, D_2O or CD_3CN). Chemical shifts (δ) in ppm are indicated with respect to residual solvent peak or tetramethylsilane (TMS, internal reference) if $CDCl_3$ or DMSO-d_6 were used in ^{1}H NMR, and respect to the solvent peak for ^{13}C NMR spectra. Signal multiplicity in ^{13}C NMR was determined by the DEPT technique (Distortion Enhancement by Polarization Transfer).

The following abbreviations were employed:

J: coupling constant in Hz

s: singlet

d: doublet

dd: doublet of doublets

t: triplet

q: quadruplet

m: multiplet or complex system

br: broad signal

CH_3: primary carbon

CH_2: secondary carbon

CH: tertiary carbon

C: quaternary carbon

Mass Spectrometry (MS):

Both low and high resolution mass spectrometry analyses were performed in a Waters LCT Premier^{TM} instrument operating in positive ESI (Electro-Spray Ionisation) mode.

Elemental analysis (EA):

Elemental analyses were performed by the scientific and technical services of the *"Universidade de Santiago de Compostela"* in an Eager 200 microanalyser.

X-Ray:

X-ray Crystal Structure Determination. Crystals were obtained by slow diffusion. The measured crystals were prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation**.**

Data collection**:** Crystal structure determinations were carried out using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_α radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 °C). Full-sphere data collection was used with ω and φ scans. *Programs used:* Data collection APEX-2[104], data reduction Bruker[105] Saint V/.60A and absorption correction SADABS.[106]

Structure Solution and Refinement: Crystal structure solution was achieved using direct methods as implemented in SHELXTL[107] and visualised using the program XP.[108] Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

[104] Data collection with APEX II. Bruker, Bruker AXS Inc., Madison, Wisconsin, **2007**, Versions v1.0-22, v2009.1-0 and v2009.1-02.
[105] Data reduction with Bruker SAINT Bruker, Bruker AXS Inc., Madison, Wisconsin, **2007**, Versions V.2.10(2003), V/.60A and V7.60A. Bruker (2007).
[106] Absorption correction with SADABS: a) Bruker, Bruker AXS Inc., Madison, Wisconsin, **2001**, Versions V.2.10(2003); V2008 and V2008/1. b) Blessing, R. H. *Acta Crystallogr., Sect. A* **1995**, *51*, 33.
[107] SHELXTL versions V6.12 and 6.14.
[108] Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

Chromatography:

Column Chromatography (CC):

Flash column chromatography was employed as a purification technique with silica gel from Merck (70–230 mesh) as stationary phase. When necessary, SiO_2/NEt_3 2.5% v/v was used to diminish silica acidity.

Thin Layer Chromatography (TLC):

TLC was performed on silica plates, on aluminium plates (Merck DC-Alufolien KIESEGEL 60 F254). To stain the different adsorbed products, a UV (Ultra-Violet) lamp (λ = 254 nm) was used. For non-UV active compounds, the following reactive solutions were employed to stain the adsorbed products:

Phosphomolybdic acid solution: 23 g of phosphomolybdic acid in 400 mL ethanol (95%).

Potassium permanganate solution: 3 g of potassium permanganate ($KMnO_4$), 20 g of potassium carbonate (K_2CO_3), and 5 mL aqueous solution of sodium hydroxide (5%), in 300 mL water.

C. Techniques and materials

Solvents:

Purified solvents (dichloromethane, diethyl ether, hexane, toluene and DMF) were all obtained from a PURESOLV^{TM} purification system.

Water from the rest of the solvents used has been removed by treatment with pellets of 4 Å molecular sieves (activated by microwave irradiation) under argon.

Molecular sieves activation:

4 Å Molecular sieves were activated by heating in a microwave reactor, followed by drying under high vacuum. The procedure was repeated at least three times and the activated molecular sieves were stored under argon atmosphere.

Anhydrous conditions:

When working under anhydrous conditions, the reaction vessel was beforehand flame-dried using a hot air gun under vacuum. The flask content was maintained under argon, and adjustable septa and direct connections to the vacuum line or to argon filled balloons were employed. All the reactants were added using Hamilton® syringes, stainless steel cannulas, or polypropylene syringes and needles.

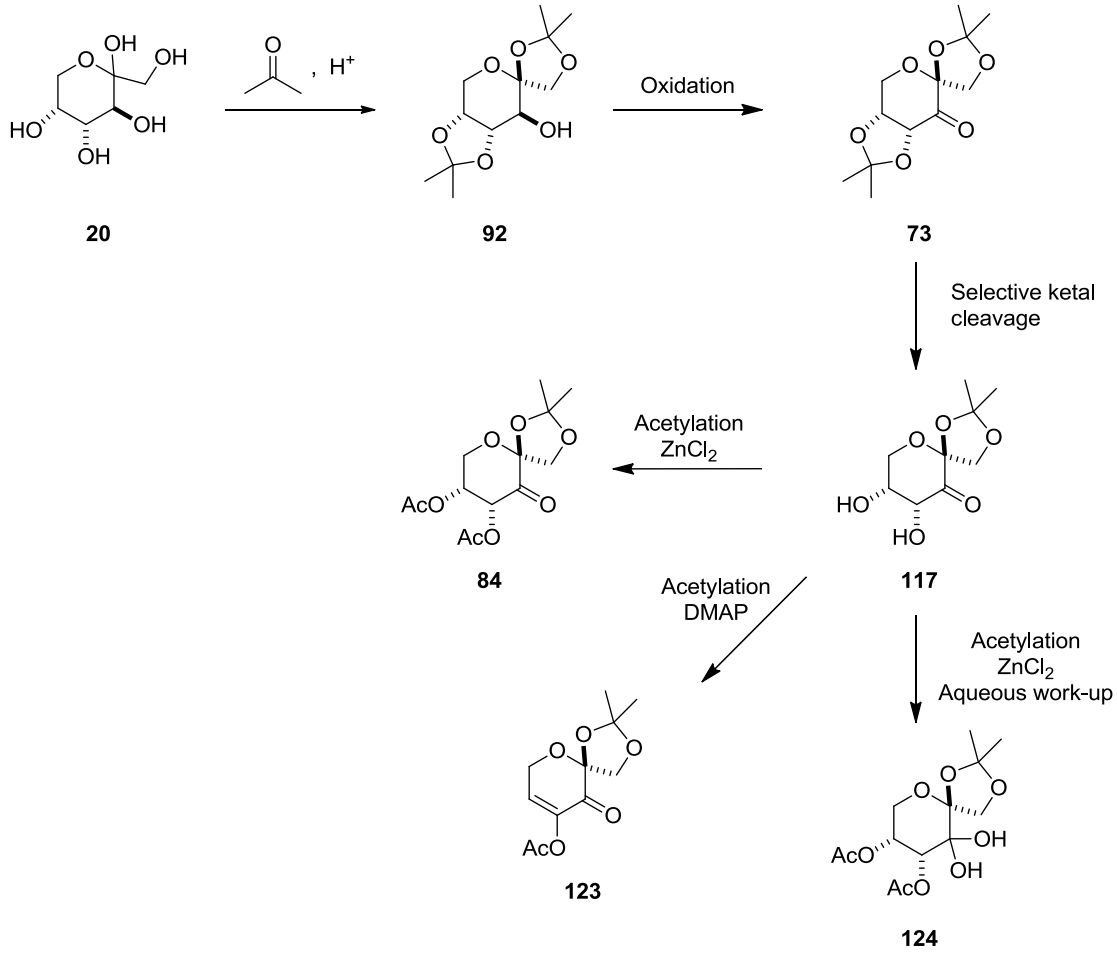
Purification of commercial compounds:

Commercial reagents were used without purification unless otherwise stated.

Low temperature baths:

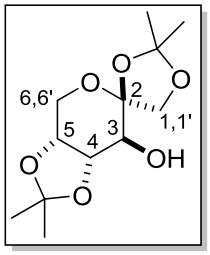
0 ºC was achieved in an ice-water bath or in a Thermo-Haake EK-90 immersion refrigerator with the required cryogenic solvent.

3.1 Practical synthesis of D-fructose derivatives 84, 123 and 124



Scheme I. 33.

3.1.1 Preparation of alcohol derivative 92



Conc. H_2SO_4 (0.33 equiv.) was added to a suspension of D-fructose (90 g, 500 mmol) in acetone (1.8 L). The reaction mixture was stirred for 5 hours at room temperature. Then, the reaction mixture was cooled to 0 ºC and quenched with NaOH (1.43 equiv.) in H_2O (28.6 equiv.). After removal of the solvent under *vacuo*, the residue was extracted with CH_2Cl_2 (2 x 500 mL) Then, the organic phase was separated and washed with water (500 mL), brine (500 mL) and dried over anh. $MgSO_4$. After filtration and removal of solvents under reduced pressure, the residue was

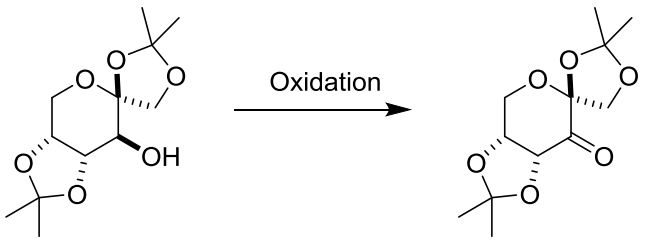
recrystallised with a mixture of diethyl ether and hexanes to afford the alcohol **92** (69 g, 53% yield).

All the spectroscopic data were in agreement with those reported in the literature.[82]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (s, 3H -CH_3-(4,5-*O*-isopropylidene)), 1.43 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 1.50 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 1.52 (s, 3H- CH_3-(4,5-*O*-isopropylidene)), 2.06 (d, $^3J_{H3,\ OH}$= 8.10 Hz, lH-OH), 3.66 (dd, $^3J_{H3,\ H4}$ = 6.92 Hz, $^3J_{H3,\ OH}$ = 8.10 Hz, lH-3), 3.96 (d, $^2J_{H1,\ H1'}$= 8.70 Hz, lH-1), 3.99 (d, $^2J_{H6,\ H6'}$= 13.49 Hz, lH-6), 4.10 (dd, $^2J_{H6,\ H6'}$= 13.49 Hz, $^3J_{H5,\ H6'}$= 2.40 Hz, lH-6'), 4.12 (m, 1H-5), 4.17 (d, $^2J_{H1,\ H1'}$= 8.70 Hz, 1H-1'), 4.20 (ddd, $^3J_{H3,\ H4}$ = 6.92 Hz, $^3J_{H4,\ H5}$= 2.4 Hz, $^4J_{H4,\ H6}$= 0.8 Hz, 1H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.1 (CH_3-(4,5-*O*-isopropylidene)), 26.4 (CH_3-(1,2-*O*-isopropylidene)), 26.6 (CH_3-(1,2-*O*-isopropylidene)), 28.1 (CH_3-(4,5-*O*-isopropylidene)), 60.9 (CH_2, C-6), 70.5 (CH, C-3), 72.5 (CH_2, C-1), 73.5 (CH, C-4), 76.8 (CH, C-5), 104.7 (C, C-2), 109.6 (C-(4,5-*O*-isopropylidene)), 111.9 (C-(1,2-*O*-isopropylidene)).

3.1.2. Oxidation of alcohol derivative 92

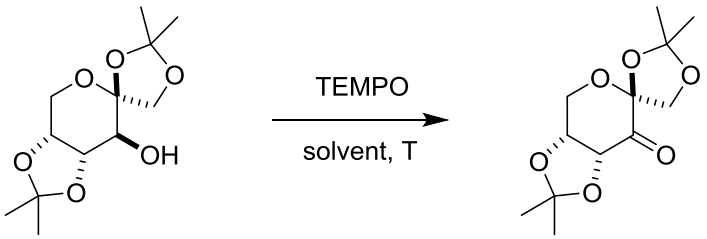


92 **73**

Scheme I. 34. Oxidation of the alcohol derivative **92**.

3.1.2.a Attempted synthesis of derivative 73

Method A: TEMPO (0.01–0.07 equiv.) and the different reagents included in the table above were added to a solution of the alcohol **92** (260 mg, 1.0 mmol) in the indicated solvent and temperature. The mixture was stirred vigorously, and the reaction was monitored by TLC. TEMPO/$NaClO_2$ (entry 1),[88] TEMPO/$NaNO_2$ (entry 2),[89] CuCl/TEMPO catalysed aerobic oxidation of alcohols in the ionic liquid, [bmim][PF6] (entry 3),[92] TEMPO/Oxone®/*n*-Bu_4NBr as a phase transfer catalyst (entry 4),[91] were used. Unfortunately, these methods failed to convert **92** into **73**. The starting material was recovered in all experiments.



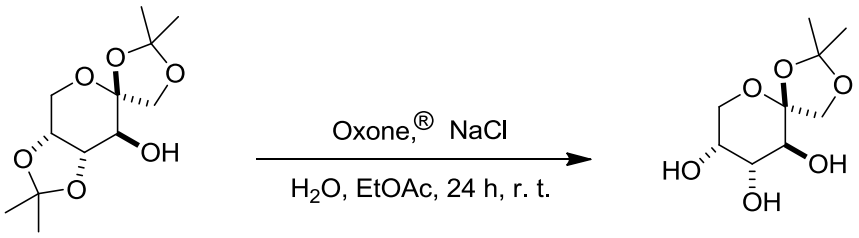
92 **73**

Entry	Comp. **92** (mmol)	TEMPO (equiv.)	Reagents (equiv.)	Solvent (mL)	T (ºC)	t (h)	Conv. (%)
1	1	0.07	$NaClO_2$ (2.0)	CH_3CN/pH 6 buffer (5.0/0.5)[a]	80	24	n. c.[c]
2	1	0.01	$NaNO_2/Br_2$ (0.08/0.04), O_2	H_2O (1.0)	reflux	24	n. c.
3	1	0.05	CuCl (0.05), O_2	(bmin)(PF_6) (1.5)	65	65	n. c.
4	1	0.01	Oxone®/*n*-Bu_4NBr (2.2/0.04)	CH_2Cl_2 (2.0)	r. t.	48	n. c.

[a] Sodium phosphate buffer. [b] Conversion determined by ^1H NMR. [c] n. c.: no conversion.

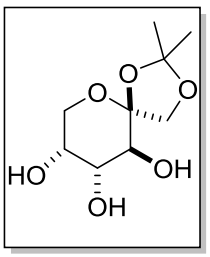
Table I. 11. Attempted oxidation reactions with TEMPO as catalyst.

Method B:[93] Oxone® (236 mg, 1.0 mmol), NaCl (2.2 mg, 0.1 mmol), and finally H_2O (0.2 mL) were added to a solution of the alcohol **92** (260 mg, 1.0 mmol) in EtOAc (0.8 mL). The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the mixture was diluted with H_2O (1 mL) and EtOAc (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 3 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oil, which corresponded to 4,5-*O*-isopropilidene deprotected derivative **122**, in quantitative conversion (Scheme I. 35).



Scheme I. 35. Attempted oxidation of compound **92**.

All the spectroscopic data were in agreement with those reported in the literature.[109]



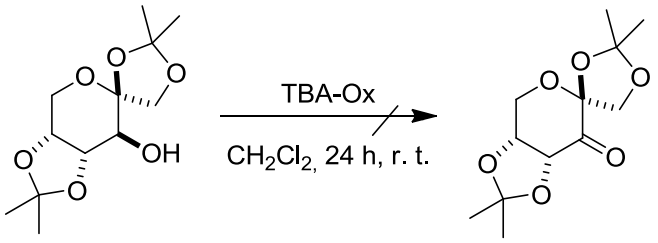
3,4,5-Tri-hydroxy-1,2-*O*-isopropylidene-*β*-D-fructopyranose, 122

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 1.44 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 1.51 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 3.74 (brs, 1H), 3.75 brs, 1H), 3.82 (dd, $^2J_{H6,\ H6'}$=12.6 Hz, $^3J_{H5,\ H6}$= 1.7 Hz, 1H-6), 3.94 (dd, $^2J_{H6,\ H6'}$= 12.6 Hz, $^3J_{H5,\ H6'}$= 1.7 Hz, 1H-6'), 4.0 (m, 1H, H-4), 4.03 (d, $^2J_{H1,\ H1'}$= 8.8 Hz, 1H-1), 4.18 (d, $^2J_{H1,\ H1'}$= 8.8 Hz, 1H-1').

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 26.4 (CH_3-(1,2-*O*-isopropylidene)), 26.6 (CH_3-(1,2-*O*-isopropylidene)), 6.4.2 (CH_2, C-6), 68.8 (CH, C-4), 69.5 (CH, C-3), 72.0 (CH, C-5), 72.0 (CH_2, C-7), 105.9 (C, C-2), 112.1 (C-(1,2-*O*-isopropylidene)).

[109] Tatibouët, A.; Yang, Y.; Morinb, C.; Holman, G. D. *Bioorg. Med. Chem.* **2000**, *8*. 1825.

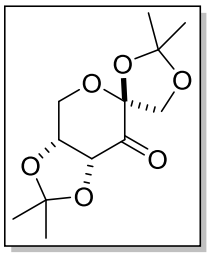
Method C:[94] 3 mmol of tetra-*n*-butylammonium peroxymonosulfate (TBA-Ox) were added to a solution of alcohol **92** (260 mg, 1.0 mmol) in CH_2Cl_2 (1 mL). After stirring at 40 ºC for 48 h the experiment failed to convert **92** into **73**. The starting material was recovered (Scheme I. 36).



92 **73**

Scheme I. 36. Attempted oxidation of compound **92**.

3.1.2.b Preparation of derivative 73



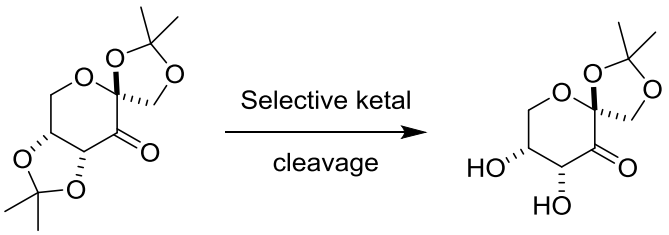
Compound **92** (10.0 g, 38.4 mmol), Et_3BnNCl (0.4 g, 1.9 mmol), $NaIO_4$ (12.4 g, 57.2 mmol) and K_2CO_3 (0.8 g, 5.9 mmol) were vigorously stirred in a mixture of 33 mL of $CHCl_3$ and 33 mL of $RuCl_3$ monohydrate (0.3 g, 1.3 mmol) was added and the reaction mixture was heated to 70 ºC. 2-Propanol (11 mL) was added after 2 h and the suspension was further stirred for 5 h. The reaction mixture was filtered through a Celite® pad which was eluted with CH_2Cl_2 (2 x 35 mL).[86] This solution was mixed with the filtrate, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with saturated Na_2SO_3 (130 mL), brine (100 mL) and water (100 mL). The solid, which was obtained after drying and evaporating the solvents, in quantitative yield, was not further purified.

All the spectroscopic data were in agreement with those reported in the literature.[86]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.38 (s, 6H- CH_3-(1,2-*O*-isopropylidene), CH_3-(4,5-*O*-isopropylidene)), 1.44 (s, 3H -CH_3-(1,2-*O*-isopropylidene)), 1.53 (s, 3H- CH_3-(4,5-*O*-isopropylidene)), 3.97 (d, $^2J_{H1,\ H1'}$ = 9.53 Hz, lH- 1), 4.11 (d, $^2J_{H6,\ H6'}$ = 13.6 Hz, 1H-6), 4.37 (dd, $^2J_{H6,\ H6'}$ = 13.6 Hz, $^3J_{H5,\ H6'}$ = 2.3 Hz, 1H-6'), 4.53 (ddd, $^3J_{H4,\ H5}$ = 5.6 Hz, $^3J_{H5,\ H6}$ = 2.3 Hz, $^3J_{H5,\ H6'}$ = 0.9 Hz, 1H-5), 4.59 (d, $^2J_{H1,\ H1'}$ = 9.53 Hz, 1H-1'), 4.71 (d, $^3J_{H4,\ H5}$ = 5.6 Hz; 1H-4).

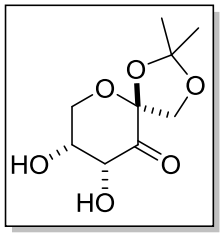
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.1 (CH_3), 26.2 (CH_3), 26.6 (CH_3-(4,5-*O*-isopropylidene)), 27.3 (CH_3-(1,2-*O*-isopropylidene)), 60.2 (CH_2, C-6), 70.1 (CH_2, C-1), 76.0 (CH, C-4), 78.1 (CH, C-5), 104.3 (C, C-2), 110.8 (C-(4,5-*O*-isopropylidene)), 113.9 (C-(1,2-*O*-isopropylidene)), 197.1 (C, C=O).

3.1.3 Preparation of derivative 117 by selective deketalisation of ketone 73



73 **117**

Scheme I. 37. Selective deketalisation of ketone **73**.



Method A:[82] AcOH and water were added at once to the oxidation raw material from the previous step (mmol referred to starting material **92**) (Table I.12). The resulting solution was stirred for 24 h at r. t. The solvents were removed *in vacuo* at r. t. Then, the crude was dissolved in CH_2Cl_2 (50 mL), dried with anh. $MgSO_4$, and filtered. The solid, which was obtained after evaporating the CH_2Cl_2, was not further purified.

Entry	Comp. **73** (mmol)	AcOH (mL)	H_2O (mL)	Conv.[a]
1	38.5	103	26	99%
2	**38.5**	**80**	**20**	**99%**

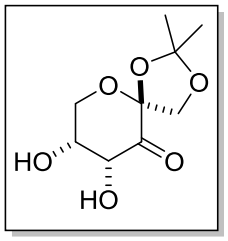
[a] Conversion determined by ^{1}H NMR.

Table I. 12. Selective deketalisation in water with acetic acid.

All the spectroscopic data were in agreement with those reported in the literature.[76a,110]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39 (s, 3H-CH_3-(1,2-*O*-isopropylidene)), 1.54 (s, 3H-CH_3-(1,2-*O*-isopropylidene)), 3.98 (dd, $^2J_{H6,\ H6'}$ = 12.78 Hz, $^3J_{H5,\ H6}$= 2.11 Hz, lH-6), 4.00 (d, $^2J_{H1,\ H1'}$ = 9.46 Hz, lH-1), 4.30 (dd, $^2J_{H6,\ H6'}$= 12.78 Hz, $^3J_{H5,\ H6}$= 1.3 Hz, lH-6), 4.39 (m, 1H-5), 4.67 (d, $^2J_{H1,\ H1'}$= 9.46 Hz, 1H-1'), 4.73 (d, $^3J_{H4,\ H5}$= 3.98 Hz, 1H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.3 (CH_3-(1,2-*O*-isopropylidene)), 26.4 (CH_3-(1,2-*O*-isopropylidene)), 63.5 (CH_2, C-6), 69.6 (CH_2, C-1), 73.7 (CH, C-4), 74.3 (CH, C-5), 104.5 (C, C-2), 113.7 (C-(1,2-*O*-isopropylidene)), 199.2 (C, C=O).

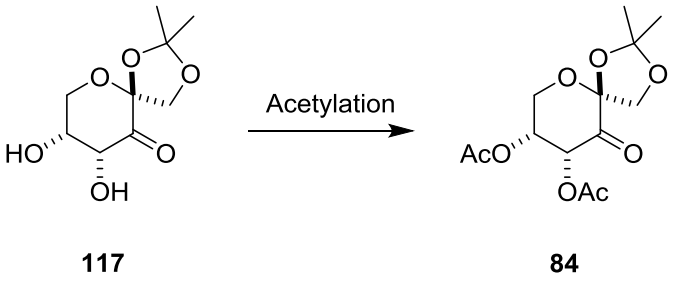


Method B: A solution of cerium(IV) ammonium nitrate (16 mg, 0.028 mmol) in water (0.5 mL) was added in one portion to a stirred solution of compound **73** (218 mg, 1.0 mmol) dissolved in acetonitrile (2.6 mL) and the mixture was stirred overnight. The crude of the reaction was filtered over a mixture of silica gel/Celite® (2 mL, 9:1 w/w). After extraction with CH_2Cl_2 (3 x 5 mL), the combined organic layers were dried over anh. $MgSO_4$, the drying agent filtered and the solvents were removed *in vacuo* to give a white solid in quantitative yield.

All the spectroscopic data were in agreement with those reported in the literature.[76a,110]

[110] Lichtenthaler, F. W.; Doleschal, W.; Hahn, S. *Liebigs Ann. Chem.* **1985**, 2454.

3.1.4 Diacetylation of Compound 117

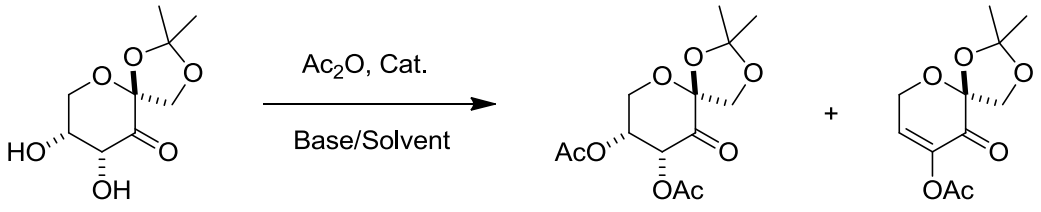


117 **84**

Scheme I. 38. Acetylation reaction.

3.1.4.a Attempted diacetylating reaction conditions in acetic anhydride catalysed by DMAP, NaOAc or $ZnCl_2$

Method A (conventional method): The catalyst (DMAP (0.2–20.0 mol %) or $ZnCl_2$ (1.0–2.5 mol %) or other additives) were added to a solution of **117** (1.0 mmol) under N_2 atmosphere in acetic anhydride (2.1–8.7 equiv.) and in CH_2Cl_2. The reaction mixture was stirred for the indicated time and at the indicated temperature (see tables below). Then, the reaction mixture was filtered through a short SiO_2 gel column and washed with CH_2Cl_2. The residue was dried under reduced pressure to give an oil, which was analysed by ^1H NMR.



117 **84** **123**

Entry	Ac_2O (equiv.)	DMAP (mol %)	py (mmol)	CH_2Cl_2 (mL/mmol)	T (ºC)	t (h)	Ratio **84**/**123**[a]	Yield (%)[b]
1	3.0	20.0	–	5.2	r. t.	24	1/99	[c]
2	3.0	2.0	–	9.3	0 → r. t.	24	65/35	36
3	7.0	1.0	–	–	r. t.	24	81/19	57
4	3.0	0.2	–	9.3	0 → r. t.	24	–/–	s. m.[d]
5	3.0	10.0	3	0.7	r. t.	24	3/97	–
6	3.0	10.0	10	–	r. t.	24	14/86	–

[a] Molar ratio between derivative **84**/**123** has been determined by ^{1}H NMR. [b] The crude was purified by flash chromatography (1:0 to 7:3 hexanes/EtOAc) to give an oil (derivative **84**). [c] Compound **123** was isolated with 43% overall yield after chromatographic purification. [d] s. m. = starting material, compound **117**.

Table I. 13. Conventional method for the synthesis of **84** using DMAP as catalyst.

Entry	Ac_2O (equiv.)	$ZnCl_2$ (mol %)	CH_2Cl_2 (mL/mmol)	T (ºC)	t (h)	Ratio **84**/**123**[a]	Yield (%)[b]
1	8.7	1.0	–	50	0.16	99/1[b]	66
2	8.7	1.0	–	0 → r. t.	3	99/1[b]	76
3	6.0	1.0	–	r. t.	3	99/2[b]	93
4	6.0	1.0	–	r. t.	3	96/4[b,c]	67
5	4.0	2.5	–	r. t.	3	99/1[b]	66
6	2.1	1.0	0.8	r. t.	3	s. m.[d]	–

[a] Determined by ^{1}H NMR. [b] Determined after purifying by flash chromatography (1:0 to 7:3 hexanes/EtOAc) to give an oil (derivative **84**). [c] In the work-up the solvent was removed under reduced pressure at 40 ºC. [d] s. m. = compound **117**.

Table I. 14. Conventional method for the synthesis of **84** using $ZnCl_2$ as catalyst.

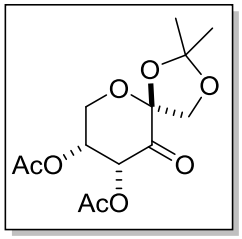
Method B (Microwave irradiation): $ZnCl_2$ (1.0–10 mol %) or NaOAc (1.0–50 mol %) was added to a suspension of diol **117** (1.0 mmol) in Ac_2O (8.7 equiv.). The reaction mixture was stirred and exposed to microwave irradiation (50 W) at 50 ºC for 5 minutes. The reaction mixture was filtered through a short SiO_2 pad, which was further eluted with CH_2Cl_2. The filtrate was concentrated to give an oil, which was analysed by ^{1}H NMR (see Table I. 15).

Entry	Cat. (mol %)	Ratio **84/123**[a]
1	NaOAc (50.0)	43/57
2	NaOAc (10.0)	42/58
3	NaOAc (1.0)	63/37
4	$ZnCl_2$ (10.0)	99/1
5	$ZnCl_2$ (1.0)	99/1

[a] Measured by ^{1}H NMR.

Table I. 15. Synthesis of derivative **84** using microwave irradiation.

3.1.4.b Preparation of 4,5-di-*O*-acetyl-1,2-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose, 84, using the optimised conditions



Method A (conventional method): $ZnCl_2$ (132 mg, 0.96 mmol) was added to a suspension of diol **117** (8.4 g, 38.4 mmol referred to as starting material **92**) in Ac_2O (19.4 mL, 154.0 mmol) and the mixture stirred under N_2 at room temperature for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and the solution was passed through a neutral SiO_2 pad (15 g). SiO_2 was washed with EtOAc (100 mL), the organic solutions were combined, EtOAc was removed *in vacuo* and the resulting oil filtered through SiO_2 (75 g neutral SiO_2, hexanes/EtOAc from 1/0 to 7/3). The oil, which was obtained after drying and evaporating the solvents, was used as the catalyst for the epoxidation of alkenes without any further purification (7.71 g, 66% overall yield).

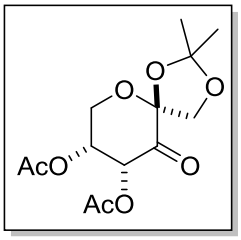
All the spectroscopic data were in agreement with those reported in the literature.[76a]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39 (s, 3H-CH_3-(1,2-*O*-isopropylidene)), 1.54 (s, 3H-CH_3-(1,2-*O*-isopropylidene)), 2.11 (s, 3H-(-$OCOCH_3$)), 2.16 (s, 3H-(-$OCOCH_3$)), 3.94 (dd, $^2J_{H6,\ H6'}$ = 13.42 Hz, $^3J_{H5,\ H6}$= 2.42 Hz, lH-6), 3.98 (d, $^2J_{H1,\ H1'}$ = 9.50 Hz, lH-1), 4.42 (dd, $^2J_{H6,\ H6'}$= 13.42 Hz, $^3J_{H5,\ H6}$= 1.13 Hz, lH-6), 5.60 (m, 1H-5), 4.67 (d, $^2J_{H1,\ H1'}$= 9.46 Hz, 1H-1'), 5.88 (d, $^3J_{H4,\ H5}$= 4.07 Hz, 1H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.4 (CH_3-(1,2-*O*-isopropylidene)), 20.8 (CH_3-(1,2-*O*-isopropylidene)), 26.1 (CH_3-(-OCOCH_3)), 26.5 (CH_3-(-OCOCH_3)), 63.5 (CH_2, C-6), 69.6 (CH_2, C-1), 73.7 (CH, C-4), 74.3 (CH, C-5), 105.1 (C, C-2), 113.9 (C-(1,2-*O*-isopropylidene)),169.4 (C=O-(-OCOCH_3)), 170.2 (C=O-(-OCOCH_3)), 199.2 (C, C=O).

EA: Anal. calcd. for $C_{13}H_{18}O_8$: C, 51.65%; H, 6.00%. Found: C, 51.36%.; H, 6.10%.

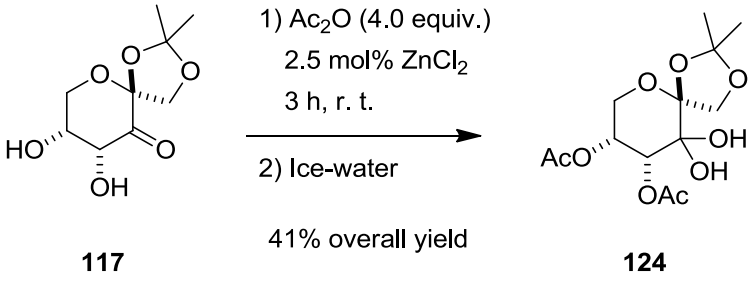
$[\alpha]^{D}_{25}$ = −104 (*c* 0.95, $CHCl_3$) [lit.[76a] $[\alpha]^{D}_{25}$ = −103 (*c* 0.98, $CHCl_3$)].



Method B (microwave irradiation):[97] $ZnCl_2$ (5.3 mg, 0.04 mmol) was added to a suspension of diol **117** (0.8 g, 3.8 mmol referred to as starting material **92**) in Ac_2O (4.2 mL, 33.4 mmol). This mixture was stirred and exposed to microwave irradiation for 5 min at 50 ºC and 50 W. After cooling to room temperature, the mixture was diluted with EtOAc (2 mL), filtered through a neutral SiO_2 pad (1.5 g) and eluted with EtOAc. The organic solutions were combined and removed *in vacuo* to give an oil. The residue was purified by chromatography (7.5 g neutral SiO_2, hexanes/EtOAc from 1/0 to 7/3). After drying and evaporating the solvents, an oil was obtained (0.5 g, 44% overall yield).

All the spectroscopic data were in agreement with those reported in the literature.[76a]

3.1.5 Preparation of compound 124

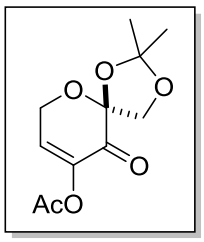


Scheme I. 39. Acetylation of **117** following an aqueous work-up.

Oxidation, selective deketalisation, and acetylation were carried out as described for **84** starting from compound **73** (10.0 g, 38.42 mmol). Ice (20.0 g) was added to the reaction mixture once the acetylation was complete (3 h stirring at room temperature). The precipitate was filtered off the solution, washed with ice-water (2 x 15 mL), and lyophilised to give **124** as a white solid (5.2 g, 41% overall yield).

^{1}H NMR (500 MHz, D_2O) δ (ppm): 1.47 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 1.55 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 2.13 (s, 3H- CH_3-(OAc)), 2.16 (s, 3H- CH_3-(OAc)), 3.85 (dd, $^2J_{H6,\ H6'}$= 13.6 Hz, $^3J_{H5,\ H6}$= 1.8 Hz, 1H-6), 4.06 (d, $^2J_{H7,\ H7'}$= 9.5 Hz, 1H-7), 4.24 (dd, , $^2J_{H6,\ H6'}$= 13.6 Hz, $^3J_{H5,\ H6}$= 1.8 Hz, 1H-6'), 4.39 (d, $^2J_{H7,\ H7'}$= 9.5 Hz, 1H-7'), 5.17 (d, $^3J_{H5,\ H4}$= 4.1 Hz, 1H-4), 5.34 (dd, $^3J_{H5,\ H4}$= 4.1 Hz, $^3J_{H5,\ H6}$=1.8 Hz, 1H-5).
^{13}C NMR (125 MHz, D_2O) δ (ppm): 20.1 (CH_3-(-OAc)), 20.3 (CH_3-(-OAc)), 24.9 (CH_3-(1,2-*O*-isopropylidene)), 26.0 (CH_3-(1,2-*O*-isopropylidene)), 61.4 (CH_2, C-6), 68.7 (CH, C-5), 69.7 (CH, C-4), 70.3 (CH_2, C-1), 91.2 (C, C-3), 106.7 (C, C-2), 113.9 (C-(1,2-*O*-isopropylidene)), 172.7 (C=O-(-$OCOCH_3$)), 173.4 (C=O-(-$OCOCH_3$)).
IR (ATR) (cm^{-1}): 3467, 1735.
EA: Anal. calcd. for $C_{13}H_{20}O_9$: C, 49.00; H, 6.51; found: C, 48.75; H, 6.29.
HRMS: calcd for $C_{13}H_{20}O_9Na$ ($[M+Na]^+$): 343.1005; found: 343.1008.
$[\alpha]^D_{25}$ = −116 (*c* 0.98, $CHCl_3$).
M.p. = 91.1–93.7 ºC.

3.1.6 Preparation of (5*S*)-9-acetoxy-2,2-dimethyl-1,3,6-trioxaspiro[4.5]dec-8-en-10-one, 123



DMAP (0.94 g, 7.7 mmol) and Ac_2O (14.5 mL, 115.5 mmol) were added to a solution of **117** (8.87 g, 38.5 mmol referred to starting material **92**) in 200 mL CH_2Cl_2 at r. t. for 24 h under N_2 atmosphere. The reaction mixture was filtered through a short SiO_2 pad. The filtrate was concentrated and the residue was purified by flash

chromatography (1:0 to 3:2 hexanes/EtOAc) to give **123** as an oil (4.26 g, 17.57 mmol, 46% overall yield). The compound can be recrystallised from hexanes to get a white solid (3.37 g, 13.91 mmol, 36% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 1.38 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 1.52 (s, 3H- CH_3-(1,2-*O*-isopropylidene)), 2.20 (s, 3H- CH_3-(OAc)), 3.98 (d, $^{2}J_{H1, H1'}$= 9.2Hz, 1H-1), 4.42 (dd, $^{2}J_{H6, H6'}$=18.6Hz, $^{3}J_{H5, H6}$=4.3 Hz, 1H-6), 4.59 (d, $^{2}J_{H1, H1'}$= 9.2 Hz, 1H-1'), 4.79 (dd, $^{2}J_{H6, H6'}$= 18.6Hz, $^{3}J_{H5, H6'}$= 1.8 Hz, 1H-6'), 6.68 (dd, $^{3}J_{H5, H6}$= 4.3 Hz, $^{3}J_{H5, H6'}$=1.8 Hz, 1H-5).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 20.2 (CH_3-(-OAc)), 25.6 (CH_3-(1,2-*O*-isopropylidene)), 26.5 (CH_3-(1,2-*O*-isopropylidene)), 59.9 (CH_2, C-6), 70.8 (CH_2, C-1), 102.9 (C, C-2), 113.7 (C-(1,2-*O*-isopropylidene)), 133.5 (CH, C-5), 140.9 (C, C-4), 168.0 (C=O-(-$OCOCH_3$)), 182.1 (C, C=O).

IR (ATR) (cm^{-1}): 1764, 1702.

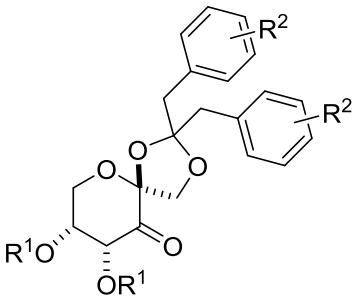
EA: Anal. calcd. for $C_{11}H_4O_6$: C, 54.54; H, 5.83. Found: C, 54.20; H, 6.07.

HRMS: calcd for $C_{11}H_4O_6$ (M^+): 265.0688; found: 265.0685.

$[\alpha]^{D}_{25}$ = –129 (*c* 0.90, $CHCl_3$).

M.p. = 63.7–64.4 ºC.

3.2. Synthetic attempts of new organocatalysts for the epoxidation of styrene or other terminal olefins

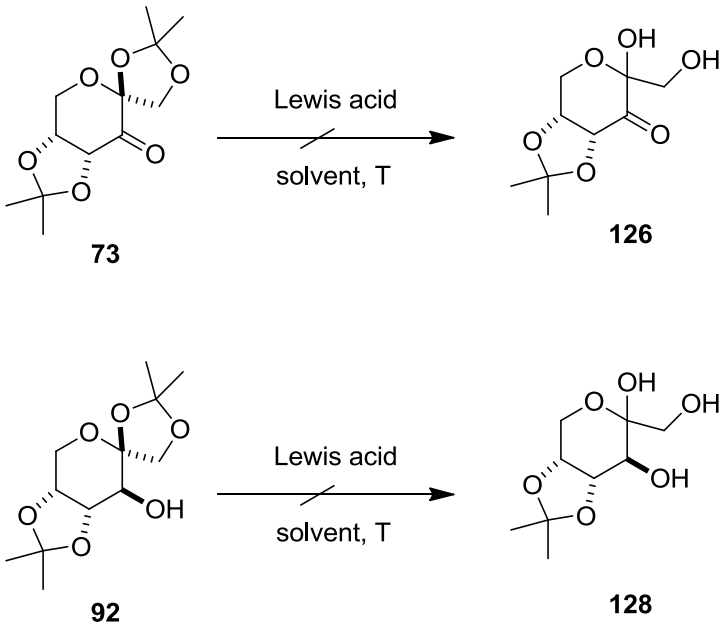


121

Figure I. 12. Attempts to synthesise new epoxidation catalysts for terminal olefins.

3.2.1 Attempted synthesis of 121 by strategy A.

Attempted synthesis of **121** by strategy A (path A). The two possible paths for the synthesis of **121** have been described throughout the discussion of this thesis (Scheme I. 27).



73 **126** **92** **128**

Scheme I. 40. Attempted deprotection of spirocyclic ketal groups in **73** and **92**.

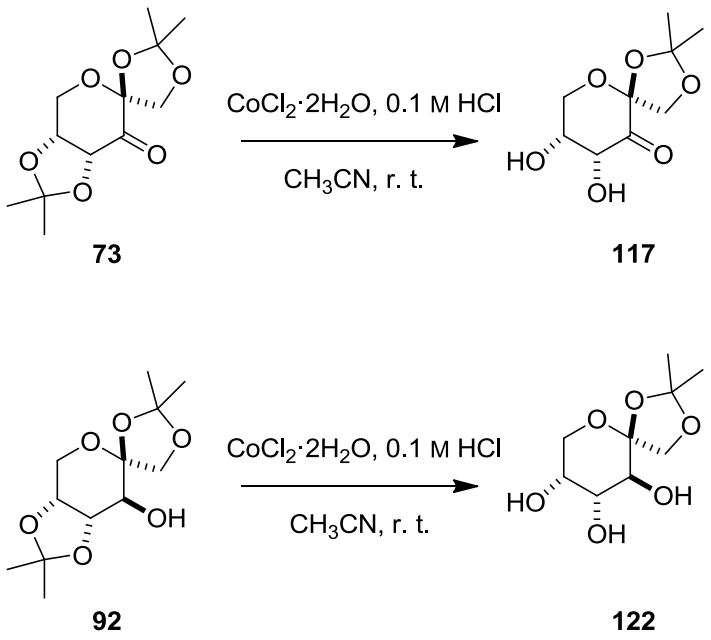
Method A (using $CoCl_2 \cdot 2H_2O$):[99] $CoCl_2 \cdot 2H_2O$ and H_2O (if necessary, see table below) were added to a solution of **73** or **92** (1.0 mmol) in acetonitrile. The solvent was removed at reduced pressure after stirring for 24 hours at the temperature indicated in the table mentioned. The starting material was recovered.

Entry	Comp. (mmol)	Lewis acid (mol %)	Solvent (mL)	T	Conv. (%)
1	**73** (1)	$CoCl_2 \cdot 2H_2O$ (1)	CH_3CN (30)	55	n. c.[b]
2	**92** (1)	$CoCl_2 \cdot 2H_2O$ (1)	CH_3CN (3)	95	n. c.
3	**92** (1)	$CoCl_2 \cdot 2H_2O$ (10)	CH_3CN (30)	55	n. c.
4	**73** (1)	$CoCl_2 \cdot 2H_2O$ (10)	CH_3CN/H_2O (3/0.3)	55	n. c.
5	**92** (1)	$CoCl_2 \cdot 2H_2O$ (10)	CH_3CN/H_2O (3/0.3)	55	n. c.

[a] Determined by ^1H NMR. [b] n. c.: no conversion (starting material was recovered).

Table I. 16. Attempts to synthesise compound **126** or **128** by strategy A.

Method B (using $CoCl_2 \cdot 2H_2O$): 0.1 M HCl (0.3 mL) was slowly added to a solution of **73** or **92** (1.0 mmol) and $CoCl_2 \cdot 2H_2O$ (1.6–16.6 mg, 1–10 mol %) in acetonitrile (3 mL). After 1 h at r. t., the solvent was removed at reduced pressure to afford **117** or derivative **122**, respectively, as a solid in quantitative yield (Scheme I. 41.).



Scheme I. 41. Ketal deprotection attempts using a cobalt salt as Lewis acid.

All the spectroscopic data were in agreement with those reported in the literature for compound **117**[76a,110] and derivative **122**.[109]

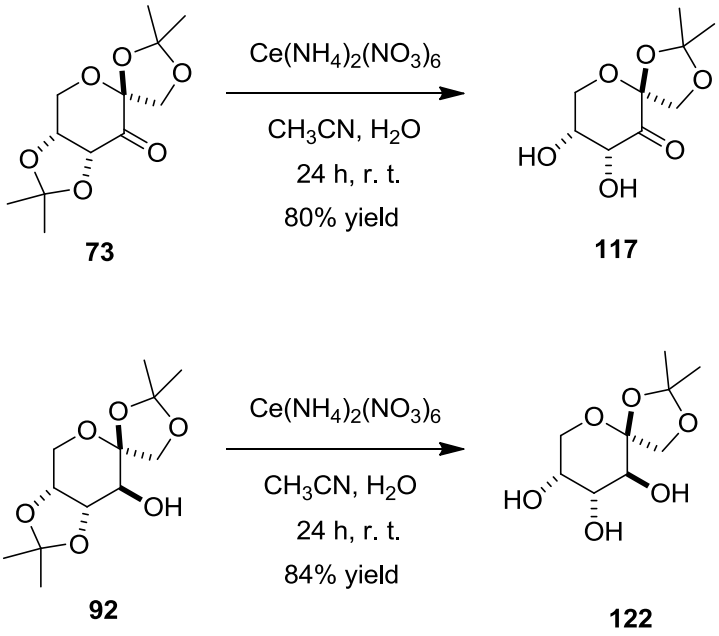
Method C (using $InCl_3$):[99] Anhydrous $InCl_3$ (5 mg, 0.039 mmol) was added to a solution of **92** (100 mg, 0.39 mmol) in methanol (1.1 mL) and the solution was heated at 60 ºC for 24 h. Once the solvent was removed under reduced pressure, the starting material was recovered.

Method D (using $CeCl_3 \cdot 7H_2O$):[100] $CeCl_3 \cdot 7H_2O$ (74 mg, 0.19 mmol) was added to a solution of **92** (100 mg, 0.39 mmol) in acetonitrile (2 mL) and the solution was heated at 60 ºC for 24 h. Once the solvent was removed under reduced pressure, the starting material was recovered.

Method E (using $FeCl_3/SiO_2$):[101a] $FeCl_3/SiO_2$ (8.6 mg, 0.039 mmol) was added to a solution of **92** (100 mg, 0.39 mmol) in $CHCl_3$ (1.2 mL) and the mixture was stirred at r. t. for 24 h. Then, the mixture was filtered and the silica gel was washed with CH_2Cl_2. Once the solvent was removed under reduced pressure, the starting material was recovered.

Preparation of ferric chloride adsorbed on silica gel: Silica gel (10 g, 70–230 mesh, E. Merck Kiesegel 60) was added to a solution of $FeCl_3 \cdot 6H_2O$ (1.2 g, 3.8 mmol) in acetone (16 mL) at r. t. The solvent was removed using a rotary evaporator at 30 ºC under reduced pressure (15 mmHg). The mixture was further kept under vacuum (0.1 mmHg) at 60 ºC for 30 min. The resulting yellow powder could be stored for extended periods under N_2 atmosphere at r. t. without any observable change.

Method F (using $Ce(NH_4)_2(NO_3)_6$):[95] $Ce(NH_4)_2(NO_3)_6$ (16 mg, 0.028 mmol) was added to a stirred solution of **73** or **92** (0.5 g, 1.9 mmol) in CH_3CN/H_2O (3.1:1.0 mL) at r. t. After 24 h, the reaction mixture was filtered through a mixture of Celite®/silica gel (9:1) and eluted with MeOH. The organic solutions were combined and removed *in vacuo*. The resulting oil was dissolved in CH_2Cl_2, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to give a white solid. Physical and spectroscopic data were in agreement with **117**[110] (80% overall yield) and **122**[109] (84% overall yield), respectively (Scheme I. 42).

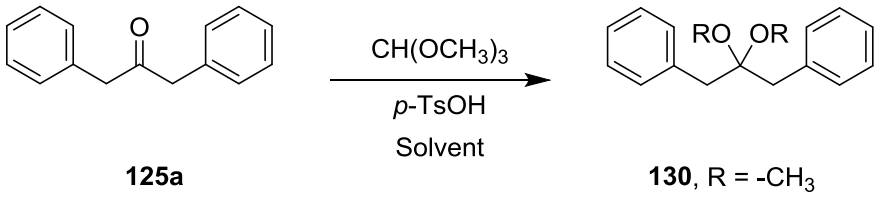


Scheme I. 42. Selective deketalisation using cerium(IV) ammonium nitrate as catalyst.

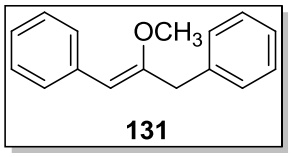
3.2.2 Attempted synthesis of 121 by strategy B.

The two possible paths for the synthesis of **121** were described in the discussion (Scheme I. 27).

3.2.2.a Synthesis of (2,2-dialkoxypropane-1,3-diyl)dibenzene, 130



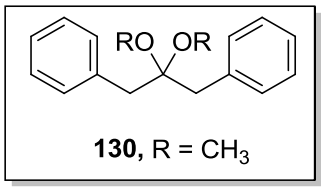
Scheme I. 43. Synthesis of (2,2-dialkoxypropane-1,3-diyl)dibenzene (**130**).



131

Method A (using H_2SO_4 as catalyst):[102a] Trimethyl orthoformate (TMOF) (0.26 mL, 2.4 mmol) and 1 drop of concentrated H_2SO_4 were added to a solution of 1,3-diphenylacetone **125a** (0.21 g, 1.0 mmol) in anhydrous MeOH (0.5 mL), and stirred for 24 h at r. t. The reaction was followed by TLC (8:2 hexanes/EtOAc) and after completion, NEt_3 (1.0 mL) was added. Solvents were removed in *vacuo* to afford compound **131** in quantitative yield.

Method B (using *p*-TsOH as catalyst):[111] Trimethyl orthoformate (0.26 mL, 2.4 mmol) and *p*-TsOH (10 mg, 0.01 mmol) were added to a solution of 1,3-diphenylacetone **125a** (0.21 g, 1.0 mmol) in anhydrous CH_2Cl_2 (5 mL), and stirred for 24 h at reflux. The reaction was followed by TLC (8:2 hexanes/EtOAc) and after completion, NEt_3 (1.0 mL) was added. Solvents were removed in *vacuo* to afford a mixture of dimethyl ketal **130** and starting material as the major product.



130, R = CH_3

Method C (using *p*-TsOH and K10 montmorillonite clay):[102b] To a well-stirred suspension of K10 montmorillonite clay (190 mg) in anhydrous methanol (4 mL), trimethyl orthoformate (3 mL, 2.95 mmol) and *p*-TsOH (10 mg, 0.01 mmol) were added successively to 1,3-diphenylacetone **125a** (1.0 g, 22.2 mmol) dissolved in the minimal amount of anhydrous methanol (4 mL). The mixture was stirred at r. t. for 24 h and the reaction was monitored by TLC (8:2 hexanes/EtOAc). After completion, solid residues were removed by filtration and washed with CH_2Cl_2 (3 x 10 mL). The filtrate was successively washed with saturated aqueous Na_2CO_3 solution (10 mL) and water (10 mL) and dried over anh. $MgSO_4$. Solvents were removed *in vacuo* to give the desired dimethyl ketal **130** as a colourless oil of high chemical purity (1.3 g, 96% yield).

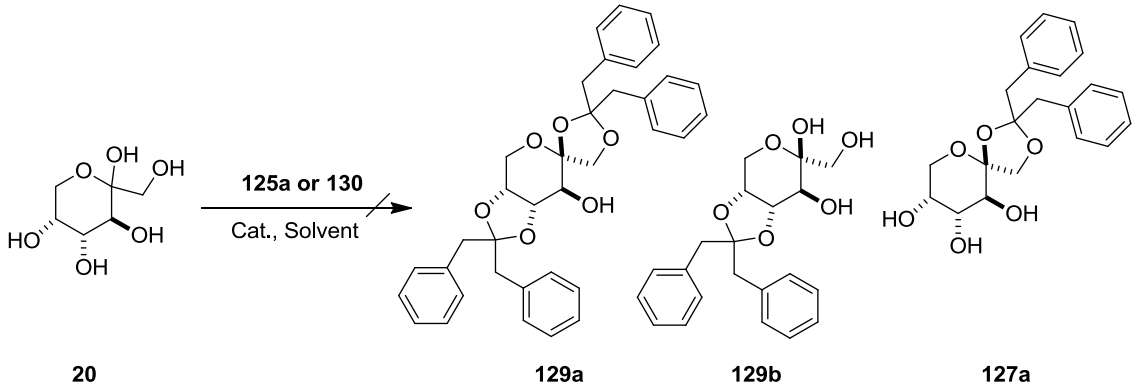
All the spectroscopic data were in agreement with those reported in the literature.[111]

[111] Altava, B.; Burguete, M. I.; García-Verdugo, E.; Santiago, V. L.; Miravet J. F.; Vicent, M. J. *Tetrahedron: Assymetry* **2000**, *11*, 4885.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.83 (s, 4H), 3.07 (s, 6H), 7.18–7.05 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 38.9, 47.3, 103.1, 125.9, 127.6, 130.2, 136.8.

3.2.2.b Attempts to synthesise 129a.



Scheme I. 44. Attempts to synthesise **129a**.

D-Fructose **20** (18 mg, 0.1 mmol) was dissolved in the required volume of solvent (2–6 mL), and 4 Å molecules sieves, 1,3-diphenylacetone **125a** (2.6–8.0 equiv.) or (2,2-dimethoxypropane-1,3-diyl)dibenzene **130** (2.6–4.0 equiv.) and the corresponding additive (*p*-TsOH (0.01 equiv.), PPTs (0.02–0.04 equiv.), perchloric acid (1 drop), H_2SO_4 (1 drop), $CuSO_4$ (1.3 equiv.), $ZnCl_2$ (0.1 equiv.)) were added into the reaction mixture (see Table I. 17). The mixture was stirred for 24 h at r. t. and the molecular sieves and other insoluble solids were filtered off. Solvents were removed at reduced pressure. ^{1}H NMR analysis of the crude mixture did not indicate the formation of ketals **129a** or **129b** or **127a**.

Entry	Comp. (equiv.)	Cat. (mol %)	Solvent (mL)	Conv. (%)[a]
1	**130** (2.6)	*p*-TsOH (1)	CH_3CN (2.0)	n. r.[b]
2	**130** (2.6)	*p*-TsOH, $HClO_4$ (1/1 drop)	THF (1.5)	n. r.
3	**130** (4.0)	PPTs (2)	THF (1.0)	n. r.
4	**130** (4.0)	PPTs (2)	CH_3CN (2.0)	n. r.
5	**130** (2.6)	PPTs (4)	DMF (1.0)	n. r.
6	**130** (4.0)	PPTs (2)	1,4-dioxane (2.0)	n. r.
7	**130** (2.6)	$CuSO_4$, PPTs (130/1)	1,4-dioxane (2.0)	n. r.
8	**130** (2.6)	$CuSO_4$, H_2SO_4 (130/1 drop)	1,4-dioxane (2.0)	n. r.
9	**130** (4.0)	$ZnCl_2$ (10)	1,4-dioxane (2.0)	n. r.
10	**130** (4.0)	$ZnCl_2$ (10)	DMF (1.0)	n. r.
11	**125a** (8.0)	H_2SO_4 (1 drop)	CH_3CN (1.0)	n. r.
12	**125a** (2.6) + **130** (2.6)	$HClO_4$ (1 drop)	1,4-dioxane (2.0)	n. r.
13	**125a** (4.0)	$ZnCl_2$ (10)	1,4-dioxane (2.0)	n. r.
14	**125a** (4.0)	$ZnCl_2$ (10)	DMF (1.0)	n. r.

[a] Determined by ^{1}H NMR (recorded in DMSO-d_6). [b] n. r. = no reaction.

Table I. 17. Attempts to synthesise compound **129a**.

4. X-Ray data

4.1 X-Ray data for compound 123

The figure below shows the Ortep-Plot (ellipsoids drawn at 50% probability level) of the molecular structure of **123**.

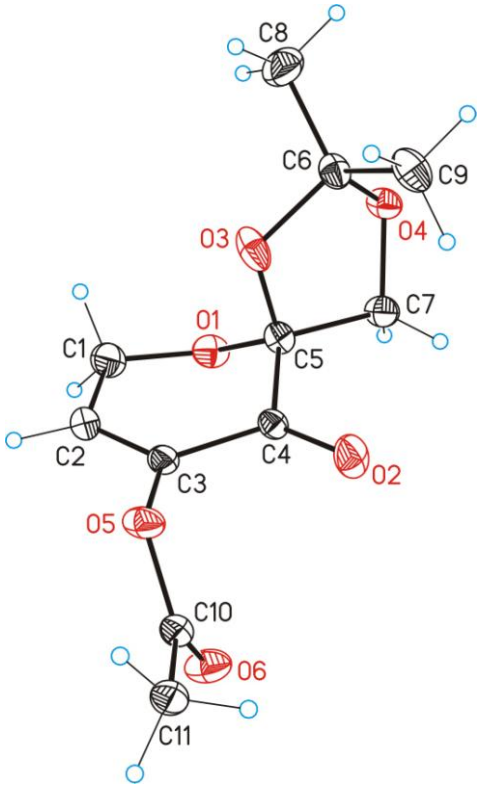


Figure I. 13. Crystal structure of compound **123**.

Parameter	Cristal Data
Identification code	Compound **123**
Empirical formula	$C_{11}H_{14}O_6$
Formula weight	242.22
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.3840(5) Å, α = 90°. b = 12.0829(12) Å, β = 90°. c = 17.7316(16) Å, γ = 90°.
Volume	1153.52(19) $Å^3$
Z	4
Density (calculated)	1.395 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	512
Crystal sise	0.40 x 0.04 x 0.02 mm^3
Theta range for data collection	2.85 to 40.31°
Index ranges	$-9 \le h \le 9$, $-21 \le k \le 17$, $-32 \le l \le$
Reflections collected	27298
Independent reflections	7110 [R(int) = 0.0299]
Completeness to theta = 40.31°	98.6 %
Absorption correction	SADABS (Bruker-Nonius)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	7110/0/229
Goodness-of-fit on F^2	1.101
Final R indices [I>2sigma(I)]	R1 = 0.0378, wR2 = 0.1030
R indices (all data)	R1 = 0.0389, wR2 = 0.1045
Absolute structure parameter	0.1(4)
Largest diff. peak and hole	0.437 and –0.514 $e.Å^{-3}$

Table I. 18. Crystal data and structure refinement for **123.**

Bond	Bond lengths [Å]	Bond	Bond lengths
O(1)-C(5)	1.3995(7)	O(5)-C(10)	1.3627(11)
O(1)-C(1)	1.4238(9)	O(5)-C(3)	1.3951(11)
C(1)-C(2')	1.489(2)	C(2)-C(3)	1.3269(15)
C(1)-C(2)	1.5021(16)	C(3)-C(4)	1.4704(12)
C(5)-O(3)	1.4155(7)	C(10)-O(6)	1.2024(12)
C(5)-C(7)	1.5240(8)	C(10)-C(11)	1.468(4)
C(5)-C(4)	1.5246(10)	O(2')-C(4')	1.214(2)
C(5)-C(4')	1.5852(18)	O(5')-C(10')	1.366(2)
C(6)-O(4)	1.4173(7)	O(5')-C(3')	1.3973(19)
C(6)-O(3)	1.4442(7)	C(2')-C(3')	1.338(3)
C(6)-C(8)	1.5103(10)	C(3')-C(4')	1.471(2)
C(6)-C(9)	1.5207(9)	C(10')-O(6')	1.204(2)
C(7)-O(4)	1.4291(7)	C(10')-C(11')	1.527(9)
O(2)-C(4)	1.2151(12)		

Table I. 19. Bond lengths [Å] **123**.

Bond	Bond angles [°]	Bond	Bond angles
C(5)-O(1)-C(1)	114.28(5)	C(10)-O(5)-C(3)	115.80(7)
O(1)-C(1)-C(2')	108.46(10)	C(3)-C(2)-C(1)	120.65(9)
O(1)-C(1)-C(2)	115.50(6)	C(2)-C(3)-O(5)	121.41(9)
C(2')-C(1)-C(2)	18.92(9)	C(2)-C(3)-C(4)	121.48(8)
O(1)-C(5)-O(3)	111.45(5)	O(5)-C(3)-C(4)	116.28(8)
O(1)-C(5)-C(7)	109.06(5)	O(2)-C(4)-C(3)	123.02(9)
O(3)-C(5)-C(7)	104.32(4)	O(2)-C(4)-C(5)	122.82(8)
O(1)-C(5)-C(4)	112.79(5)	C(3)-C(4)-C(5)	113.77(7)
O(3)-C(5)-C(4)	99.53(6)	O(6)-C(10)-O(5)	122.35(8)
C(7)-C(5)-C(4)	118.87(6)	O(6)-C(10)-C(11)	124.76(14)
O(1)-C(5)-C(4')	103.99(8)	O(5)-C(10)-C(11)	112.88(14)
O(3)-C(5)-C(4')	116.81(9)	C(10')-O(5')-C(3')	114.66(12)
C(7)-C(5)-C(4')	111.17(8)	C(3')-C(2')-C(1)	122.07(16)
C(4)-C(5)-C(4')	17.28(6)	C(2')-C(3')-O(5')	121.81(15)
O(4)-C(6)-O(3)	104.51(4)	C(2')-C(3')-C(4')	121.09(15)
O(4)-C(6)-C(8)	109.54(6)	O(5')-C(3')-C(4')	117.08(13)
O(3)-C(6)-C(8)	108.35(6)	O(2')-C(4')-C(3')	123.09(16)
O(4)-C(6)-C(9)	111.65(5)	O(2')-C(4')-C(5)	123.37(15)
O(3)-C(6)-C(9)	109.24(5)	C(3')-C(4')-C(5)	112.98(13)
C(8)-C(6)-C(9)	113.14(6)	O(6')-C(10')-O(5')	122.25(14)
O(4)-C(7)-C(5)	103.04(4)	O(6')-C(10')-C(11')	124.3(4)
C(5)-O(3)-C(6)	109.33(4)	O(5')-C(10')-C(11')	113.2(4)
C(6)-O(4)-C(7)	106.05(4)		

Table I. 20. Bond angles [°] for **123**.

Bond	Torsion angles [°]	Bond	Torsion angles [°]
C(5)-O(1)-C(1)-C(2')	-58.79(12)	O(1)-C(5)-C(4)-O(2)	148.28(12)
C(5)-O(1)-C(1)-C(2)	-39.82(10)	O(3)-C(5)-C(4)-O(2)	-93.50(13)
C(1)-O(1)-C(5)-O(3)	-55.67(6)	C(7)-C(5)-C(4)-O(2)	18.77(16)
C(1)-O(1)-C(5)-C(7)	-170.32(5)	C(4')-C(5)-C(4)-O(2)	86.2(3)
C(1)-O(1)-C(5)-C(4)	55.31(8)	O(1)-C(5)-C(4)-C(3)	-38.65(11)
C(1)-O(1)-C(5)-C(4')	71.01(9)	O(3)-C(5)-C(4)-C(3)	79.56(9)
O(1)-C(5)-C(7)-O(4)	96.53(5)	C(7)-C(5)-C(4)-C(3)	-168.17(7)
O(3)-C(5)-C(7)-O(4)	-22.65(6)	C(4')-C(5)-C(4)-C(3)	-100.8(3)
C(4)-C(5)-C(7)-O(4)	-132.28(7)	C(3)-O(5)-C(10)-O(6)	-7.53(14)
C(4')-C(5)-C(7)-O(4)	-149.39(9)	C(3)-O(5)-C(10)-C(11)	171.5(2)
O(1)-C(5)-O(3)-C(6)	-115.25(5)	O(1)-C(1)-C(2')-C(3')	16.2(3)
C(7)-C(5)-O(3)-C(6)	2.30(7)	C(2)-C(1)-C(2')-C(3')	-99.0(4)
C(4)-C(5)-O(3)-C(6)	125.53(6)	C(1)-C(2')-C(3')-O(5')	-175.66(17)
C(4')-C(5)-O(3)-C(6)	125.43(8)	C(1)-C(2')-C(3')-C(4')	6.1(4)
O(4)-C(6)-O(3)-C(5)	19.21(7)	C(10')-O(5')-C(3')-C(2')	-106.9(2)
C(8)-C(6)-O(3)-C(5)	135.94(6)	C(10')-O(5')-C(3')-C(4')	71.3(2)
C(9)-C(6)-O(3)-C(5)	-100.40(6)	C(2')-C(3')-C(4')-O(2')	179.1(2)
O(3)-C(6)-O(4)-C(7)	-34.25(6)	O(5')-C(3')-C(4')-O(2')	0.8(3)
C(8)-C(6)-O(4)-C(7)	-150.16(5)	C(2')-C(3')-C(4')-C(5)	7.4(3)
C(9)-C(6)-O(4)-C(7)	83.71(6)	O(5')-C(3')-C(4')-C(5)	-170.86(13)
C(5)-C(7)-O(4)-C(6)	35.24(6)	O(1)-C(5)-C(4')-O(2')	146.2(2)
O(1)-C(1)-C(2)-C(3)	7.22(16)	O(3)-C(5)-C(4')-O(2')	-90.6(2)
C(2')-C(1)-C(2)-C(3)	79.2(3)	C(7)-C(5)-C(4')-O(2')	28.9(2)
C(1)-C(2)-C(3)-O(5)	177.45(10)	C(4)-C(5)-C(4')-O(2')	-90.9(3)
C(1)-C(2)-C(3)-C(4)	8.27(19)	O(1)-C(5)-C(4')-C(3')	-42.20(17)
C(10)-O(5)-C(3)-C(2)	113.21(12)	O(3)-C(5)-C(4')-C(3')	81.04(16)
C(10)-O(5)-C(3)-C(4)	-77.07(11)	C(7)-C(5)-C(4')-C(3')	-159.42(13)
C(2)-C(3)-C(4)-O(2)	-179.83(14)	C(4)-C(5)-C(4')-C(3')	80.7(3)
O(5)-C(3)-C(4)-O(2)	10.46(17)	C(3')-O(5')-C(10')-O(6')	2.4(2)
C(2)-C(3)-C(4)-C(5)	7.12(16)	C(3')-O(5')-C(10')-C(11')	177.0(5)
O(5)-C(3)-C(4)-C(5)	-162.59(8)		

Table I. 21. Torsion angles [°] for **123.**

4.2 X-Ray data for compound 124

The figure below shows the Ortep-Plot (ellipsoids drawn at 50% probability level) of the molecular structure of **124**.

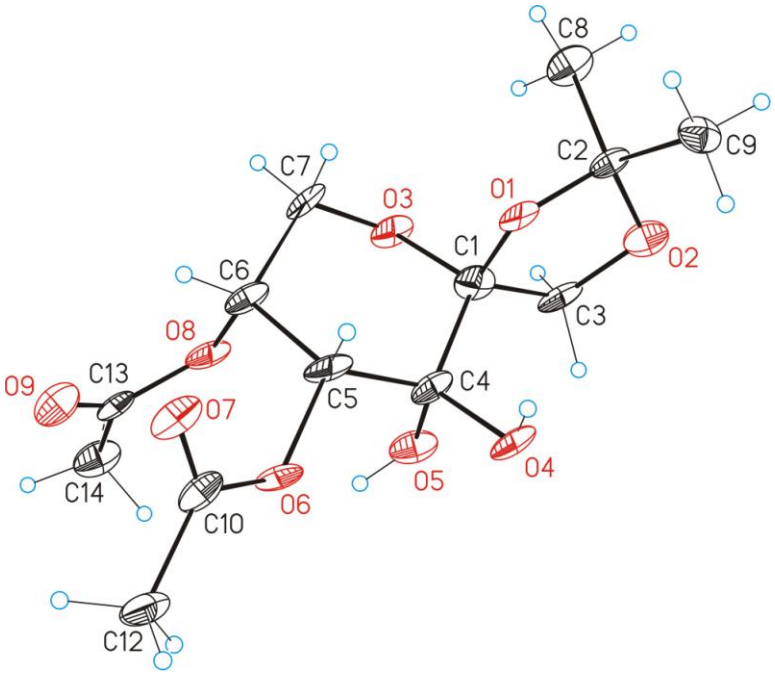


Figure I. 14. Crystal structure of compound **124**.

Parameter	Crystal Data
Identification code	**Hydrate 124**
Empirical formula	$C_{13}H_{20}O_9$
Formula weight	320.29
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12$
Unit cell dimensions	a = 22.246(11) Å, α = 90°. b = 23.698(11) Å, β = 90° c = 5.599(2) Å, γ = 90°
Volume	2952(2) $Å^3$
Z	8
Density (calculated)	1.441 Mg/m^3
Absorption coefficient	0.123 mm^{-1}
F(000)	1360
Crystal sise	0.30 x 0.01 x 0.01 mm^3*
Theta range for data collection	2.51 to 23.50°.*
Index ranges	$-22 \leq h \leq 24$, $-26 \leq k \leq 26$, $-6 \leq l \leq 6$
Reflections collected	21494
Independent reflections	4304 [R(int) = 0.2741]
Completeness to theta = 23.50°	98.6%
Absorption correction	SADABS (Bruker-Nonius)
Max. and min. transmission	0.9988 and 0.9640
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4304/72/409
Goodness-of-fit on F^2	0.979
Final R indices [I>2sigma(I)]	R1 = 0.0701, wR2 = 0.1512
R indices (all data)	R1 = 0.1505, wR2 = 0.1906
Absolute structure parameter	–2(2)
Largest diff. peak and hole	0.401 and –0.463 e.$Å^{-3}$

* Only extremely small crystal needles of **124** could be grown. The structure obtained using these crystal needles is of low resolution but of enough quality to unambiguously confirm its chemical structure.

Table I. 22. Crystal data and structure refinement for **124**.

Bond	Bond lengths [Å]	Bond	Bond lengths [Å]
O(1B)-C(1B)	1.402(8)	O(7B)-C(10B)	1.200(8)
O(1B)-C(2B)	1.445(8)	O(8B)-C(13B)	1.355(9)
C(1B)-O(3B)	1.440(9)	O(9B)-C(13B)	1.201(8)
C(1B)-C(3B)	1.513(10)	C(10B)-C(12B)	1.484(10)
C(1B)-C(4B)	1.538(10)	C(6A)-O(8A)	1.444(8)
O(2B)-C(3B)	1.410(8)	C(6A)-C(7A)	1.517(10)
O(2B)-C(2B)	1.413(8)	O(6A)-C(10A)	1.365(8)
C(2B)-C(9B)	1.490(10)	O(7A)-C(10A)	1.212(8)
C(2B)-C(8B)	1.526(10)	O(8A)-C(13A)	1.339(9)
O(3B)-C(7B)	1.397(8)	C(13B)-C(14B)	1.480(10)
C(4B)-O(5B)	1.397(8)	C(1A)-O(3A)	1.404(9)
C(4A)-O(5A)	1.387(8)	C(1A)-O(1A)	1.408(8)
C(4A)-O(4A)	1.401(9)	C(1A)-C(3A)	1.523(9)
C(4A)-C(5A)	1.513(9)	C(1A)-C(4A)	1.575(10)
C(5A)-O(6A)	1.461(8)	O(1A)-C(2A)	1.438(8)
C(5A)-C(6A)	1.538(10)	C(2A)-O(2A)	1.421(8)
C(4B)-O(4B)	1.398(9)	C(2A)-C(8A)	1.487(10)
C(4B)-C(5B)	1.528(10)	C(2A)-C(9A)	1.523(10)
C(5B)-O(6B)	1.448(8)	O(2A)-C(3A)	1.402(8)
C(5B)-C(6B)	1.528(10)	O(3A)-C(7A)	1.430(8)
C(6B)-O(8B)	1.460(8)	O(9A)-C(13A)	1.196(9)
C(6B)-C(7B)	1.533(10)	C(10A)-C(11A)	1.466(10)
O(6B)-C(10B)	1.356(8)	C(13A)-C(14A)	1.486(10)

Table I. 23. Bond lengths [Å].

Bond	Bond angles [°]	Bond	Bond angles [°]
C(1B)-O(1B)-C(2B)	107.0(5)	C(5A)-C(4A)-C(1A)	108.3(6)
O(1B)-C(1B)-O(3B)	111.3(6)	O(2B)-C(2B)-O(1B)	104.3(5)
O(1B)-C(1B)-C(3B)	104.8(5)	O(2B)-C(2B)-C(9B)	109.7(6)
O(3B)-C(1B)-C(3B)	107.4(6)	O(1B)-C(2B)-C(9B)	109.6(5)
O(1B)-C(1B)-C(4B)	109.6(6)	O(2B)-C(2B)-C(8B)	111.5(6)
O(3B)-C(1B)-C(4B)	109.1(5)	O(1B)-C(2B)-C(8B)	109.7(6)
C(3B)-C(1B)-C(4B)	114.5(6)	C(9B)-C(2B)-C(8B)	111.9(6)
C(3B)-O(2B)-C(2B)	107.2(5)	C(7B)-O(3B)-C(1B)	113.7(5)
O(5B)-C(4B)-O(4B)	106.8(5)	O(2B)-C(3B)-C(1B)	105.8(5)
O(5B)-C(4B)-C(5B)	113.2(6)	C(4B)-C(5B)-C(6B)	113.5(6)
O(4B)-C(4B)-C(5B)	110.9(6)	O(8B)-C(6B)-C(5B)	111.4(6)
O(5B)-C(4B)-C(1B)	104.2(6)	O(8B)-C(6B)-C(7B)	106.9(6)
O(4B)-C(4B)-C(1B)	110.8(6)	C(5B)-C(6B)-C(7B)	108.3(6)
C(5B)-C(4B)-C(1B)	110.8(6)	C(10B)-O(6B)-C(5B)	117.2(5)
O(6B)-C(5B)-C(4B)	106.3(5)	O(3B)-C(7B)-C(6B)	112.1(5)
O(6B)-C(5B)-C(6B)	108.7(6)	C(13B)-O(8B)-C(6B)	117.2(5)
O(7B)-C(10B)-C(12B)	124.6(7)	O(7B)-C(10B)-O(6B)	124.2(7)
O(6B)-C(10B)-C(12B)	111.2(6)	O(3A)-C(1A)-O(1A)	112.1(5)
O(9B)-C(13B)-O(8B)	122.8(7)	O(3A)-C(1A)-C(3A)	108.0(6)
O(9B)-C(13B)-C(14B)	126.6(7)	O(1A)-C(1A)-C(3A)	104.4(6)
O(8B)-C(13B)-C(14B)	110.6(6)	O(3A)-C(1A)-C(4A)	110.7(6)
C(3A)-C(1A)-C(4A)	113.3(6)	O(1A)-C(1A)-C(4A)	108.3(5)
C(1A)-O(1A)-C(2A)	108.0(5)	O(6A)-C(5A)-C(4A)	105.6(5)
O(2A)-C(2A)-O(1A)	104.3(5)	O(6A)-C(5A)-C(6A)	109.1(5)
O(2A)-C(2A)-C(8A)	109.3(6)	C(4A)-C(5A)-C(6A)	112.6(6)
O(1A)-C(2A)-C(8A)	109.0(6)	O(8A)-C(6A)-C(7A)	109.2(6)
O(2A)-C(2A)-C(9A)	111.2(6)	O(8A)-C(6A)-C(5A)	109.9(5)
O(1A)-C(2A)-C(9A)	109.2(5)	C(7A)-C(6A)-C(5A)	109.9(6)
C(8A)-C(2A)-C(9A)	113.5(6)	C(10A)-O(6A)-C(5A)	117.1(5)
C(3A)-O(2A)-C(2A)	107.9(5)	O(3A)-C(7A)-C(6A)	110.5(6)
O(2A)-C(3A)-C(1A)	105.9(5)	C(13A)-O(8A)-C(6A)	118.2(6)
C(1A)-O(3A)-C(7A)	113.9(5)	O(7A)-C(10A)-O(6A)	122.8(7)
O(5A)-C(4A)-O(4A)	107.3(5)	O(7A)-C(10A)-C(11A)	126.2(7)
O(5A)-C(4A)-C(5A)	116.0(6)	O(6A)-C(10A)-C(11A)	110.9(6)
O(4A)-C(4A)-C(5A)	111.6(6)	O(9A)-C(13A)-O(8A)	123.3(7)
O(5A)-C(4A)-C(1A)	103.3(5)	O(9A)-C(13A)-C(14A)	125.9(7)
O(4A)-C(4A)-C(1A)	110.0(6)	O(8A)-C(13A)-C(14A)	110.8(7)

Table I. 24. Bond angles [°]for **124**.

Bond	Torsion angles [°]	Bond	Torsion angles [°]
C(2B)-O(1B)-C(1B)-O(3B)	-94.6(6)	O(5B)-C(4B)-C(5B)-O(6B)	52.3(8)
C(2B)-O(1B)-C(1B)-C(3B)	21.2(7)	O(4B)-C(4B)-C(5B)-O(6B)	-67.7(7)
C(2B)-O(1B)-C(1B)-C(4B)	144.5(6)	C(1B)-C(4B)-C(5B)-O(6B)	168.9(5)
C(3B)-O(2B)-C(2B)-O(1B)	31.5(7)	O(5B)-C(4B)-C(5B)-C(6B)	-67.1(8)
C(3B)-O(2B)-C(2B)-C(9B)	148.7(6)	O(4B)-C(4B)-C(5B)-C(6B)	172.9(6)
C(3B)-O(2B)-C(2B)-C(8B)	-86.8(7)	C(1B)-C(4B)-C(5B)-C(6B)	49.5(8)
C(1B)-O(1B)-C(2B)-O(2B)	-33.0(7)	O(6B)-C(5B)-C(6B)-O(8B)	-49.6(7)
C(1B)-O(1B)-C(2B)-C(9B)	-150.3(6)	C(4B)-C(5B)-C(6B)-O(8B)	68.5(7)
C(1B)-O(1B)-C(2B)-C(8B)	86.5(6)	O(6B)-C(5B)-C(6B)-C(7B)	-166.9(5)
O(1B)-C(1B)-O(3B)-C(7B)	-59.7(7)	C(4B)-C(5B)-C(6B)-C(7B)	-48.8(7)
C(3B)-C(1B)-O(3B)-C(7B)	-174.0(6)	C(4B)-C(5B)-O(6B)-C(10B)	158.3(6)
C(4B)-C(1B)-O(3B)-C(7B)	61.4(7)	C(6B)-C(5B)-O(6B)-C(10B)	-79.2(7)
C(2B)-O(2B)-C(3B)-C(1B)	-18.4(7)	C(1B)-O(3B)-C(7B)-C(6B)	-63.8(7)
O(1B)-C(1B)-C(3B)-O(2B)	-2.0(7)	O(8B)-C(6B)-C(7B)-O(3B)	-65.4(7)
O(3B)-C(1B)-C(3B)-O(2B)	116.5(6)	C(5B)-C(6B)-C(7B)-O(3B)	54.7(7)
C(4B)-C(1B)-C(3B)-O(2B)	-122.1(6)	C(5B)-C(6B)-O(8B)-C(13B)	95.0(7)
O(1B)-C(1B)-C(4B)-O(5B)	-168.4(5)	C(7B)-C(6B)-O(8B)-C(13B)	-146.9(6)
O(3B)-C(1B)-C(4B)-O(5B)	69.4(7)	C(5B)-O(6B)-C(10B)-O(7B)	-7.0(10)
C(3B)-C(1B)-C(4B)-O(5B)	-51.0(8)	C(5B)-O(6B)-C(10B)-C(12B)	173.3(6)
O(1B)-C(1B)-C(4B)-O(4B)	-53.9(8)	C(6B)-O(8B)-C(13B)-O(9B)	4.4(10)
O(3B)-C(1B)-C(4B)-O(4B)	-176.1(5)	C(6B)-O(8B)-C(13B)-C(14B)	-176.1(6)
C(3B)-C(1B)-C(4B)-O(4B)	63.5(8)	O(3A)-C(1A)-O(1A)-C(2A)	-97.7(6)
O(1B)-C(1B)-C(4B)-C(5B)	69.6(7)	C(3A)-C(1A)-O(1A)-C(2A)	19.0(7)
O(3B)-C(1B)-C(4B)-C(5B)	-52.6(8)	C(4A)-C(1A)-O(1A)-C(2A)	139.9(6)
C(3B)-C(1B)-C(4B)-C(5B)	-173.1(6)	C(1A)-O(1A)-C(2A)-O(2A)	-30.4(7)
C(1A)-O(1A)-C(2A)-C(8A)	-147.0(6)	O(5A)-C(4A)-C(5A)-O(6A)	54.7(8)
C(1A)-O(1A)-C(2A)-C(9A)	88.5(6)	O(4A)-C(4A)-C(5A)-O(6A)	-68.6(7)
O(1A)-C(2A)-O(2A)-C(3A)	29.8(7)	C(1A)-C(4A)-C(5A)-O(6A)	170.1(5)
C(8A)-C(2A)-O(2A)-C(3A)	146.2(6)	O(5A)-C(4A)-C(5A)-C(6A)	-64.3(8)
C(9A)-C(2A)-O(2A)-C(3A)	-87.7(7)	O(4A)-C(4A)-C(5A)-C(6A)	172.4(5)
C(2A)-O(2A)-C(3A)-C(1A)	-18.2(8)	C(1A)-C(4A)-C(5A)-C(6A)	51.2(7)
O(3A)-C(1A)-C(3A)-O(2A)	118.8(6)	O(6A)-C(5A)-C(6A)-O(8A)	-49.1(7)
O(1A)-C(1A)-C(3A)-O(2A)	-0.6(8)	C(4A)-C(5A)-C(6A)-O(8A)	67.8(7)
C(4A)-C(1A)-C(3A)-O(2A)	-118.1(7)	O(6A)-C(5A)-C(6A)-C(7A)	-169.3(5)
O(1A)-C(1A)-O(3A)-C(7A)	-59.6(7)	C(4A)-C(5A)-C(6A)-C(7A)	-52.4(7)
C(3A)-C(1A)-O(3A)-C(7A)	-174.0(5)	C(4A)-C(5A)-O(6A)-C(10A)	159.2(6)
C(4A)-C(1A)-O(3A)-C(7A)	61.4(7)	C(6A)-C(5A)-O(6A)-C(10A)	-79.6(7)
O(3A)-C(1A)-C(4A)-O(5A)	68.9(7)	C(1A)-O(3A)-C(7A)-C(6A)	-61.7(7)
O(1A)-C(1A)-C(4A)-O(5A)	-167.9(5)	O(8A)-C(6A)-C(7A)-O(3A)	-66.0(7)
C(3A)-C(1A)-C(4A)-O(5A)	-52.6(7)	C(5A)-C(6A)-C(7A)-O(3A)	54.6(7)
O(3A)-C(1A)-C(4A)-O(4A)	-176.8(5)	C(7A)-C(6A)-O(8A)-C(13A)	-140.9(6)
O(1A)-C(1A)-C(4A)-O(4A)	-53.6(7)	C(5A)-C(6A)-O(8A)-C(13A)	98.5(7)
C(3A)-C(1A)-C(4A)-O(4A)	61.6(7)	C(5A)-O(6A)-C(10A)-O(7A)	-1.9(10)
O(3A)-C(1A)-C(4A)-C(5A)	-54.6(7)	C(5A)-O(6A)-C(10A)-C(11A)	174.9(6)
O(1A)-C(1A)-C(4A)-C(5A)	68.6(7)	C(6A)-O(8A)-C(13A)-O(9A)	5.7(11)
C(3A)-C(1A)-C(4A)-C(5A)	-176.1(6)	C(6A)-O(8A)-C(13A)-C(14A)	-173.3(6)

Table I. 25. Torsion angles [°] for **123**

CHAPTER II

Asymmetric Organocatalytic Epoxidation of Unfunctionalised Alkenes

1. Background

1.1 Dioxiranes, a new class of electrophilic oxidants

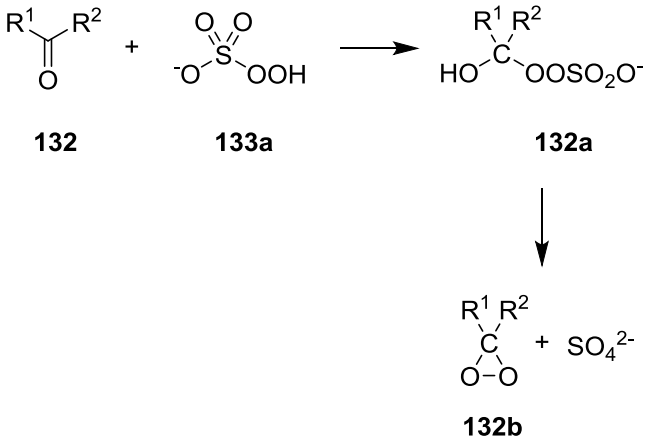
During the last two decades a new class of electrophilic oxidants, the dioxiranes, has been developed and used extensively in modern oxidation chemistry.[112]

Currently, the most common method of preparing dioxiranes involves the oxidation of ketones by peracids and, particularly, monoperoxysulfuric acid. The successful isolation of dioxiranes began with an observation by Montgomery in 1974.[113] Essentially, what Montgomery observed was that certain ketones enhanced the rate of decomposition of monoperoxysulfuric acid (Caro's acid). Furthermore, he discovered that a number of oxidation reactions involving peroxymonosulfates (caroates) were catalysed by the presence of ketones. These observations led Montgomery to propose that the monoperoxysulfate anion reacted with the ketone to give adduct **132a** (Scheme II. 1)**.**

Since a variety of ketones could enhance decomposition of caroates, Montgomery further proposed that intermediate **132a** reacted further to give dioxirane **132b** (Scheme II. 1).

[112] a) M. D. Wittman, S. J. Danishefsky, *J. Org. Chem.* **1990,** *55*, 1981. b) Rousch, W. R.; *Tetrahedron Lett.* **1990**, *31*, 7567. c) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T; Curci, R. *J. Org. Chem.* **1992**, *57*, 5052. d) Herrmann, W. A. *Top. Curr. Chem.* (*Organic Peroxygen Chemistry*), Springer Gmb, Berlin, 1993, Vol. 164. e) Armstrong, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1460. f) Armstrong, A. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 1460. g) Berkessel, A.; Gröger, H. *Asymmetric Catalysis in Organic Synthesis*, Wiley-VCH, Weinheim, 2005. h) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, 2006. i) Dalko, P. *Organocatalysis*, Wiley-VCH, Weinheim, 2007. j) Waldemar, A.; Cong-Gui, Z.; Chantu, R. S. M.; Kavitha, J. *Oxidation of Organic Compounds by Dioxiranes*, John Wiley & Sons, Inc., Hoboken, 2009. k) Adam, W.; Zhao, C.-G.; Saha-Möller, C. R.; Jakka, K. *Organic Compounds by Dioxiranes*, Jonh Wiley & Sons, Inc., Hoboken, 2009. l) List, B. *Asymmetric Organocatalysis*, Springer Gmb, Berlin, 2010. m) Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry Publishing, Cambrigde, 2010 and the cited therein.

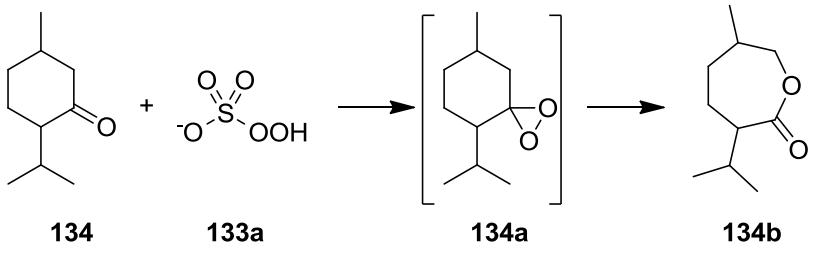
[113] Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820.



Scheme II. 1. Decomposition of monoperoxysulfuric acid observed by Montgomery.

While convinced that dioxiranes were involved as intermediates in the catalysed decomposition of caroates, Montgomery did not categorically state that these dioxiranes were acting as oxidants.[114]

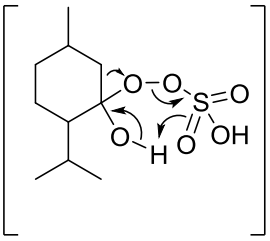
The first literature reference to a dioxirane was made by Baeyer and Villiger, who described the reaction that today bears their names. In 1899 these authors suggested that the intermediate in the conversion of ketone (**134**) to its corresponding lactone (**134b**) by monoperoxysulfate anion (**133a**) was a dioxirane (**134a**). However, the Baeyer-Villiger (B.-V.) reaction was carried out in acidic conditions (Scheme II. 2**).**[113,114]



Scheme II. 2. The original proposed mechanism for the Baeyer-Villiger reaction.

Subsequently, ^{18}O-labeling experiments clarified the mechanism.[115] Nowadays, it is known that the intermediate in the Baeyer-Villiger oxidation is unstable (**134c**) and not the corresponding dioxirane **134a** (Figure II. 1).[116]

[114] a) Baeyer, A. V.; Villiger, V. *Chem. Ber*. **1899**, *32*, 3625. b) Murray, R.W. *Chem. Rev*. **1989**, *89*, 1187.



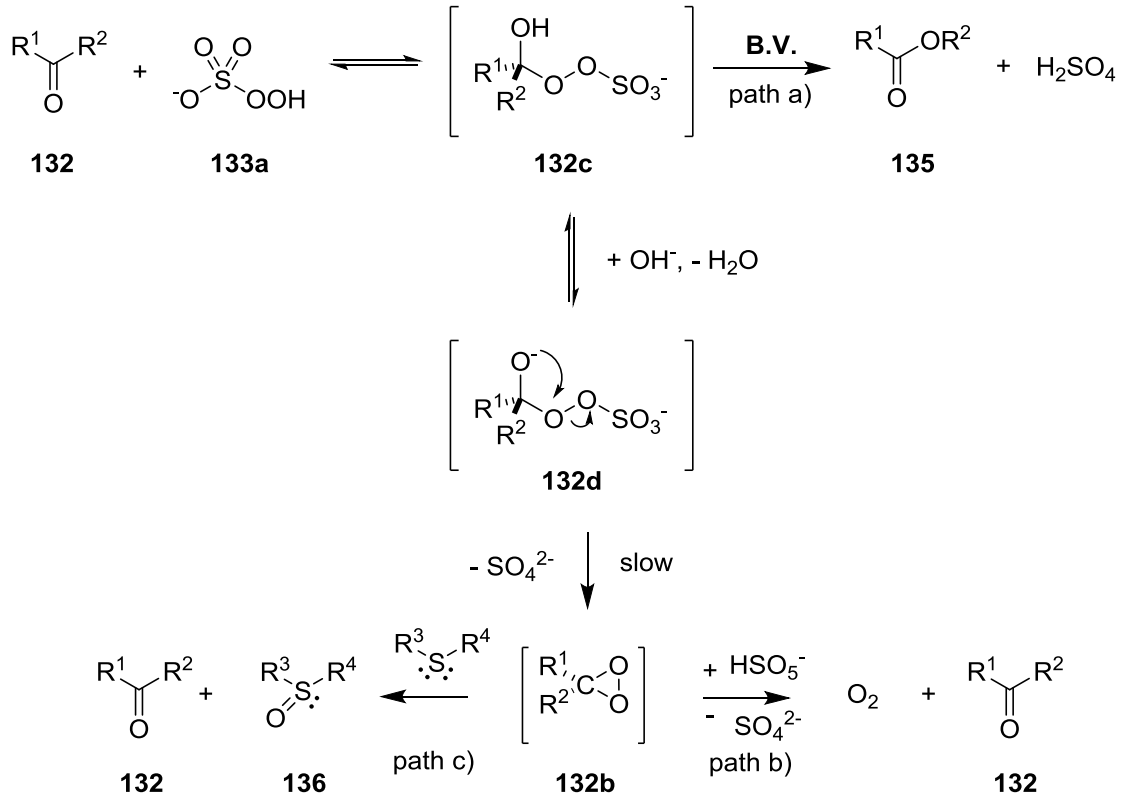
134c

Figure II. 1. Intermediate in the Baeyer-Villiger oxidation.

The next chapter in this story was written by Edwards, Curci and their co-workers.[116] Kinetics and ^{18}O-labeling experiments provided evidence for the involvement of dioxirane intermediate **132b** in the ketone-catalysed decomposition of potassium peroxomonosulfate present in the oxidising agent Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).[113,116]

These investigations have also shown that, under the reaction conditions (water, pH = 7.5, 2–10 ºC), the side reaction involving Baeyer-Villiger (B.-V.) oxidation of the ketone (path a) was negligible with most ketones (acetone, dialkyl ketones, acetophenones, etc.), whereas it became significant at lower pH values or with certain ketones (*e.g.* cyclobutanone and cyclopentanone). In competition with path b, which is related to ketone catalysis of caroate decomposition, the dioxirane **132b** was capable of oxidising organic substrates with nucleophilic character, such as sulfur derivatives (path c, Scheme II. 3).

[115] Doering, W. E.; Dorfman, E. *J. Am. Chem. Soc*. **1953**, *75*, 5595.
[116] a) Edwards, J. O.; Pater, B. H.; Curci, R.; DiFuria, F. *Photochem. Photobiol.* **1979**, *30*, 63**.** b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. For the mechanism proposed, see also: c) Gallooo, A. R.; Edwards, J. O. *J. Org. Chem.* **1981**, *46*, 1684. d) Adam, W.; Curci, R.; González-Núñez, M. E.; Mello, R. *J. Am. Chem. Soc.* **1991**, *113*, 7654. e) Liu, J.; Houk, K. N.; Dinoi, A.; Fusco, C.; Curci, R. *J. Org. Chem.* **1998**, *63*, 8565. f) Curi, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1. g) Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. *J. Am. Chem. Soc.* **2008**, *130*, 1197.

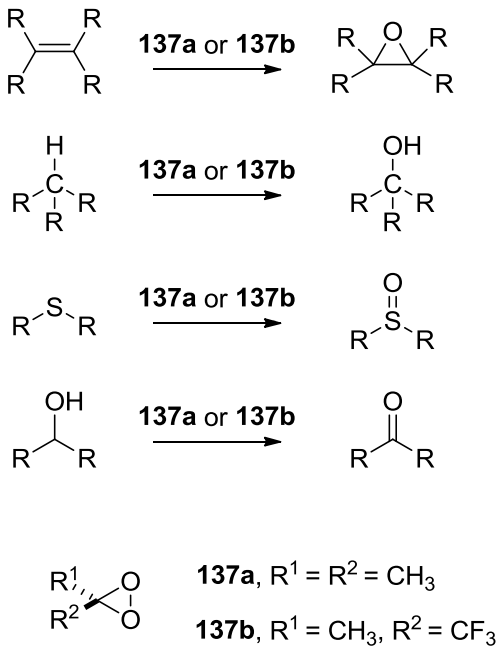


Scheme II. 3. Evidence for the involvement of dioxirane intermediate **132b** in the oxidation of organic substrates.

Curci *et al.* carried out numerous O-atom transfer reactions using dimethyldioxirane (DMD) (**137a**) and the even stronger methyl(trifluoromethyl)dioxirane (MTFD) (**137b**) generated *in situ* from Oxone® and the corresponding ketone.[117] The oxidation of olefins, saturated hydrocarbons, sulfides and alcohols using these two reagents have been extensively reported (Scheme II. 4).[118]

[117] a) Adam, W.; Curci, R.; Edwards. *Acc. Chem. Res.* **1989**, *22*, 202. b) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.

[118] a) Cicala, G.; Curci, R.; Fiorentino, M; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670. b) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. c) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. d) Mello, R.; Cassidei, L.; Fiorentino, M.; Fusco, C.; Hiimmer, W.; Jager,V.; Curci, R. *J. Am. Chem. Soc.* **1991**, *113*, 2205. e) Curci, R.; Detomaso, A.; Prencipe, T.; Gene B. Carpenter, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 8112. f) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa. A. *Tetrahedron Lett.* **1995**, *36*, 5831. g) Curci, R.; Detomaso, A.; Lattanzio, M. E.; Carpenter, G. B. *J. Am. Chem. Soc.* **1996**, *118*, 11089. h) D'Accolti, L.; Fiorentino, M.; Fusco, C.; Rosa, A.; Curci, R. *Tetrahedron Lett.* **1999**, *40*, 8023. i) D'Accolti, L.; Fusco, C.; Annese, C.; Rella, M. R.; Turteltaub, J. S.; Williard, P.; Curci, R. *J. Org. Chem.* **2004**, *69*, 8510.



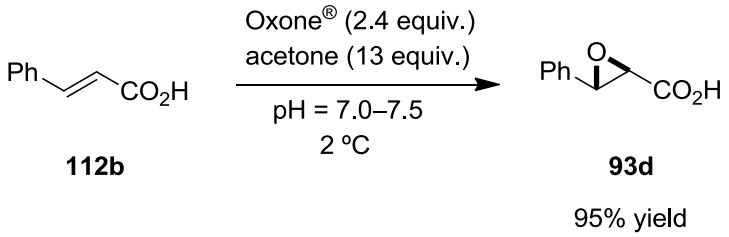
Scheme II. 4. Most common oxidation reactions employing dioxiranes reported by Curci *et al.*[118]

DMD and MTFD had previously been isolated and characterised by physical and chemical methods by Murray *et al.*[119] and Talbot and Thompson.[120]

Currently, epoxidation of olefins using dioxiranes as oxidants has been widely studied. Numerous examples of all types of alkenes (electron-rich, unfunctionalised and electron-poor) have been successfully described.[112]

For instance, oxidation of *(E)*-cinnamic acid (**112b**), which had failed to react with alkaline hydrogen peroxide, with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 or with Oxone® alone, could be achieved by Curci *et al.* in high yield using Oxone® and acetone (Scheme II. 5).[116b]

[119] Murray, R.W.; Jeyaraman. R. *J. Org. Chem.* **1985**, *50*, 2847.
[120] Talbott, R. I.; Thompson P. G. U.S. Patent 03,632,606, 1972.

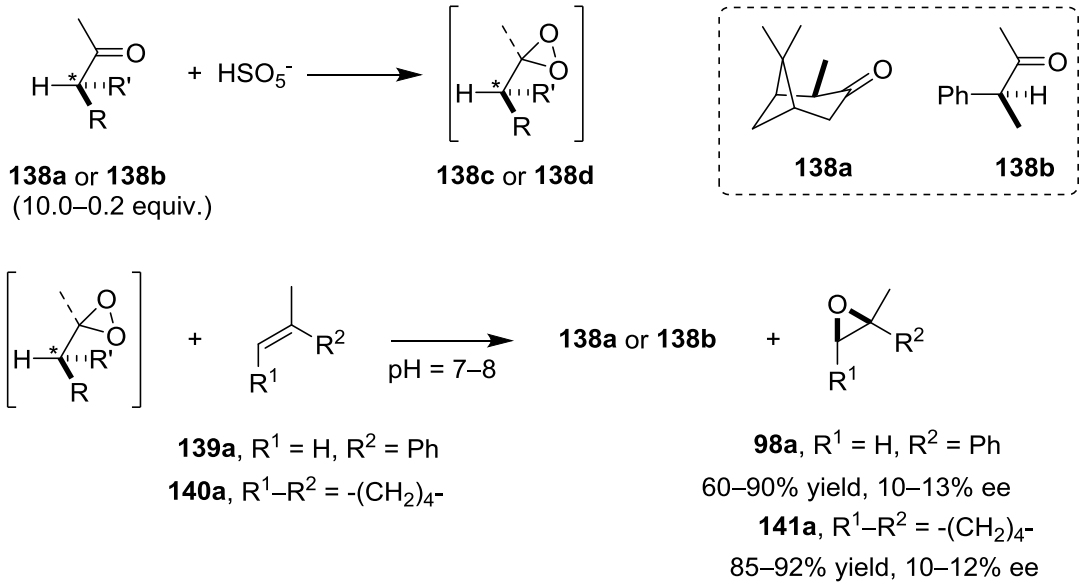


Scheme II. 5. Epoxidation of *(E)*-cinnamic acid (**112b**) by the Oxone®/acetone system.

Moreover, epoxidation of water soluble and water insoluble alkenes was achieved. Since the Oxone®/acetone system had also been employed by Curci *et al.* to epoxidise water-soluble olefins, a water biphasic system (benzene-buffer solution (pH = 7.5)) under conditions of phase-transfer catalysis (PTC) was used for the epoxidation of insoluble olefins, using first 18-crown-6 and then, tetra-*n*-butylammonium hydrogen sulfate (*n*-Bu_4NHSO_4, which will be abbreviated as TBAHS) as phase-transfer catalyst.

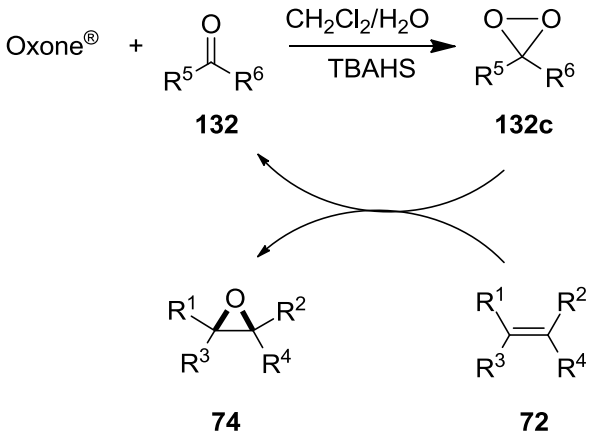
1.2 Organocatalytic asymmetric epoxidation of olefins by chiral ketones

The first asymmetric organocatalytic epoxidation was reported by Curci *et al*. in 1984.[118b] (+)-Isopinocamphone **(138a)** and (*S*)-(+)-3-phenylbutan-2-one **(138b)** were chosen as chiral ketones and 2-phenylpropene (**139a**) and 1-methylcyclohexene (**140a**) as prochiral alkenes in a biphasic mixture of CH_2C1_2-buffer solution (pH = 7–8), with TBAHS as phase-transfer catalyst using different alkene to ketone ratios (5:1, 3:10, 2:1, 1:2 and 1:1) (Scheme II. 6).



Scheme II. 6. First asymmetric organocatalytic epoxidation using chiral ketones **138a** and **138b**.

They observed that although long reaction times were needed, the amount of ketone could be reduced down to 20 mol % without reducing neither conversions nor enantioselectivities. Therefore, dioxiranes could be generated *in situ* from ketones and Oxone® in a catalytic reaction (Scheme II. 7).



Scheme II. 7. Dioxiranes generated *in situ* from ketones and Oxone® as catalysts.

In 1995, they also reported the possible geometry of the transition state in dioxirane epoxidations.[117b] They observed that *cis*-epoxides were obtained from (*Z*)-olefins and that *trans*-epoxides were obtained from their corresponding (*E*)-unsaturated precursors.

Consequently, they concluded that a *syn*-sterospecific O-transfer was taking place from the dioxiranes to the alkene. Extreme geometries for the postulated transition states (planar and spiro geometries) are depicted in Figure II. 2.

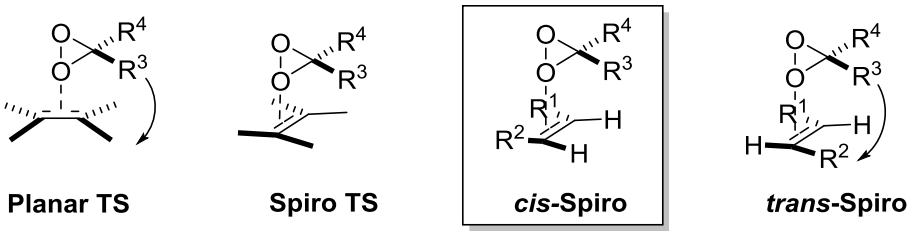


Figure II. 2. Transition state geometries for dioxirane epoxidations.

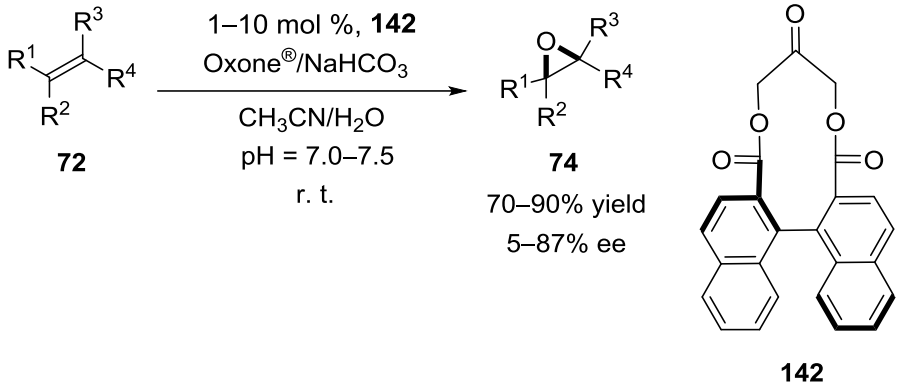
Through a kinetic study, Baumstark *et al.* observed that the steric interactions appeared to be very important: several (*E*)-olefins were found to be 8-fold less reactive than their (*Z*) isomers. This finding seemed to indicate a spiro geometry of the transition state. For both (*Z*)- and (*E*)-olefins, severe steric repulsion cannot be avoided in a planar arrangement. Thus, as originally proposed by Baumstark *et al.*,[121] a spiro arrangement in the transition state seemed to be favoured, based on the observation that (*Z*)-olefins were more reactive than the corresponding (*E*)-olefins for epoxidation using dimethyldioxirane.

Nevertheless, low enantioselectivities using the chiral ketones **138a** and **138b** as catalysts in the epoxidation of alkenes were reported. This observation was obviously an indication that a rationalisation of the enantioselectivity cannot be simply made in terms of a general preference for spiro transition states (Figure II. 2).

Although low enantioselectivities were afforded, this seminal work form Curci *et al*. demonstrated that dioxirane-mediated asymmetric epoxidation of alkenes was feasible.[116–118]

[121] a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. b) Baumstark, A. L.; Vasquez. P. C. *J. Org. Chem.* **1988**, *53*, 3437.

The breakthrough came in 1996, only one year after Curci's work, when Yang and co-workers reported an intriguing C_2-symmetric binaphthalene-derived ketone organocatalyst (**142**) for asymmetric epoxidation of (*E*)-olefins (Scheme II. 8).[122]



Scheme II. 8. Asymmetric organocatalytic epoxidation using **142** as catalyst.

Chiral ketone **142** gave from moderate to good enantioselectivities for the epoxidation of a number of (*E*)-di- (47–87% ee) and trisubstituted olefins (33–50% ee). However, lower enantioselectivities (5–18% ee) were obtained for (*Z*)-diolefins or terminal olefins. An (*S*,*S*)-epoxide derivative with 87% ee was obtained in the epoxidation of (*E*)-1,2-di([1,1'-biphenyl]-4-yl)ethane using 10 mol % of chiral ketone **142**.

Yang *et al.*[122e] examined the structural features of (*E*)-di- and trisubstituted olefins, and noticed that both of them had one large and one small substituent at one terminus of the C=C double bond (Figure II. 3).

[122] a) Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887.; b) Yang, D.; Wong, M. K.; Yip, Y. C.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. c) Yang, D.; Wang, X. C.; Wong, M. K.; Yip, Y. C.; Tang, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. d) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. e) Yang, D. *Acc. Chem. Res*. **2004**, 37, 497. f) Wong, M. K.; Yip, Y. C.; Yang, D. *Top. Organomet. Chem. (Asymmetric Catalysis from a Chinese Perspective. Asymmetric Epoxidation Catalyzed by Chiral Ketones)*, Springer, Berlin, 2011.

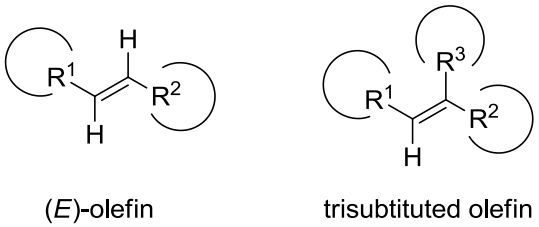


Figure II. 3. Recognising olefin substitution patterns.

Therefore, both in a spiro or planar transition state (Figure II. 2), chiral dioxiranes bearing large and small substituents, respectively, on each face of the dioxiranes should have the potential to discriminate between the large and small groups on the C=C double bond and, hence, could offer a promising solution to the problem of asymmetric epoxidation of (*E*)-di- and trisubstituted olefins.

Yang's catalyst **142** incorporates a binaphthyl unit which provides C_2-symmetry to the whole molecule, and to the dioxirane which is formed *in situ* during epoxidation.

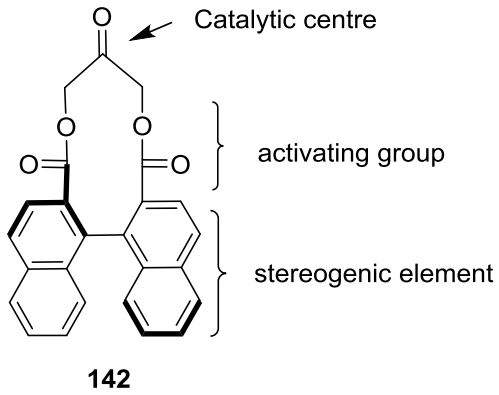
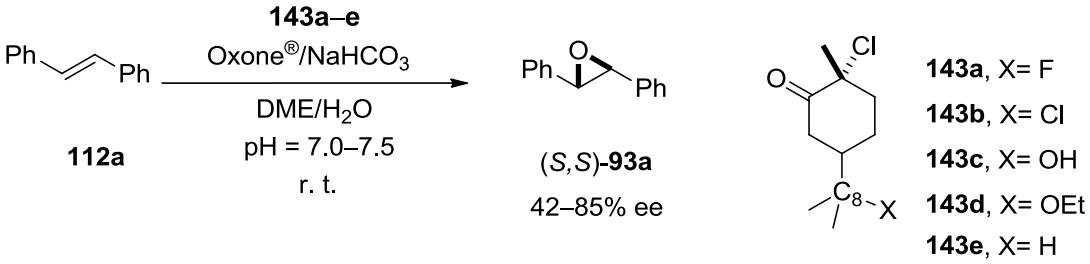


Figure II. 4. The first catalyst used in the asymmetric organocatalytic epoxidation of (*E*)-di- and trisubstituted olefins.

Following this seminal work on organocatalysed asymmetric epoxidation by Yang *et al.*, the same research group came up with a new organocatalyst design, chiral ketone **143**, which lacks C_2-symmetry. A chlorine substituent was introduced at the position α to the carbonyl group, since ketones having electron-withdrawing groups in such α-positions displayed higher activities. [123]

[123] a) Yang, D.; Yip, Y. C.; Chen, J.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. b) Wong, M. K.; Ho, L. M.; Zheng, Y. S.; Ho, C. Y. Yang, D. *Org. Lett.* **2001**, *3*, 2587.

Epoxidation yields were good when catalyst **143** was used, although enantioselectivities proved to be only moderate (Scheme II. 9).[123]



Scheme II. 9. Asymmetric organocatalytic epoxidation of (*E*)-1,2-diphenylethene (**112a**) with ketones **143a–e**.

The catalyst bearing one of the most electron-withdrawing substituents (**143c**) gave the highest catalyst reactivity and also the highest enantioselectivity for the (*S*,*S*)-epoxide **93a** (85% ee).

Therefore, the remote electronegative substituent at the C8 position of the catalyst (see Scheme II. 9) could stabilise the favoured transition state more than it does the disfavoured one by through-space electrostatic interactions (*i.e.* an electronic effect) (Figure II. 5).

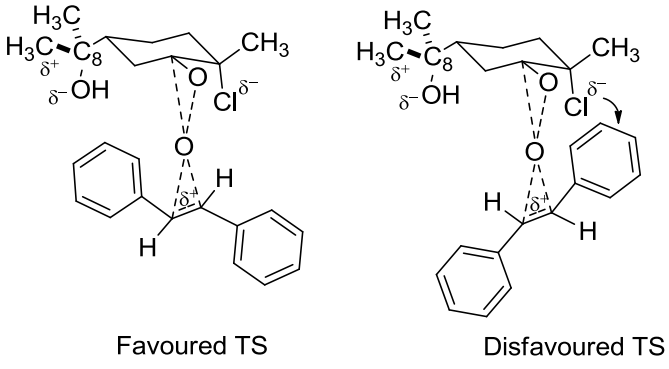
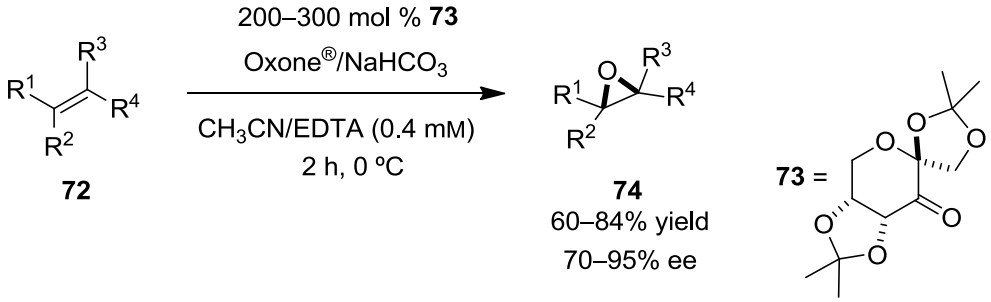


Figure II. 5. Electrostatic effects observed in the dioxirane derived from ketone **143c**.

But the greatest progress in the asymmetric epoxidation of (*E*)-di- and trisubstituted olefins came in 1996, when Shi and co-workers reported the use of fructose-derived ketone **73** in the epoxidation of unfunctionalised alkenes using Oxone® as oxidant.[124]

The first report involved the use of a two to three-fold excess of ketone **73**, Oxone® (5-fold excess) as the oxidising agent and a large excess of sodium bicarbonate (15-fold excess) in a buffered solution CH_3CN-aqueous EDTA (0.4 mM) (1.5:1 v/v) at pH > 7 (Scheme II. 10).



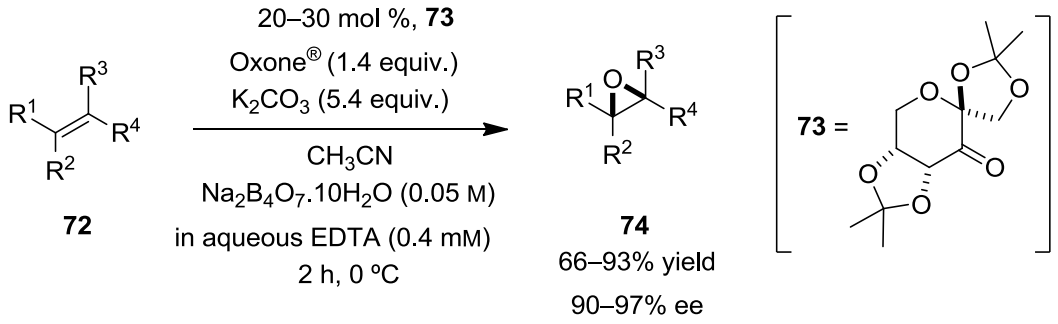
Scheme II. 10. Initial studies of Shi´s epoxidation with ketone **73**.

Initial studies involving ketone **73** in the epoxidation of (*E*)-1,2-diphenylethene (**112a**) revealed that while the yield of (*E*)-1,2-diphenylethene epoxide increased with the reaction time, the enantiomeric excess decreased. Upon examination, Shi *et al.* determined that ketone **73** decomposed over time under the reaction conditions and that at least 300 mol % of catalyst was required. The decreased enantioselectivity was attributed to epoxidation being catalysed by an achiral or less enantioselective carbonyl derivative resulting from the decomposition of ketone **73**.[124,125]

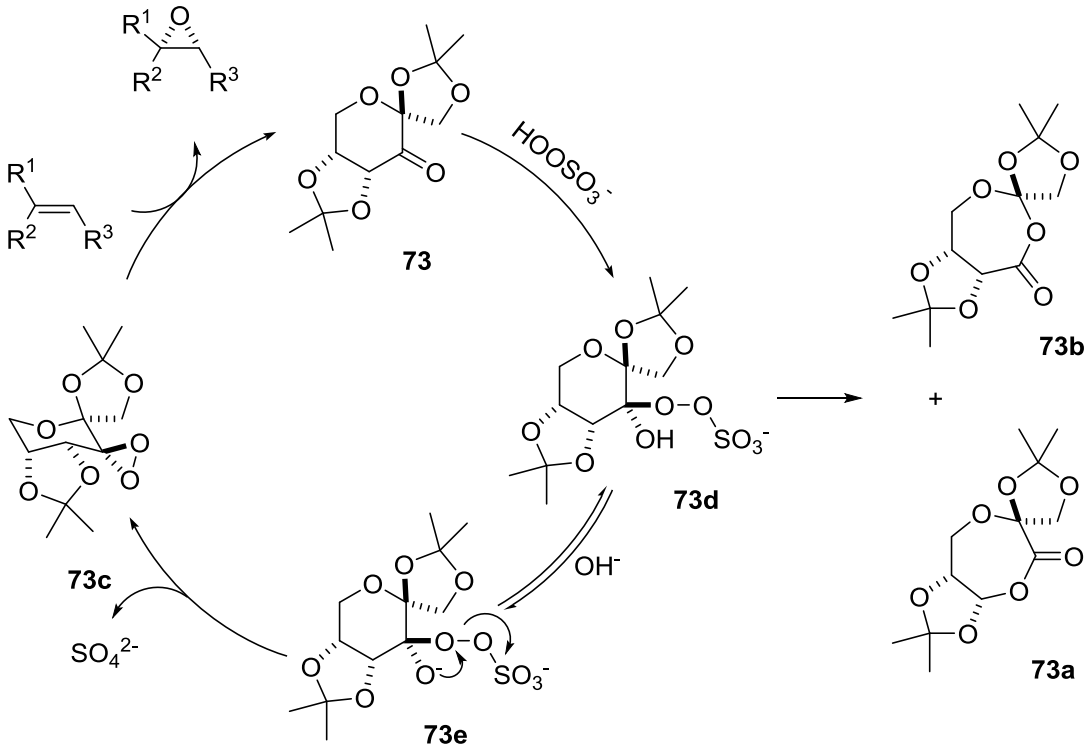
In 1997, Shi *et al.* described a highly effective catalytic asymmetric epoxidation method for (*E*)-di- and trisubstituted olefins using Oxone® as oxidant and the fructose-derived ketone (**73**) as catalyst (30 mol %) (Scheme II. 11).[126] Strict control of the reaction pH was critical for the efficiency of the epoxidation mediated by *in situ* generated

[124] Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.
[125] The possible decomposition pathways for ketone **73** were being investigated by Shi *et al.* at that time.
[126] Wang, Z. X.; Tu, Y.; Frohn, M.;Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

dioxiranes. Typically, epoxidations were carried out at pH values of 7–8.[127] Shi and co-workers reasoned that the catalyst decomposition could be avoided if the epoxidation was carried out at higher pH values, which would favour formation of the anion **73e** leading to the formation of dioxirane **73c** (Scheme II. 12).



Scheme II. 11. First asymmetric organocatalytic epoxidation of (*E*)-olefins with ketone **73**.



Scheme II. 12. Decomposition of ketone **73** by the Baeyer-Villiger reaction.

[127] Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224.

A part of the organocatalysts previously mentioned, a number of chiral ketone organocatalysts have also been developed by a number of research groups for the synthesis of optically active epoxides, from simple and functionalised alkenes, and we summarise in the following figures (Figure. II 6–Figure. II 8) the major advances in this dioxirane chemistry.[112,128,129]

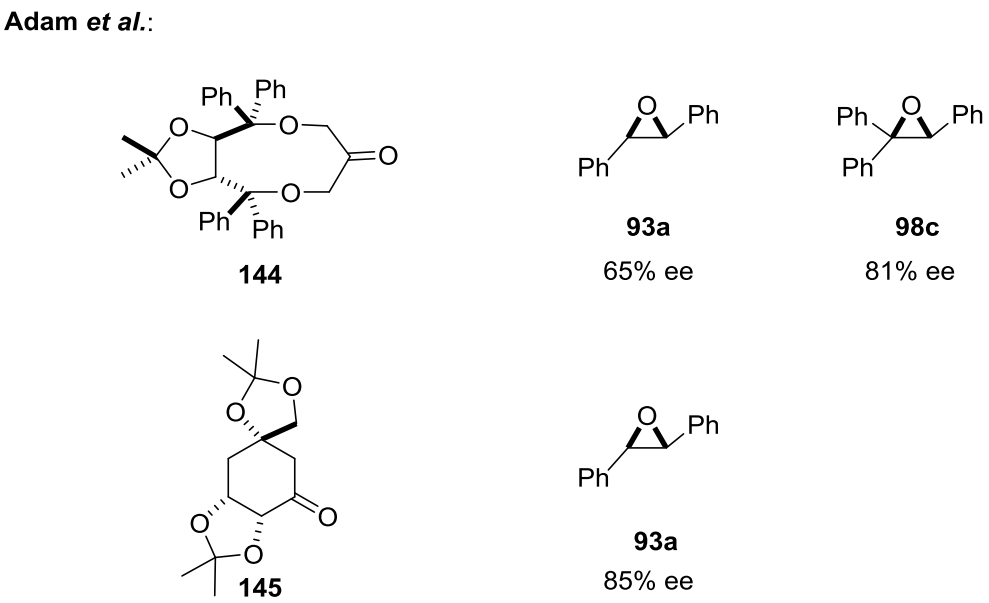
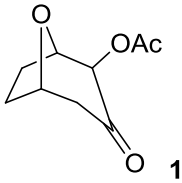


Figure II. 6. Asymmetric epoxidation with chiral ketones.

[128] For instance, see: a) Boninia, C.; Righib. G. *Tetrahedron* **2002**, *58*, 4981. b) Roberts, S. M.; Whittal, J. *Catalysts for Fine Chemical Synthesis*, *Regio- and Stereo-Controlled*, John Wiley & Sons, Ltd., Chichester, 2007. c) Shi, Y. *Acc. Chem. Res*. **2004,** *37*, 488. d) Wong, O. A.; Shi, Y. *Chem. Rev*. **2008**, *108*, 3958. e) Bäckvall, J. E. *Modern Oxidation Methods (Chapter 3)*, Wiley-VCH, Weinheim, 2010. f) Wong, O. A, Shi, Y. *Top. Curr. Chem*. **2010**, *291*, 201.

[129] a) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; De Pue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. b) Adam, W.; Zhao, C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. c) Song, E. C.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. d) Kim, Y. H.; Lee, K. C.; Chi, D. Y.; Lee, S. G.; Song, C. E. *Bull. Korean Chem. Soc.* **1999**, *20*, 831. e) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. f) Adam, W.; Saha-Möller, C. R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. g) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. h) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610. i) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479. j) Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545. k) Shing, T. K. M.; Leung, Y. C.; Yeung, K. W. *Tetrahedron* **2003**, *59*, 2159. l) Shing, T. K. M.; Leung, G. Y. C.; Yeung, K. W. *Tetrahedron Lett.* **2003**, *44*, 9225. m) Shing, T. K. M.; Leung, G. Y. C.; Luk, T. *J. Org. Chem.* **2005**, *70*, 7279. n) Armstrong, A.; Tsuchiya, T. *Tetrahedron* **2006**, *62*, 257. o) Shing, T. K. M.; Luk, T.; Lee, C. M. *Tetrahedron* **2006**, *62*, 6621.

Armstrong *et al.*:



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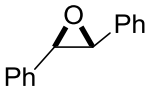
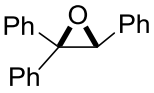
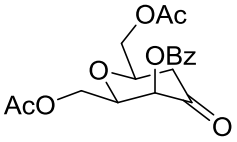


93a
93% ee



98c
98% ee



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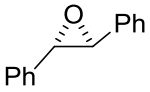
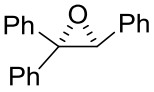
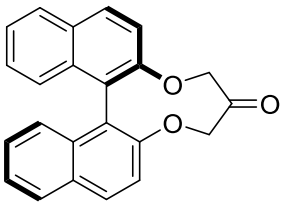


(*S*,*S*)-93a
83% ee



(*S*)-98c
82% ee

Song *et al.*:



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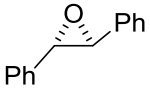
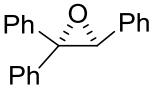
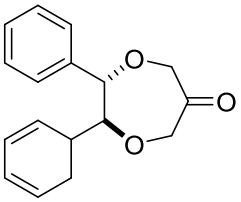


(*S*,*S*)-93a
26% ee



(*S*)-98c
29% ee



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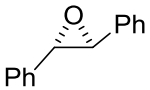
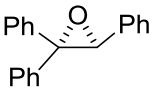
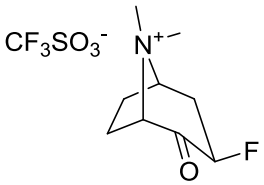


(*S*,*S*)-93a
59% ee



(*S*)-98c
20% ee

Denmark *et al.*:



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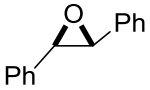
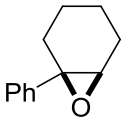


93a
58% ee



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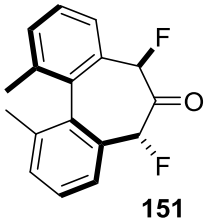
58% ee



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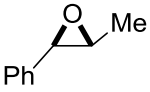
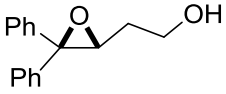


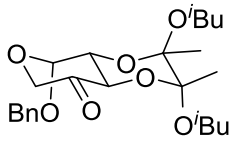
93b
88% ee



98e
89% ee

Figure II. 7. Asymmetric epoxidation with chiral ketones.

Shing *et al.*:



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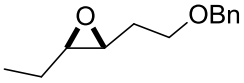
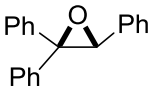
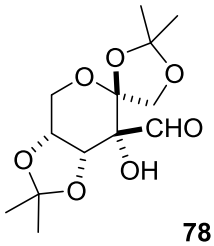


154a
93% ee



98c
90% ee

Zhao *et al.*:



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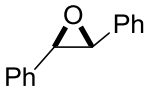


93a
94% ee

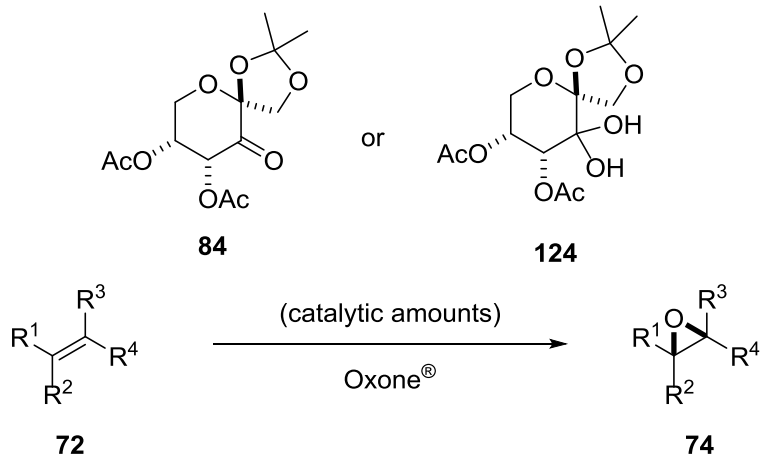
Figure II. 8. Asymmetric epoxidation with chiral ketones.

2. D-Fructose derivative-catalysed asymmetric epoxidation reactions

Following our efforts in the development of a practical synthesis of diester **84**, we turned our attention to the epoxidation studies of unfunctionalised alkenes using the mentioned compound as the chiral organocatalyst. It is worth recalling at this point that there were no precedents on the use of **84** as asymmetric catalyst for the epoxidation of unfunctionalised electron-rich alkenes, when this work started in the laboratory. Whilst, Shi *et al.* had studied the catalytic activity of **84** towards the epoxidation of a number of α,β-unsatured alkenes, no results on the epoxidation of unfunctionalised alkenes were reported.

The practical preparation method described in the last section allowed isolating hydrate **124** just by changing the final work-up procedure.

With a practical preparation method for hydrate **124** (derivative not described in the literature previously) in hand, we also studied its catalytic properties in the enantioselective organocatalysed epoxidation of alkenes.



Scheme II. 13. Asymmetric epoxidation of olefins using diester **84** and hydrate **124** as organocatalysts.

Results on the catalytic activity of both D-fructose derivatives (**84** and **124**) in the enantioselective epoxidation of alkenes are provided in the following sections.

2.1 Organocatalytic asymmetric epoxidation of olefins

It has been described in the literature that the pH is the most important factor that governs epoxidation reactions. Generally, high pH values result in a faster autodecomposition of Oxone®, which leads to a decrease in the epoxidation efficiency. Shi's epoxidation conditions using this kind of organocatalyst involve working in a buffered aqueous-organic solution at pH values higher than 7–8 (catalyst decomposition also takes place under these conditions).

We chose (*E*)-1,2-diphenylethene (**112a**) as a model substrate for the optimisation of the epoxidation conditions. Standard experimental conditions for this chemistry were chosen: 10 mol % of catalyst amount, a buffered aqueous-organic medium involving acetonitrile and dimethoxymethane (DMM) as organic solvents and 4 mol % of a phase transfer catalyst (TBAHS).

The substrate **112a** and the chiral organocatalyst **84** were dissolved in the aqueous-organic mixture mentioned above. Then, a solution of Oxone® in a buffered solution and an aqueous solution of an auxiliary base (K_2CO_3 or $NaHCO_3$) were simultaneously added over a 2 h period onto the substrate containing solution. The use of an auxiliary base is necessary as the commercially available oxidising agent Oxone® is constituted by a 2:1:1 molar mixture of $2KHSO_5$, $KHSO_4$ and K_2SO_4, respectively and two of its components ($KHSO_5$ and $KHSO_4$) have a strong acidic character. Thus, neutralisation with stoichiometric amounts of base during Oxone® addition is required to keep the pH values basic.

We first turned our attention to the optimisation of the pH value, as this variable appears to be the most critical.[124]

We envisaged that different pH values could be achieved by using buffer solutions at different pH values for dissolving Oxone® and for preparing the initial solution containing the substrate and catalyst. Simultaneous addition of an auxiliary base (K_2CO_3 or $NaHCO_3$) should allow pH control at the desired value.

The epoxidation reaction was carried out in a three-necked flask equipped with a magnetic stirrer, and a pH meter. A solution of Oxone® in the buffer and another aqueous solution of the base were simultaneously added over a 2 h period with the aid of two syringe pumps. The reaction set-up is shown in Figure II. 9.

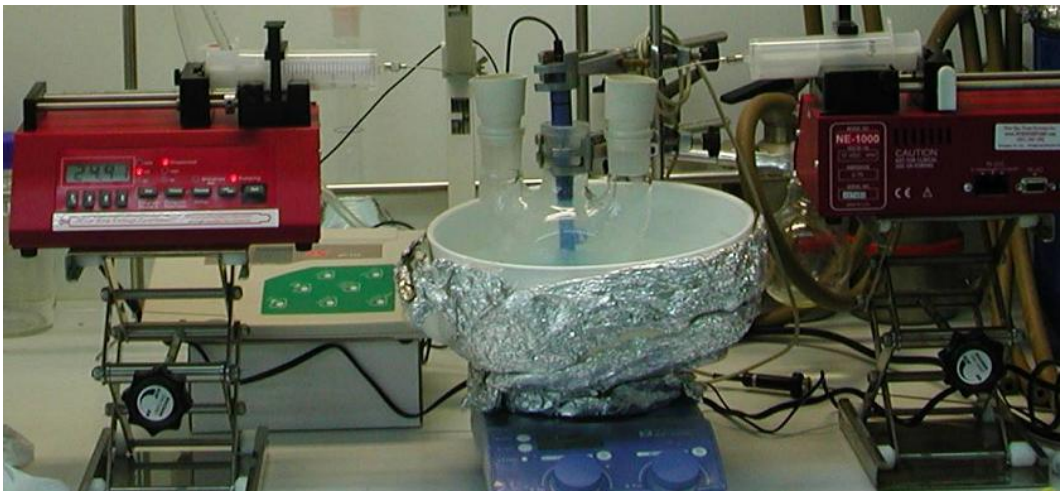
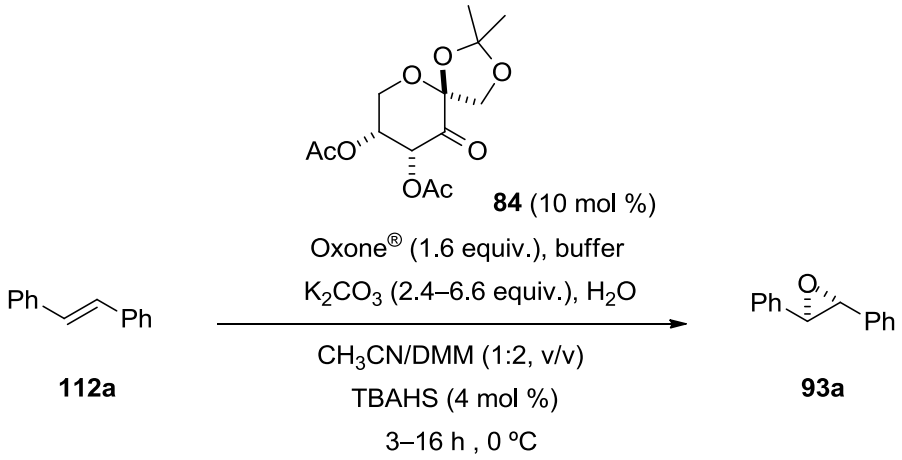


Figure II. 9. Reaction set-up for the epoxidation of **112a**.

The results of the epoxidation of (*E*)-1,2-diphenylethene (**112a**) using diester **84** are summarised in Table II. 1.



Entry	Buffer pH	Diester **84** (mol %)	K_2CO_3 (mmol)	pH[b]	t (h)[c]	Conv. (%)[d]	ee (%) [(*R*,*R*)]
1	pH = 8	10	6.6	10.5	5	< 5	n. d.[f]
2	pH = 10	10	6.6	10.0	3	< 5	n. d.
3	pH = 6	10	6.6	9.5	5	10	n. d.
4	pH = 7	8	2.4	9.5	16	45	n. d.
5	pH = 6	5	2.4	9.0	16	31	88
6	pH = 6	10	2.4	9.0	16	75[e]	96.6
7	pH = 6	10	2.4	9.0	16	53	90
8	pH = 6	30	2.4	9.0	16	76	94

[a] All reactions were carried out at 0 ºC with (*E*)-1,2-diphenylethene (**112a**) as substrate, Shi's diester **84** as catalyst, TBAHS (4 mol %) as phase transfer catalyst, and CH_3CN/DMM (1:2 v/v) as solvent. A solution of Oxone® (1.6 equiv.) in buffer and an aqueous solution of K_2CO_3 (the volumes of the two solutions were the same) were simultaneously added to the substrate containing solution within 2 h with the aid of two syringe pumps. The reactions were stopped at the indicated time. [b] Final pH after Oxone® and K_2CO_3 addition. [c] Time of stirring after Oxone® and K_2CO_3 addition. [d] Measured by ^{1}H NMR. [e] This experiment was carried out using a mechanical stirrer. [f] n. d. = not determined.

Table II. 1. Test to optimise the asymmetric organocatalytic epoxidation mediated by diester **84**.

Epoxidation reactions were carried out using sufficient amount of solvents (CH_3CN/DMM, 1:2 v/v) to dissolve the substrate and the quantities of phase transfer catalysts and buffer solution.[130] After simultaneous addition of Oxone® and K_2CO_3

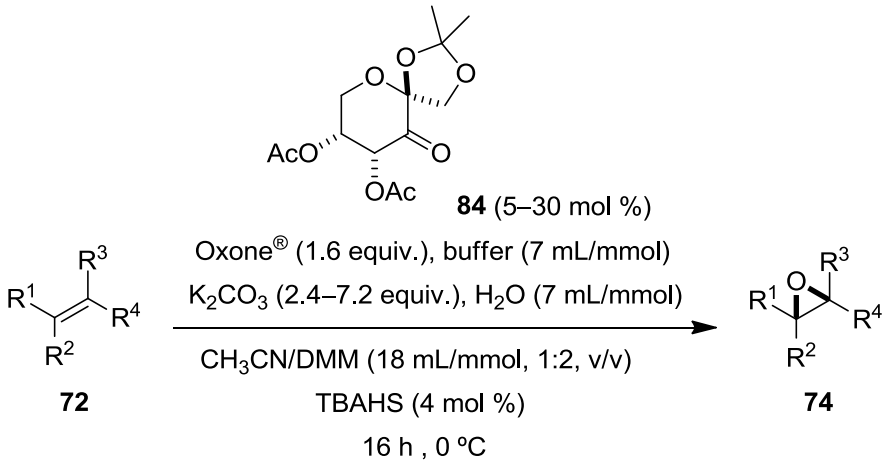
[130] Buffer solution at pH = 6 (0.05 M potassium dihydrogen phosphate and 1.0 M potassium hydroxide, 5.7 mL/L). Buffer solution at pH = 7 (0.026 M potassium dihydrogen phosphate and 0.10 M di-sodium hydrogen phosphate). Buffer solution at pH = 8 (di-sodium tetraborate, calcium chloride, and hydrochloric acid). Buffer solution at pH = 9 (0.05 M boric acid, 0.05 M potassium chloride, and 0.02 M sodium hydroxide). Buffer solution at pH = 10 (0.05 M sodium tetraborate decahydrate and 0.4 mM Na_2(EDTA)).

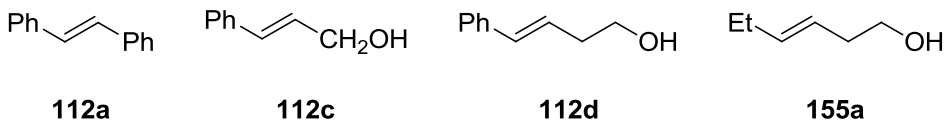
solutions over a 2 h period, the reaction mixture was allowed to stir for the indicated time.

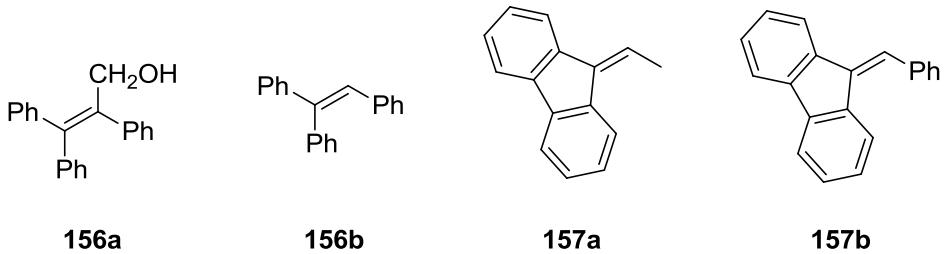
We observed that the longer the stirring time after the 2 hour addition period, the higher the conversion (compare entry 3 with 4 in Table II. 1). For this reason, reaction time after addition was set to 16 h. Regarding the pH value of the oxidative medium, slightly higher conversions were achieved at a pH value of 9 (53%, entry 7) than the ones observed at pH = 9.5 (45%, entry 4) under similar reaction conditions.

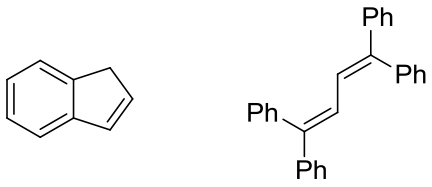
A uniform addition rate of Oxone® and base was required in order to achieve high conversions. We also observed that buffer solutions had to be freshly prepared in order to get reproducible results and that the use of a mechanical stirrer instead of a magnetic one brought an important improvement in the conversion (compare entries 6 and 7).

With the optimised epoxidation conditions in hand, we extended the substrate scope of diester **84** to a number of unfunctionalised alkenes. Epoxidation of a number of alkenes was carried out using the optimised conditions, in organo-aqueous media with 8–10 mol % catalyst at 0 ºC, since this temperature offers a good balance between conversion and selectivity. As mentioned before, pH is a key parameter in dioxirane-catalysed epoxidations. The optimal pH values for epoxidation with **84** using (*E*)-1,2-diphenylethene (**112a**) as a test substrate ranging from 9 to 10 were obtained by simultaneously adding aqueous K_2CO_3 and a solution of Oxone® in a pH 6 buffer (See Table II. 2). After addition was complete the reaction mixture was further stirred for 16 h without meaningful changes in the pH value. The results summarised in Table II. 2 show that the epoxidation reaction catalysed by ketone **84** is quite effective toward a variety of (*E*)-di- and trisubstituted olefins (Scheme II. 14).

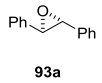
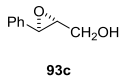
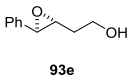
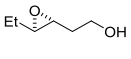
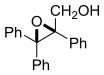
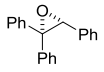
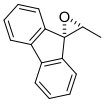
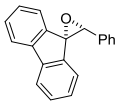
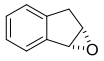
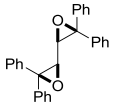








Scheme II. 14. Asymmetric organocatalytic epoxidation of unfuctionalised olefins with ketone **84**.

Entry	Product[a]	Cat. **84** (mol %)	Final pH[b]	Yield (%)	ee (%)	ee enrichment[c]
1	 **93a**	5	9.0	31	88	–
2		10	9.0	53[d]	90[d]	hexanes, 46% yield, >99% ee
3		30	9.0	75	94	–
4	 **93c**	10	9.0	68	96	–
5	 **93e**	8	9.0	66	75	–
6		8	10.0	67	81	–
7		8	9.0	[e]	62	–
8	 **154b**	24	9.0	[e]	76	–
9		24	9.5	[e]	79	–
10		24	10.0	[e]	83	–
11	 **160a**	30	9.0	–	–	–
12		30	9.5	–	–	–
13	 **98c**	8	9.0	58	87	Hexanes, 45% yield, 90% ee
14	 **161a**	8	9.0	58	80	–
15		24	9.0	56	93	–
16	 **161b**	10	9.0	53	73	–
17	 **162a**	10	9.0	97	46	–
18	 **163a**	30	9.0	–[f]	–	–

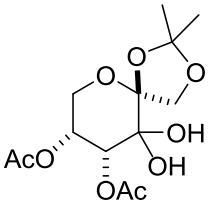
[a] Method: All reactions were carried out at 0 ºC (bath temperature) with substrate (1 mmol), TBAHS (4 mol %), CH_3CN/DMM (1:2 v/v), buffer pH = 6. Solutions of Oxone® (1.6 equiv.) in buffer and K_2CO_3 in water were simultaneously added for 2 h with the aid of two syringe pumps. The pH value increased from 6 to the value reported in the table throughout the 2 h addition period. After the addition was complete the reaction mixture was further stirred for 16 h without meaningful changes in the pH value. [b] Final pH = 9 was obtained using 2.4 equiv. of K_2CO_3; pH = 9.5 using 4.8 equiv. K_2CO_3; and pH = 10 using 7.2 equiv. of K_2CO_3. [c] The epoxide was recrystallised after chromatography in order to enrich its optical purity. The solvent, overall yield and ee are shown. [d] Mean value of 4 experiments. [e] Not determined (epoxyalcohol **154b** was distilled together with the solvents during the work-up. [f] In this case 3.3 equiv. of Oxone® and 4.8 equiv. of K_2CO_3 were added.

Table II. 2. Asymmetric organocatalytic epoxidation of representative olefins by ketone **84**.

We have observed that diacetate **84** is very effective as an epoxidation catalyst toward a variety of (*E*)-aryl-substituted olefins (Table II. 2). For example, (*E*)-1,2-diphenylethene (**112a**) could be epoxidised with good yield and enantioselectivity (53% yield, 90% ee) using 10 mol % of catalyst at 0 °C (entry 2). The epoxidation product **93a** could be enantiomerically enriched up to >99% ee by recrystallisation from hexanes (entry 2). The enantioselectivity of the epoxidation reaction could be increased up to 94% ee by using 30 mol % organocatalyst (normal catalyst ratio for the standard Shi's catalyst **73**; entry 3) at the same reaction temperature. A number of disubstituted (*E*)-allylic and homoallylic alcohols (entries 4–12) were also epoxidised with the procedure described in this work. The final epoxy alcohols were obtained in good to very high enantioselectivities (81–96% ee), and it should be mentioned that 24 mol % amount of catalyst **84** was required to achieve 83% ee for epoxy alcohol **154b**. It should also be noted that at higher pH values (pH = 10), higher enantioselectivities were obtained (compare entries 5 and 6, and 8 and 10). Trisubstituted olefins such as triphenylethylene **156b** (entry 13) or 9-ethylidenefluorene **157a** (entries 14 and 15) could be epoxidised with high selectivity using diester **84** and the epoxidation procedure described in this work. Different behaviour followed the 9-benzylidenefluorene **157b**, which could only be epoxidised with moderate selectivity (entry 16). On the other hand, lower enantioselectivity was obtained for (*Z*)-alkenes such as indene **158a** (entry 17), suggesting that diester **84** has a similar behaviour to Shi's ketone **73** towards these kind of epoxides. Finally, no reaction was observed neither for tetrasubstituted alkene **156a** (entries 11 and 12) nor for conjugated olefin **159a** (entry 18), with the starting material being recovered.

2.2 Organocatalytic asymmetric epoxidation of olefins catalysed by hydrate 124

With a practical preparation method for hydrate **124** in hand (compound **124** had not been described in the literature previously) we studied its catalytic properties in the epoxidation of alkenes.

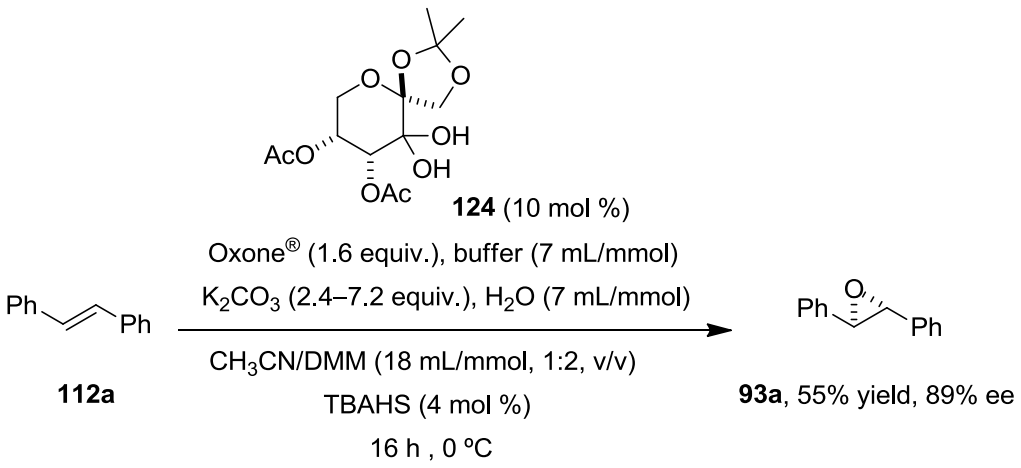


124

Figure II. 10. Hydrate of carbonyl compound **84** (the *gem*-diol **124**).

We first tested the epoxidation of (*E*)-1,2-diphenylethene (**112a**) mediated by **124** under the optimised reaction conditions which were used for its ketone analogue **84** (organo-aqueous media with 10 mol % of **124**, 0 ºC, pH = 9; see Scheme II. 15).

Excellent results were observed when the chiral hydrate **124** was used as organocatalyst, as both the conversion (55%) and enantioselectivity (89% ee) were the same as those obtained for **84** (53%, 90% ee, see entry 2 in Table II. 2).



Scheme II. 15. Asymmetric organocatalytic epoxidation of (*E*)-1,2-diphenylethene (**112a**) by hydrate **124**.

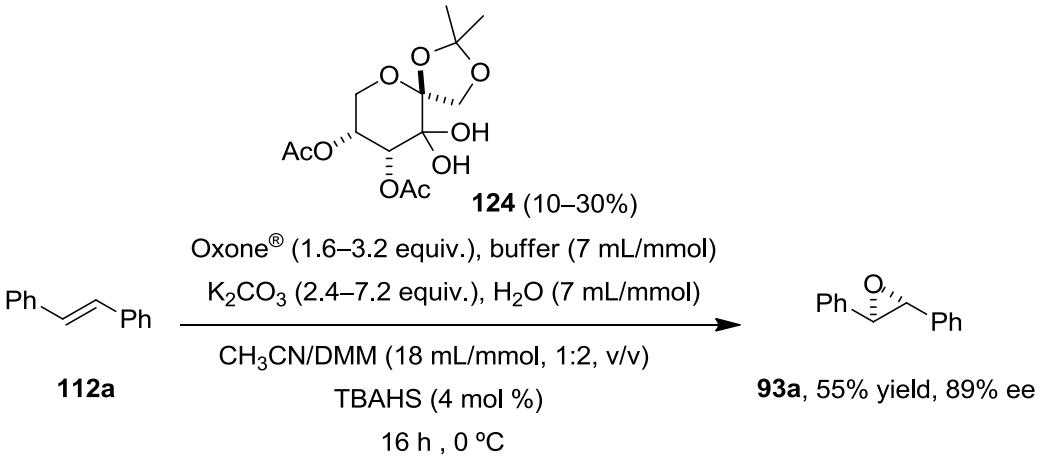
This experiment suggested that hydrate **124** shows the same high catalytic activity as its parent compound **84** in epoxidation studies of (*E*)-1,2-diphenylethene as the model substrate.

We assumed that pH would be once more a key parameter in the hydrate **124**-mediated epoxidations, and we hence investigated the optimal pH value using (*E*)-1,2-diphenylethene as the test substrate (Table II. 3).

pH values ranging from 8 to 10 were obtained in an analogous way to the one described for the epoxidation of (*E*)-1,2-diphenylethene catalysed by **84** (simultaneous addition of variable amounts of K_2CO_3 dissolved in water together with the addition of oxidant dissolved in pH = 6 buffer solution). Results on the influence of the pH value in the epoxidation of (*E*)-1,2-diphenylethene are shown in Table II. 3.

An interesting trend in the results of the epoxidation of **112a** was observed as a function of the pH value:

Under the standard epoxidation conditions (1.6 equiv. of Oxone®), the enantioselectivity increased with the pH whilst conversion decreased (compare entries 1–3 in Table II. 3). A higher conversion was achieved when 30 mol % of catalyst **124** was used (65%, entry 4), whilst ee remained unchanged. The lower stability of the oxidant (Oxone®) could account for the lower conversion at the highest pH value (entry 3). In order to overcome this problem, a larger amount of oxidant (3.2 equiv. of Oxone®) was used (entries 5–7). Again, the enantioselectivity of the reaction increased with the pH value, whilst conversion decreased (compare entries 5 and 6 in Table II. 3). The highest yield (95%) and enantioselectivity (96% ee) of all the epoxidation conditions tested, was obtained by switching from catalytic to substoichiometric amounts of organocatalyst (30 mol %) and doubling the amount of Oxone® while keeping the pH constant at pH 10 (entry 7).

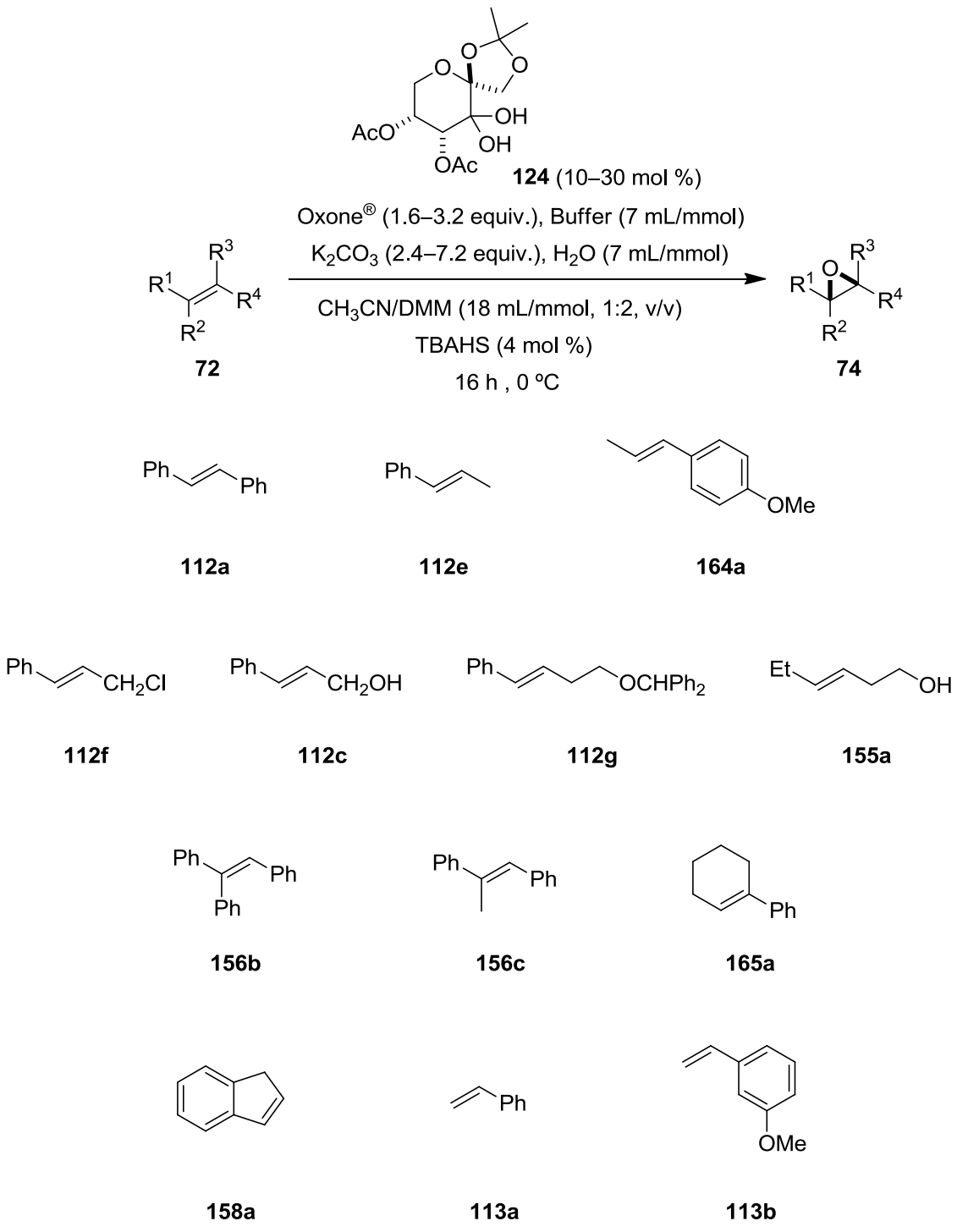


Entry	Oxone® [a] (equiv.)	K_2CO_3 (equiv.)	Cat. **124** (mol %)	pH	Yield (%)[b]	ee (%) [(*R*,*R*)-**93a**]
1	1.6	2.4	10	9.0	55	89
2	1.6	3.4	10	9.5	41	92
3	1.6	4.4	10	10.0	39	95
4	1.6	4.4	30	10.0	65	95
5	3.2	3.8	10	8.5	72	90
6	3.2	6.8	10	10.0	63	94
7	3.2	6.8	30	10.0	95	96

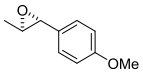
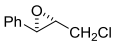
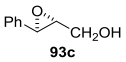
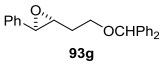
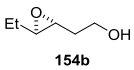
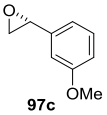
[a] Method: All reactions were carried out at 0 ºC (bath temperature) with substrate (1 mmol), TBAHS (4 mol %), CH_3CN/DMM (1:2 v/v), buffer pH = 6. Solutions of Oxone® (1.6–3.2 equiv.) in buffer and K_2CO_3 (2.4–7.2 equiv.) in water were simultaneously added for 2 h with the aid of two syringe pumps. The pH value increased from 6 to the value reported in the table throughout the 16 h addition period. After the addition was complete the reaction mixture was further stirred for 16 h without meaningful changes in the pH value. [b] Isolated yield.

Table II. 3. Testing different pH values in the epoxidation of (*E*)-1,2-diphenylethene (**112a**) mediated by hydrate **124**.

We considered that the epoxidation at pH = 9 offers a good balance between conversion, selectivity and amounts of required reagents and was thus selected to study the asymmetric epoxidation of a series of structurally diverse alkenes (see Scheme II. 16).



Scheme II. 16. Asymmetric organocatalytic epoxidation of a series of structurally diverse olefins with **124**.

Entry	Product[a]	Cat. **124** (mol %)	Oxone® (equiv.)	K_2CO_3 (equiv.)	pH	Yield (%)[b]	ee (%)[c]
1	 **93a**	10	1.6	2.4	9	55	89
2	 **93b**	10	1.6	2.4	9	60	83
3		30	1.6	2.4	9	61	87
4	 **166a**	10	1.6	2.4	9	99	83[e]
5		30	1.6	2.4	9	99	94[e]
6	 **93f**	10	1.6	2.4	9	41	81
7		30	3.2	6.8	10	80	90
8	 **93c**	10	3.2	6.8	10	89	86
9	 **93g**	10	1.6	2.4	9	52	90[d]
10	 **154b**	10	1.6	2.4	9	[f]	60
11		10	1.6	7.2	10	[f]	75
12		30	1.6	7.2	10	[f]	80
13	 **98c**	10	1.6	2.4	9	52	92
14	 **98a**	10	1.6	2.4	9	41	83
15	 **99**	10	1.6	2.4	9	82	92
16	 **162a**	10	1.6	2.4	9	98	48
17	 **97a**	10	1.6	2.4	9	99[g]	26
18	 **97c**	10	1.6	2.4	9	99	11[h]

[a] Method: All reactions were carried out at 0 ºC (bath temperature) with substrate (1 mmol), TBAHS (4 mol %), CH_3CN/DMM (1:2 v/v), buffer pH = 6. Solutions of Oxone® (1.6–3.2 equiv.) in buffer and K_2CO_3 (2.4–7.2 equiv.) in water were simultaneously added for 2 h with the aid of two syringe pumps. The pH value increased from 6 to 9 when 2.4 equiv. of K_2CO_3 were used, and to *ca.* 10 in the other cases throughout the 2 h addition period. After the addition was complete the reaction mixture was further stirred for 16 h without meaningful changes in the pH value. [b] Isolated yield.
[c] Enantiomeric excesses. [d] Unreported epoxide. The configuration was assumed to be (*R*,*R*). [e] The configuration was assumed to be (*R*,*R*). [f] Not determined (**154b** distilled together with the solvent during the work-up). [g] Reaction conducted at –10 ºC. [h] The configuration was assumed to be (*R*).

Table II. 4. Substrate scope of epoxidations mediated by hydrate **124** as chiral organocatalyst.

The hydrate **124** effectively catalysed the epoxidation of a variety of (*E*)-aryl-disubstituted olefins (entries 1–12 in Table II. 4), providing ee's ranging from 80% to

94%. Olefin substrates with a wide range of groups, such as aryl or alkyl substituents, benzhydryloxy ethers (**112g**), hydroxyalkyl (**112c** and **155a**) or chloromethyl (**112f**) substituents were all well tolerated. Under the same experimental conditions, the epoxidation of diaryl-substituted alkenes (entry 1) proceeds with the highest selectivity, followed by aryl-alkyl-substituted alkenes (entry 2).

Once more, it should be mentioned that 30 mol % amount of catalyst **124**, or large amounts of K_2CO_3 to obtain high pH values (pH = 10) were required to efficiently deliver the desired final epoxy alcohols and to achieve good enantioselectivities of up to 80% ee in the epoxidation of **155a** (compare entries 10–12 in Table II. 4). It has been established in the literature that the hydroxyl group can give hydrogen bonding interactions with the dioxirane to affect the regio- and diastereoselectivities of the epoxides.[118e,131] Our results are in accordance with Shi *et al.*, who postulated that the asymmetric epoxidation of hydroxyalkenes is highly pH dependent.[132] When the pH increased, Oxone® was more likely to react with the chiral ketone to form the corresponding dioxirane which subsequently reacted with the olefin, yielding a higher enantioselectivity (see entries 1–3, 5 and 6 in Table II. 3 and entries 10 and 11 in Table II. 4).

Additionally, several trisubstituted olefins, for instance, triphenylethylene **156b**, (*E*)-prop-1-ene-1,2-diyldibenzene **156c** and 1-phenyl-1-cyclohexene **165a** (Scheme II. 16) were also epoxidised with high enantioselectivity (entries 13–15 in Table II. 4).

Finally (and disappointingly), the epoxidation of (*Z*)- and terminal olefins organocatalysed by **124** showed only poor enantioselectivities (entries 16–18 in Table II. 4), though conversions remained high, under all tested conditions.

[131] For the leading references on the epoxidation of hydroxyalkenes by dioxiranes, see: a) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *Tetrahedron Lett.* **1995**, *36*, 2437. b) Adam, W.; Smerz, A. K. *Tetrahedron* **1995**, *51*, 13039. c) Adam, W.; Smerz, A. K. *J. Org. Chem*. **1995**, *61*, 3506. d) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem*. **1996**, *61*, 1830.
[132] Wand, Z-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 3099.

In all cases, the absolute configurations of the obtained products were in agreement with those obtained using Shi's diester or the standard catalyst **73**. The rationalisation of the stereochemical outcome of the reaction will be discussed in the next section.

In summary, the catalytic properties of diester **84** were assessed in the epoxidation of unfunctionalised alkenes rendering from good to excellent enantioselectivities. Most interestingly, we have expanded the substrate scope of epoxidation reactions catalysed by the hydrate **124** and involving Oxone® for a number of (*E*)-di- and trisubstituted alkenes obtaining very close catalytic activity to that of its parent compound **84.** Yields ranged from 41% to 99% and enantioselectivities from 60% to 94% ee. The epoxidation of terminal olefins by **84** or **124** showed poor enantioselectivities, though conversions remained high, under all tested conditions.

3. Experimental section

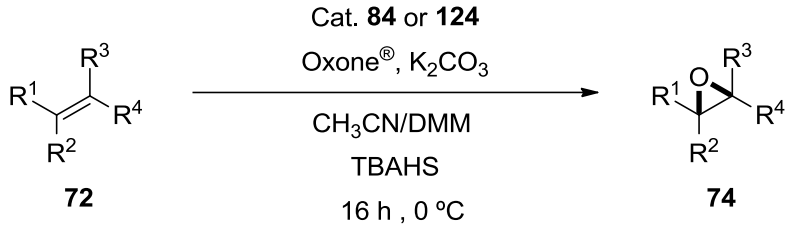
A. Experimental section organisation

The different compounds synthesised are not presented strictly in the same order of appearance as in the discussion sections of this Thesis.

B. Instrumentation

Please see Chapter I for the instrumentation conditions.

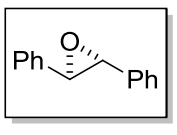
3.1 Organocatalytic asymmetric epoxidation of olefins by chiral D-fructose derivatives (diester 84 and hydrate 124)



Scheme II. 17. Organocatalytic epoxidation mediated by diester **84** or hydrate **124**.

Optimised procedure: The corresponding alkene (1 mmol) and the required amount of catalyst **84** or **124** (8–30 mol %) were dissolved in the solvent mixture CH_3CN/DMM (18 mL, 1:2 v/v). A pH = 6 buffer solution (4 mL) was slowly added at room temperature. After cooling to 0 ºC, TBAHS (4 mol %) was also added. The flask was equipped with two syringe pumps; one of them was filled with a solution of Oxone® (1.6–3.2 equiv.) in pH = 6 buffer (7 mL) and the other one with a solution of K_2CO_3 (2.4–7.2 equiv.) in water (7 mL). The two solutions were added dropwise at the same rate over a 2 h period to the cooled reaction mixture, which was stirred vigorously. The resulting suspension was stirred at 0 ºC for an additional time and then was quenched. The results obtained are included in the following pages.

3.1.1 Synthesis of (2*R*,3*R*)-2,3-diphenyloxirane, 93a



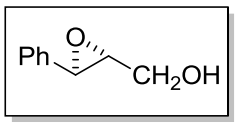
Compound **93a** was prepared according to the general procedure from (*E*)-1,2-diphenylethene (**112a**). The crude mixture was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with hexanes (4 x 20 mL/mmol). The combined organic fractions were collected and washed with brine (22 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The resultant residue was purified by flash chromatography using silica gel (hexanes/diethyl ether from 1/0 to 9/1) to give the epoxide **93a** as a white solid. Optical

purity could be increased by recrystallising the product after chromatography in hot hexane (0.7 mL/mmol).

All spectroscopy data were in agreement with those previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.88 (s, 2H), 7.15–7.41 (m, 10H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 63.0, 125.7, 128.5, 137.3.
HPLC conditions:[128b] Column Chiralpak AD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/EtOH (90:10); Flow rate: 1 mL/min; Detection: UV 254 nm. (*R*,*R*)-enantiomer (5.4 min); (*S*,*S*)-enantiomer (8.6 min).

3.1.2 Synthesis of (2*R*,3*R*)-3-(phenyloxiran-2-yl)methanol, 93c



Compound **93c** was prepared according to the general procedure from (*E*)-cinnamyl alcohol (**112c**). The crude mixture was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (3 x 20 mL/mmol). The combined organic fractions were collected and washed with brine (20 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The resultant residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 1/0 to 9/1) to give a white solid.

All spectroscopy data were in agreement with those previously reported in the literature.[133]

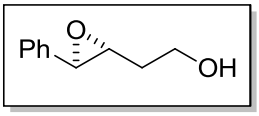
[133] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.25 (br s, 1H), 3.30-3.37 (m, 1H), 3.81 (dd, *J* = 14.2, 6.1 Hz, 1H), 4.01 (d, *J* = 3.3 Hz, 1H), 4.20 (dd, *J* = 14.2, 6.1 Hz, 1H), 7.25–7.55 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 58.2, 58.9, 64.4, 127.0, 128.5 (2C), 129.2 (2C), 138.5.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (95:5); Flow rate: 1.0 mL/min; Detection: UV 254 nm. (*R*,*R*)-enantiomer (18.0 min); (*S*,*S*)-enantiomer (16.1 min).

3.1.3 Synthesis of (2*R*,3*R*)-3-(Phenyl-oxiran-2-yl)-ethanol, 93e



Compound **93e** was prepared according to the general procedure from (*E*)-4-phenylbut-3-en-1-ol (**112d**), and using CH_2Cl_2 as solvent in the extraction. The residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 1/0 to 9/1) to give a white solid.

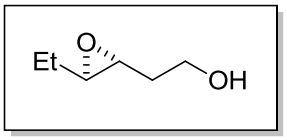
All spectroscopy data were in agreement with those previously reported in the literature.[132]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.86 (ddt, *J* = 14.7, 6.3, 6.0 Hz, 1H), 1.99 (br s, 1H), 2.1 (dtd, *J* = 14.7, 6.0, 4.2 Hz, 1H), 3.15 (ddd, *J* = 6.3, 4.2, 2.1 Hz, 1H), 3.73 (d, *J* = 2.1 Hz, 1H), 3.86 (t, *J* = 6.0 Hz, 2H), 7.20–7.40 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 34.8, 58.3, 60.0, 61.2, 125.8, 128.4, 128.7, 137.5.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (80:20); Flow rate: 0.8 mL/min; Detection: UV 216nm. (*R*,*R*)-enantiomer (9.2 min); (*S*,*S*)-enantiomer (7.6 min).

3.1.4 Synthesis of (3*R*,4*R*)-3,4-epoxyhexan-1-ol, 154b

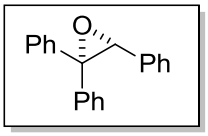


Compound **154b** was prepared according to the general procedure from (*E*)-hex-3-en-1-ol (**155a**) and using CH_2Cl_2 as solvent in the extraction. The yield was not determined as the oxirane distilled together with the solvent during the work-up.

All spectroscopy data were in agreement with those previously reported in the literature.[132]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35–1.90 (m, 4H), 2.39 (br s, 1H), 2.75 (ddd, *J* = 10.8, 5.6, 2.0 Hz, 1H), 2.87 (m, 1H), 3.78 (t, *J* = 5.6 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 9.9, 25.2, 34.3, 56.6, 59.4, 60.3.
GC Conditions: Column Alpha–Dex^{TM} 120 (Supelco); Temperature program: 5 min at 70 ºC, heating rate 0.5 ºC/min up to 90 ºC. Injector and detector: 200 ºC. (*R*,*R*)-enantiomer (27.4 min); (*S*,*S*)-enantiomer (26.9 min).

3.1.5 Synthesis of (2*R*,3*R*)-2,2,3-triphenyloxirane, 98c



Compound **98c** was prepared according to the general procedure from 2,2,3-triphenylethylene (**156b**) and using CH_2Cl_2 as solvent in the extraction. The residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes 100%) to give a white solid. Optical purity could be increased by recrystallising the product after chromatography from hot hexanes (0.9 mL/mmol).

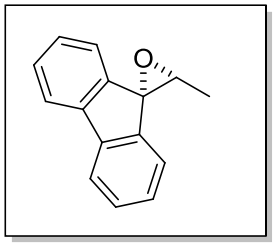
All spectroscopy data were in agreement with those previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.37 (s, 1H), 7.04–7.49 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 68.2, 68.8, 126.6, 127.0, 127.8, 127.9, 127.9, 128.0, 128.1, 128.6, 129.4, 135.7, 136.0, 141.2.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: MeOH 100%; Flow rate: 0.5 mL/min; Detection: UV 254 nm. (*R*)-enantiomer (17.4 min); (*S*)-enantiomer (10.6 min).

3.1.6 (*R*)-3′-Methylspiro[fluorene-9,2′-oxirane], 161a



Compound **161a** was prepared according to the general procedure from 9-ethylidenefluorene (**157a**) and using CH_2Cl_2 as solvent in the extraction. The residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 100/0 to 99/1) to give a yellow oil.

All spectroscopy data were in agreement with those previously reported in the literature.[134]

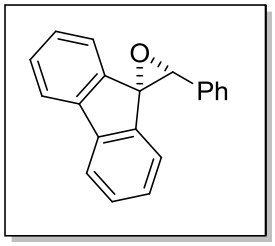
^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm): 1.70 (d, J = 5.4 Hz, 3H), 3.87 (q, J = 5.4 Hz), 7.21–7.33 (m, 3H), 7.35–7.47 (m, 3H), 7.74–7.76 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.6, 61.8, 66.6, 120.1, 120.5, 121.5, 124.2, 127.0, 128.9, 139.6, 140.2, 141.7, 142.5.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (99:1); Flow rate: 0.5 mL/min; Detection: UV 254 nm. (*R*)-enantiomer (26.5 min); (*S*)-enantiomer (30.4 min).

[134] Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, 165.

3.1.7 (*R*)-3′-Phenylspiro[fluorene-9,2′-oxirane], 161b



Compound **161b** was prepared according to the general procedure from 9-benzylidinefluorene (**157b**) and using CH_2Cl_2 as solvent in the extraction. The residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 100/0 to 99/1) to give a yellow oil.

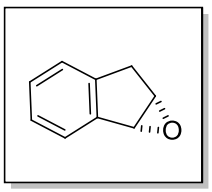
All spectroscopy data were in agreement with those previously reported in the literature.[134]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.82 (s, 1H), 6.42 (d, *J* = 11 Hz, 1H), 6.77–6.81 (m, 1H), 7.00–7.50 (m, 11H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 65.7, 67.6, 120.1, 120.3, 122.0, 123.9, 127.0, 127.2, 127.7, 128.0, 128.2, 129.1, 129.3, 135.2, 138.7, 140.6, 141.9, 142.0.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: MeOH 100%; Flow rate: 0.5 mL/min; Detection: UV 254 nm. (*R*)-enantiomer (16.4 min); (*S*)-enantiomer (20.6 min).

3.1.8 (1*R*,6*S*)-6,6-dihydro-1a*H*-indeno[1,2-*b*]oxirene, 162a



Compound **162a** was prepared according to the general procedure from 1*H*-indene (**158a**). The crude mixture was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 20 mL/mmol). The combined organic fractions were collected and washed with brine (22 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and the solvents removed under reduced pressure to give a white solid.[135]

[135] Mitrochkine, A.; Eydour, F.; Martres, M.; Gil, G.; Heumann, A.; Reglier, M. *Tetrahedron: Asymmetry* **1995**, *6*, 59.

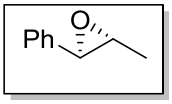
All spectroscopy data were in agreement with those previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.93 (dd, *J* = 17.9, 2.9 Hz, 2H), 3.26 (d, *J* = 17.9 Hz, 1H), 4.20 (d, *J* = 2.9 Hz, 1H), 7.00–7.23 (m, 3H), 7.48 (d, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 35.1, 58.2, 59.9, 125.7, 126.6, 126.7, 129.0, 141.4, 144.1.

HPLC conditions: Column Chiralcel OJ-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (98:2); Flow rate: 1.0 mL/min; Detection: UV 254 nm. (*R*,*S*)-enantiomer (48.7 min); (*S*,*R*)-enantiomer (14.8 min).

3.1.9 Synthesis of (2*R*,3*R*)-2-methyl-3-phenyloxirane, 93b



Compound **93b** was prepared according to the general procedure from (*E*)-prop-1-en-1-ylbenzene (**112e**). The crude of the reaction was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 20 mL/mmol). The combined organic fractions were collected and washed with brine (22 mL), dried over anhydrous Na_2SO_4, filtered, and the solvents removed under reduced pressure. The resultant residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 1/0 to 9/1) to give the title compound as an oil.

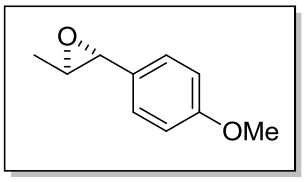
All spectroscopy data were in agreement with those previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46 (d, *J* =5.1 Hz, 3H), 3.03 (dq, *J* = 5.1, 2.1 Hz, 1H), 3.57 (d, *J*= 2.1 Hz, 1H), 7.40–7.23 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.9, 59.0, 59.5, 125.5, 128.0, 128.4, 137.7.

GC Conditions: Column Gamma-Dex^{TM} 120 (Supelco); Temperature program: 5 min at 80 ºC, heating rate 2 ºC/min up to 100 ºC, 100 ºC for 15 min. Injector and detector: 250 ºC. (*R*,*R*)-enantiomer (18.3 min); (*S*,*S*)-enantiomer (18.0 min).

3.1.10 Synthesis of (2*R*,3*R*)-2-(4′-methoxyphenyl)-3-methyloxirane, 166a

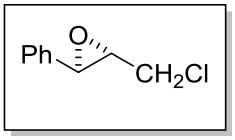


Compound **166a** was prepared according to the general procedure from (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene (**164a**). The crude of the reaction was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 20 mL/mmol). The combined organic fractions were collected and washed with brine (22 mL), dried over anhydrous Na_2SO_4, filtered, and the solvents removed under reduced pressure. The resultant residue was not further purified; conversion was determined by ^{1}H RMN.

All spectroscopy data were in agreement with those previously reported in the literature.[136]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.13 (d, *J* = 5.2 Hz, 3H), 3.81 (s, 3 H), 4.25 (qd, *J* = 5.2, 2.0 Hz, 1H), 5.72 (d, *J* = 2.0 Hz, 1H), 6.75–6.85 (m, 2H), 7.17–7.27 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.5, 58.9, 59.9, 61.2, 114.6 (2C), 127.8 (2C), 131.4, 162.1.
HPLC conditions: Column Chiralpak AD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (99:1); Flow rate: 1 mL/min; Detection: UV 230 nm. (*R*,*R*)-enantiomer (9.4 min); (*S*,*S*)-enantiomer (11.1 min).

3.1.11 (2*S*,3*R*)-2-(Chloromethyl)-3-phenyloxirane, 93f



Compound **93f** was prepared according to the general procedure from (*E*)-cinnamyl chloride (**112f**) and using CH_2Cl_2 as solvent in the extraction. The resultant residue was purified by flash chromatography using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 1/0 to 9/1) to give a colourless oil.

[136] Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Spannenberg, A.; Döbler, C.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1875.

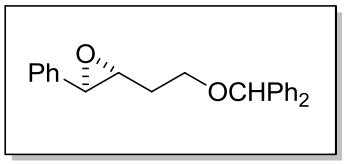
All spectroscopy data were in agreement with those previously reported in the literature.[132]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.29 (ddd, *J* = 10.8, 5.6, 2.0 Hz, 1H), 3.71 (ddd, *J* = 16.7, 10.8, 5.6 Hz, 1H), 3.74 (ddd, *J* = 16.7, 10.8, 5.6 Hz, 1H), 3.82 (d, *J* = 2.0 Hz, 1H), 7.15–7.35 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 55.6, 61.2, 62.4, 125.7, 128.3, 128.5, 136.6.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (90:10); Flow rate: 1.0 mL/min; Detection: UV 254 nm. (*S*,*R*)-enantiomer (6.5 min); (*R*,*S*)-enantiomer (7.0 min).

3.1.12 (2*R*,3*R*)-2-(2-[Benzhydryloxy]ethyl)-3-phenyloxirane, 93g



Compound **93g** was prepared according to the general procedure from (*E*)-4-phenyl-1-benzylhydryloxybut-3-ene (**112g**). The crude mixture was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 20 mL/mmol). The raw material was purified by flash chromatography using silica gel (hexanes/EtOAc from 1/0 to 9/1) to obtain a white solid.

$[\alpha]_D^{25}$ = + 28.5 (*c* 0.12, CH_2Cl_2).

M.p.: 56 ºC.

IR (cm^{-1}): 3066, 2871, 1599, 1491, 1097, 1037, 855.

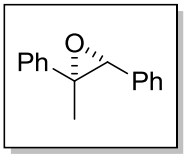
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.02 (td, 2H, *J* = 6.0, 5.6 Hz, 2H), 3.13 (td, *J*= 5.6, 1.9 Hz, 1H), 3.65 (t, 2H, *J*= 6.0 Hz, 2H), 3.69 (d, 1H, *J*= 1.9 Hz, 1H), 5.36 (s, 1H), 7.36–7.21 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 33.1 (CH_2), 58.8 (CH), 61.1 (CH), 65.7 (CH_2), 84.0 (CH), 125.7 (CH), 127.0 (CH), 127.1 (CH), 127.3 (CH), 127.6 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 137.8 (CH), 142.3 (C), 142.3 (C).

HRMS: calcd. for $C_{23}H_{22}O_2Na$ ($[M+Na]^+$): 353.1517; found: 353.1520.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (95:5); Flow rate: 0.8 mL/min; Detection: UV 216 nm. Tentative assignment: (*R*,*R*)-enantiomer (10.8 min); (*S*,*S*)-enantiomer (11.7 min).

3.1.13 (2*R*,3*R*)-2-Methyl-2,3-diphenyloxirane, 98a



Compound **98a** was prepared according to the general procedure from (*E*)-1,2-diphenylpropene (**156c**). The crude mixture was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 20 mL/mmol). The raw material was purified by flash chromatography column using SiO_2 treated with 2.5% NEt_3 (hexanes/diethyl ether from 1/0 to 9/1) to give a colourless oil.

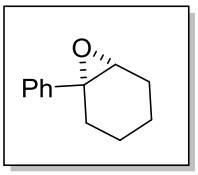
All spectroscopy data were in agreement with those previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.51 (s, 3H), 4.00 (s, 1H), 7.28–7.50 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 16.95, 63.27, 67.28, 125.4, 126.7, 127.7, 127.9, 128.4, 128.7, 136.2, 142.6.

HPLC conditions: Column Chiralcel OD-H (Chiral Technologies Inc.), Eluent: *n*-hexane/2-propanol (85:15); Flow rate: 0.8 mL/min; Detection: UV 254 nm. (*R*,*R*)-enantiomer (10.2 min); (*S*,*S*)-enantiomer (5.5 min).

3.1.14 (1*R*,2*R*)-1-Phenyl-7-oxa-bicyclo[4.1.0]heptane, 99

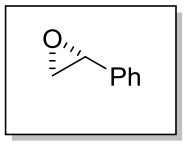


Compound **99** was prepared according to the general procedure from 1-phenylcyclohexene (**165a**). The crude mixture was quenched by addition of water (40 mL). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 40 mL). The raw material was purified by flash chromatography column using SiO_2 treated with 2.5% NEt_3 (hexanes/EtOAc from 1/0 to 9/1) to give an oil.

All spectroscopy data were in agreement with those previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25–1.65 (m, 4H), 1.95–2.03 (m, 2H), 2.12 (dt, *J* = 14.9, 4.9 Hz, 1H), 2.29 (ddd, *J* = 14.9, 8.4, 4.9 Hz, 1H), 3.09 (br s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.9, 20.3, 24.8, 28.9, 60.3, 62.0, 125.4, 127.3, 128.3, 142.6.
GC Conditions: Column Beta-Dex^{TM} 120 (Supelco); Temperature program: 60 min at 95 ºC, heating rate: 2 ºC/min up to 150 ºC, 150 ºC for 5 min. Injector and detector: 250 ºC. (*R*,*R*)-enantiomer (67.1 min); (*S*,*S*)-enantiomer (66.2 min).

3.1.15 (*R*)-2-Phenyloxirane, 97a



Compound **97a** was prepared according to the general procedure from styrene (**113a**). The crude mixture was quenched by addition of water (20 mL/mmol). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 20 mL/mmol). The combined organic fractions were collected and washed with brine (22 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and the solvents removed under reduced pressure to give a colourless oil.

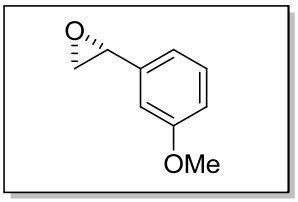
All spectroscopy data were in agreement with those previously reported in the literature.[136]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.79 (dd, *J* = 6.0, 2.4 Hz, 1H), 3.14 (dd, *J* = 6.0, 4.6 Hz, 1H), 3.8 (dd, *J* = 4.0, 2.4 Hz, 1H), 7.16–7.29 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 53.2, 55.5, 128.2 (2C), 128.9 (2C), 139.8.

GC Conditions: Column Beta-Dex^{TM} 120 (Supelco); Temperature program: 5 min at 100 ºC, heating rate: 2 ºC/min up to 190 ºC, then 190 ºC. Injector and detector: 220 ºC. (*R*)-enantiomer (31.2 min); (*S*)-enantiomer (30.8 min).

3.1.16 (*R*)-2-(3′-Methoxyphenyl)oxirane, 97c



Compound **97c** was prepared according to the general procedure from 1-methoxy-3-vinylbenzene (**113b**). The crude mixture was quenched by addition of water (40 mL). The reaction mixture was transferred into a separating funnel and extracted with CH_2Cl_2 (4 x 40 mL). The combined organic fractions were collected and washed with brine (44 mL), dried over anhydrous Na_2SO_4, filtered, and the solvents removed under reduced pressure to give a colourless oil.

All the spectroscopic data were in agreement with those previously reported in the literature.[137]

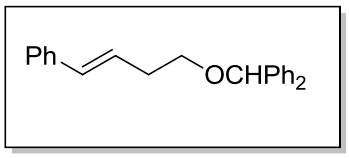
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.96 (dd, *J* = 5.2, 2.1 Hz, 1H), 3.45 (d, *J* = 2.1 Hz, 1H), 3.73 (s, 3H), 7.10–7.40 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 45.7, 50.3, 51.7, 108.9, 112.1, 117.9, 130.6, 139.2, 160.5.

GC Conditions: Column Beta-Dex^{TM} 120 (Supelco); Temperature program: 120 min at 80 ºC, heating rate: 1 ºC/min up to 150 ºC. Then, heating rate: 5 ºC/min up to 190 ºC. Injector and detector: 220 ºC. (*R*)-enantiomer (155.81 min); (*S*)-enantiomer (155.76 min).

[137] Cordes, D. B.; Kwong, T. J.; Morgan, K. A.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 349.

3.2 Synthesis of (*E*)-4-phenyl-1-benzylhydryloxybut-3-ene, 112g



A solution of (*E*)-4-phenylbut-3-en-1-ol (**112d**) (0.39 g, 2.63 mmol) in anhydrous DMF (4 mL) was added dropwise under Ar atmosphere to a suspension of NaH (0.12 g, 3.05 mmol) in anhydrous DMF (4 mL) at –20ºC. The mixture was stirred for 20 min, a solution of benzhydryl bromide (0.86 g, 3.29 mmol) in anhydrous DMF (4 mL) was then syringed into the suspension, which was further stirred at –20ºC for 4 h and at r. t. for 24 h. The reaction mixture was quenched by careful addition of methanol (40 mL) and brine (40 mL). The combined organic layers after extracting with Et_2O (2 x 100 mL) were washed with brine (3 x 30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed after filtering the drying agent and the residue was purified by flash chromatography using silica gel (hexanes/EtOAc from 1/0 to 7/3) to give a colourless oil **112g** (0.37 g, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.60 (qd, *J* = 6.9, 3 Hz, 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 5.42 (s, 1H), 6.28 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.48 (dt, *J* = 16.0, 1.3 Hz, 1H), 7.27–7.40 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 33.6, 68.7, 83.7, 126.0, 127.0, 127.2, 127.3, 127.4, 128.4, 128.5, 131.6, 137.7, 142.4.

CHAPTER III

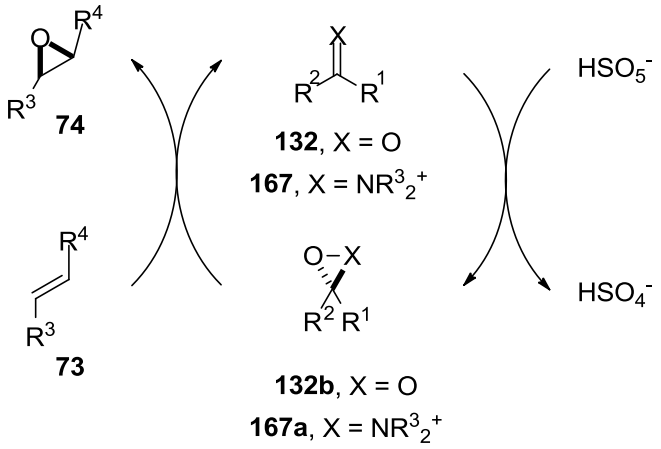
Stereochemical Studies of Dioxirane-Mediated Asymmetric Epoxidations.

1. Background

As has already been explained in the previous chapter, kinetic and labelling studies conducted during the 1970s established that the interaction of ketones with Oxone® led to the formation of a dioxirane intermediate. Dimethyloxirane, which is generated from acetone and Oxone®, is a stable molecule that can be isolated in an acetone solution, constituting a remarkably versatile new oxidant for organic synthesis.[138]

Two major classes of chiral organocatalysts have been found for Oxone®-mediated enantioselective epoxidation, which will be in turn considered: ketones and iminium salts.[139] These organocatalysts are believed to operate in mechanistically similar ways (Scheme III. 1). The interaction of Oxone® with a ketone **132** or iminium salt **167** produces a reactive three-membered heterocyclic intermediate (dioxirane **132a** or oxaziridinium derivative **167a**, respectively). These species are capable of transferring oxygen to alkenes in a concerted manner, resulting in a stereospecific epoxidation (the relative position of the substituents in the starting alkene is preserved in the product), which is a major synthetic advantage. Importantly, the starting ketone or iminium salt is regenerated, and it can thus be used in substoichiometric quantities. Moreover, in seminal experiments in the field of asymmetric catalysis, Curci *et al.* demonstrated that, if an optically pure ketone is used, there exists the opportunity for catalytic asymmetric epoxidation.[140]

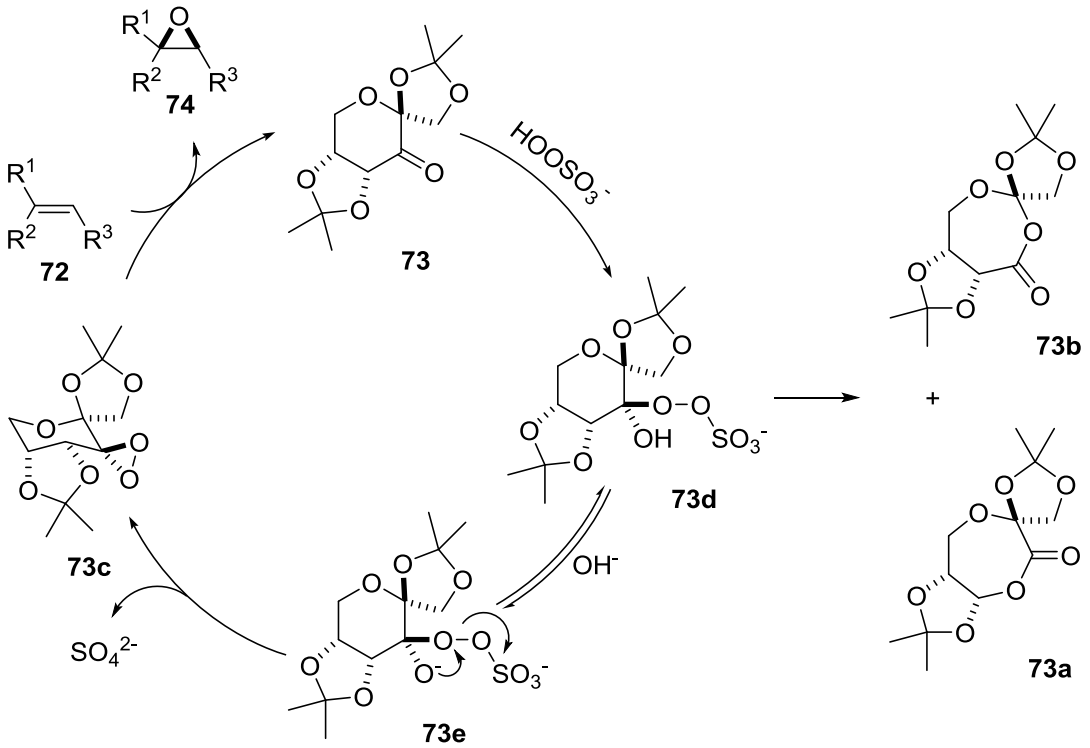
[138] Murray, R. W. *Chem. Rev*. **1989**, *89*, 1187.
[139] a) Berkessel, A. *Asymmetric Catalysis in Organic Synthesis*, Wiley-VCH, Weinheim, 2005. b) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, 2006. c) Dalko, P. I. *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, 2007. d) List, B. *Asymmetric Organocatalysis*, Springer GmbH, Berlin, 2010. e) Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry Publishing, Cambrigde, 2010.
[140] For a seminal work, see: a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. For general leading reviews, see: b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res*. **1989**, *22*, 205. c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure & Appl. Chem*. **1995**, *67*, 811. d) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847.



Scheme III. 1. Ketone- and iminium salt-catalysed alkene epoxidation.

Based on these considerations, Shi *et al.* proposed a related catalytic cycle for the asymmetric epoxidation mediated by D-fructose derivative **73**.[141,142] The following scheme shows the reaction pathways that are believed to be involved in the catalytic cycle. Chiral dioxirane **73c** is formed in three steps from ketone **73**. First, addition of $HOOSO_3^-$ into the carbonyl group affords **73d**. This intermediate then evolves into **73c** by a base-catalysed intramolecular dioxirane ring-closing reaction. The higher pH value favours the equilibrium toward intermediate **73e**. This would consequently lead to a more efficient formation of the active chiral catalyst species, the dioxirane **73**c. The newly formed dioxirane then transfers an oxygen atom to the olefin to form the corresponding epoxide, and consequently regenerates ketone **73**, which re-enters the catalytic cycle. Low pH values are both detrimental for the formation of the reactive dioxiranes and the stability of the catalysts which is degraded by a B.-V. (Baeyer-Villiger) process to lactones **73b** and **73a**. pH values ranging from 9 to 10 have proven to be optimal, as the oxidising agent (Oxone®) is stable under these conditions and the reactive dioxirane is formed at an adequate rate.

[141] Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224.
[142] For general leading references on mechanism of asymmetric epoxidation by ketone **73**, see: a) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. b) Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. c) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807. d) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818. e) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. f) Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521. g) Shi, Y. *Acc. Chem. Res.* **2004,** *37*, 488. h) Wong, O. A.; Shi, Y. *Chem. Rev*. **2008**, *108*, 3958. i) Wang, B.; Wu, X. W.; Wong, O. A.; Nettles, B.; Zhao, M. X.; Chen, D.; Shi. Y. *J. Org. Chem.* **2009**, *74*, 398. j) Bäckvall, J. E. *Modern Oxidation Methods*, Wilety-VCH, Weinheim, 2010.



Scheme III. 2. Asymmetric epoxidation catalysed by ketone **73**.

On the other hand, Shi's model for epoxidations involving the tricyclic system **73** is based on the analysis of the stereochemistry of the produced epoxides. It was known that epoxidation reactions proceed *via* transition states with geometries ranging between two extreme situations: planar or spiro.[140c,143]

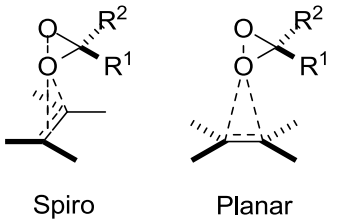


Figure III. 1. Spiro and planar transition states for the dioxirane epoxidation of olefins.

The chiral dioxirane derived from **73**, adopting a chair conformation, has two diastereotopic oxygens and, on the basis of steric arguments, the equatorial oxygen is

[143] a) Yang, D.; Wang, X. C.; Wong, M. K.; Yip, Y. C.; Tang, M. W. *J. Am. Chem. Soc*. **1996**, *118*, 11311. b) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806, and references cited therein.

likely to be the more accessible to the olefin approach, with the major enantiomer resulting *via* a spiro-like transition state (Figure III. 2).[142]

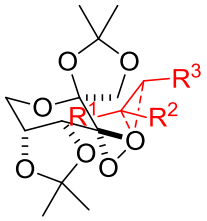


Figure III. 2. Spiro transition state favoured by **73** based on the major enantiomer resulting in the asymmetric epoxidation.

Singleton and Wang, studying the epoxidation of (*E*)-prop-1-en-1-ylbenzene **112e** with Shi's ketone **73**, measured experimental kinetic isotopic effects (KIE) and performed DFT calculations. Their results support Shi's earlier analysis and revealed that the observed major enantiomer arises from an asynchronous spiro transition state (TS).[144] Interestingly, the geometry of the TS leading to the minor enantiomer does not fit with either a planar or a spiro arrangement. Rather, the plane of the developing epoxide is twisted *ca*. 45˚ from the plane of the dioxirane, thereby increasing the asynchronicity of the TS. The following figure includes the asynchronous transition states for the reaction of the parent dioxirane with ethylene.

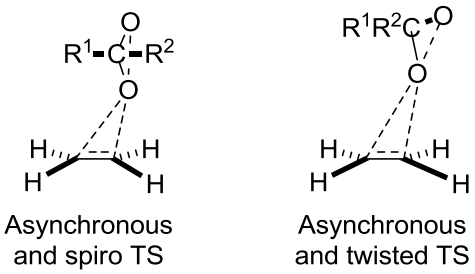


Figure III. 3. Type and geometry of the TS in the epoxidation of alkenes according to Singleton and Wang.[144]

Dioxiranes are being widely adopted as a new class of efficient, selective and mild oxidising agents for a wide variety of substrates. Despite the ever-increasing number of applications of dioxiranes in synthesis, many aspects related to their mechanism of action and to the ongoing stereodifferentiating proceses are still understudied.

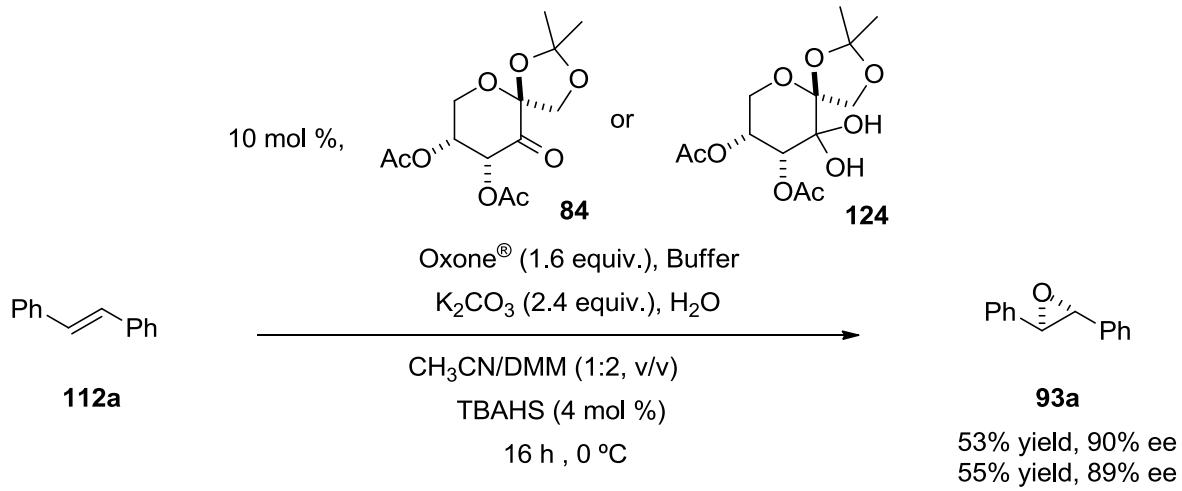
[144] Singleton, D. A.; Wang, Z. *J. Am. Chem. Soc*. **2005**, *127*, 6679.

We became also interested in understanding why hydrate **124** was an active catalyst in this chemistry and in gaining insight into the origin of the stererodifferentiating proceses in the organocatalysed epoxidation of unfunctionalised alkenes mediated by ketone **84** or hydrate **124**.

The following sections of this chapter will detail our research efforts in these directions.

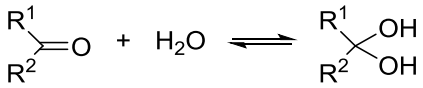
2. Dioxirane-mediated asymmetric epoxidation: Studies on the role of hydrate species

As has already been mentioned in the previous chapter, both ketone **84** and hydrate **124** mediate the asymmetric epoxidation of unfunctionalised alkenes with the same conversion and selectivity (see Chapter II for the full discussion**).**



Scheme III. 3. Asymmetric epoxidation of olefins using **84** or **124** as catalyst.

It is well known that the addition of water to an aldehyde or ketone may lead to the formation of hydrates or *gem*-diols.[145] Hydrates are usually only stable in water solutions, as the equilibrium shifts back towards the carbonyl compound in anhydrous solvents (Scheme III. 4).



Scheme III. 4. Ketone-hydrate equilibrium.

[145] For instance, see: a) Bell, R. P. *The Proton in Chemistry*, Cornell University Press, Ithaca, NY, 1973. b) Bell, R. P. *Adv. Phys. Org. Chem*. **1966**, *4*, 1. c) Le Hénaff, P. *Bull. Soc. Chim. Fr*. **1968**, 4687. d) Brown, W. H.;, Foote, C. S.; Iverson, B. L. *Organic chemistry*, Brooks/Cole Cengage learning, EEUU, 2009. e) McMurry, J. *Organic Chemistry*, Brooks/Cole Cengage learing, EEUU, 2011. f) Parsons, A. *Keynotes in Organic Chemistry*, Blackwell Science Ltd., Oxford, 2003.

The position of the equilibrium greatly depends on the structure of the hydrate. Whilst formaldehyde in water at 20 ºC exists 99.99% in the hydrated form, acetaldehyde is partially hydrated at 58% under the same conditions.[146]

Dialkyl-substituted ketones do not tend to form hydrates (the concentration of acetone hydrate in water at 20 ºC is negligible),[146] but the presence of electron-withdrawing groups in the α-carbonyl carbons favours hydrate formation. The hydrate of trichloroacetaldehyde is a stable crystalline solid.[147]

It has also been found that the hydration of C=O compounds is accelerated by acid or basic catalysis.[146]

With all of these precedents, it seemed plausible to us that hydratation of catalyst **84** could take place in the epoxidation reaction mixture. Diester **84** incorporates one electron-withdrawing group (I-) in each of the two α-carbonyl carbons. Furthermore, epoxidation is carried out in an aqueous medium in the presence of a base: therefore prerequisites for an effective C=O hydration are fulfilled.

Most interestingly, ^{13}C NMR analysis of diester **84** in the same solvent mixture as the one used during the epoxidation (CD_3CN/DMM, buffer solution at pH = 9) revealed that the signal attributable to the ketonic carbonyl in **84** (δ = 193.6) had a very low intensity and had almost disappeared (see Figure III. 4).

[146] a) Bell, R. P.; Clunie, J. C. *Trans. Faraday Soc.* **1952**, *48*, 439. b) Bell, R. P.; McDougall, A. O. *Trans. Faraday Soc.* **1960**, *56*, 1281.
[147] Luknitskii, F. I. *Chem. Rev*. **1975**, *75*, 259.

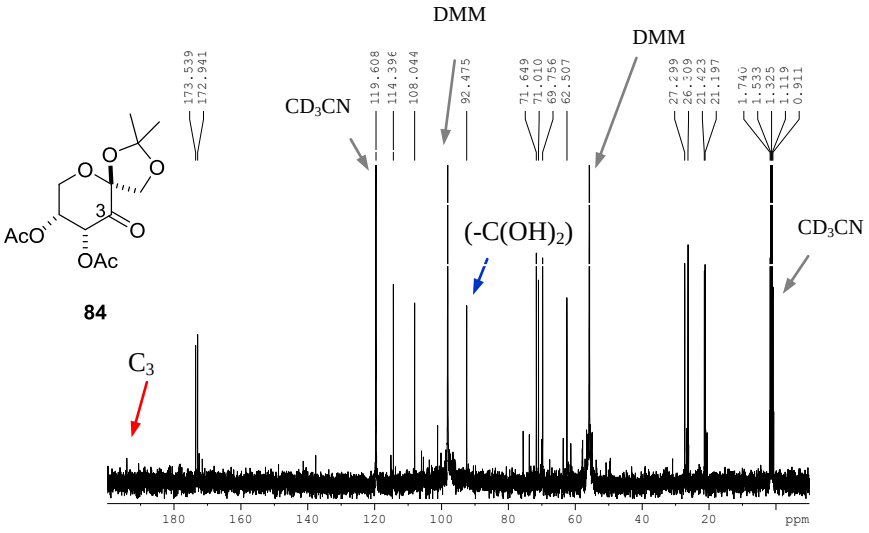


Figure III. 4. ^{13}C NMR spectrum of ketone **84** in CD_3CN, dimethoxymethane and buffer at pH = 9.

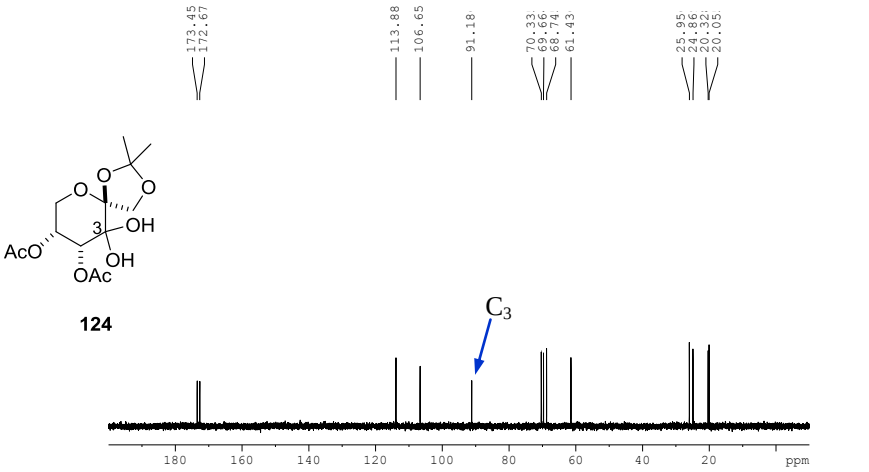


Figure III. 5. ^{13}C NMR spectrum of hydrate **124** in D_2O.

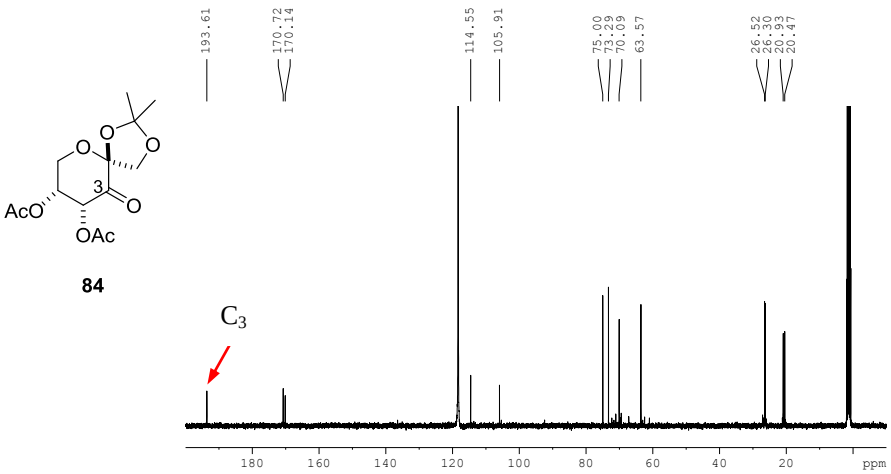


Figure III. 6. ^{13}C NMR spectrum of ketone **84** in CD_3CN.

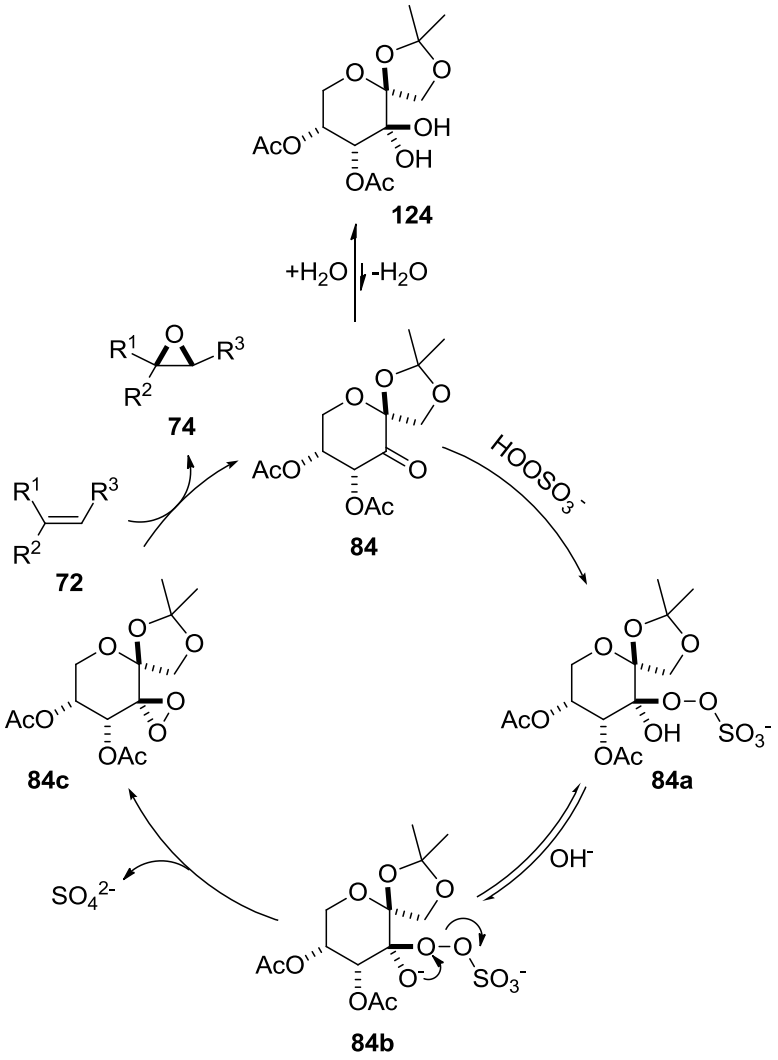
Conversely, an intense signal at 91.3, which is characteristic of the $C(OH)_2$ carbon in hydrate **124**, was observed.

These results clearly indicate that ketone **84** is mainly transformed into its hydrate in the epoxidation reaction medium.

In light of these results, Scheme III. 5 shows the proposed reaction pathways involved in the catalytic cycle. We assume that an equilibrium is established between **84** and **124** under the epoxidation conditions.[142e,146–148]. According to the commonly accepted mechanism, chiral dioxirane **84c** is thus formed in three steps from ketone **84**.[149] First, addition of the HSO_5^- anion onto the carbonyl group affords **84a**. This intermediate then evolves to dioxirane **84c** by a base-catalysed intramolecular dioxirane ring-closing reaction. The high pH value, favours the equilibrium toward intermediate **84b**. This would consequently lead to a more efficient formation of the active chiral catalytic species, dioxirane **84c**. The newly formed dioxirane then transfers an oxygen atom to the olefin to form the corresponding epoxide, while **84** is regenerated.

[148] For ketone-hydrate equilibria in referable systems, see: a) Follmann, H.; Hogenkamp, H. P. C. *J. Am. Chem. Soc*. **1970**, *92*, 671. b) Denmark, S. E.; Wu, Z.; Crudden, C. M.;. Matsuhashi, H. *J. Org. Chem*. **1997**, *62*, 8288. c) Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715.

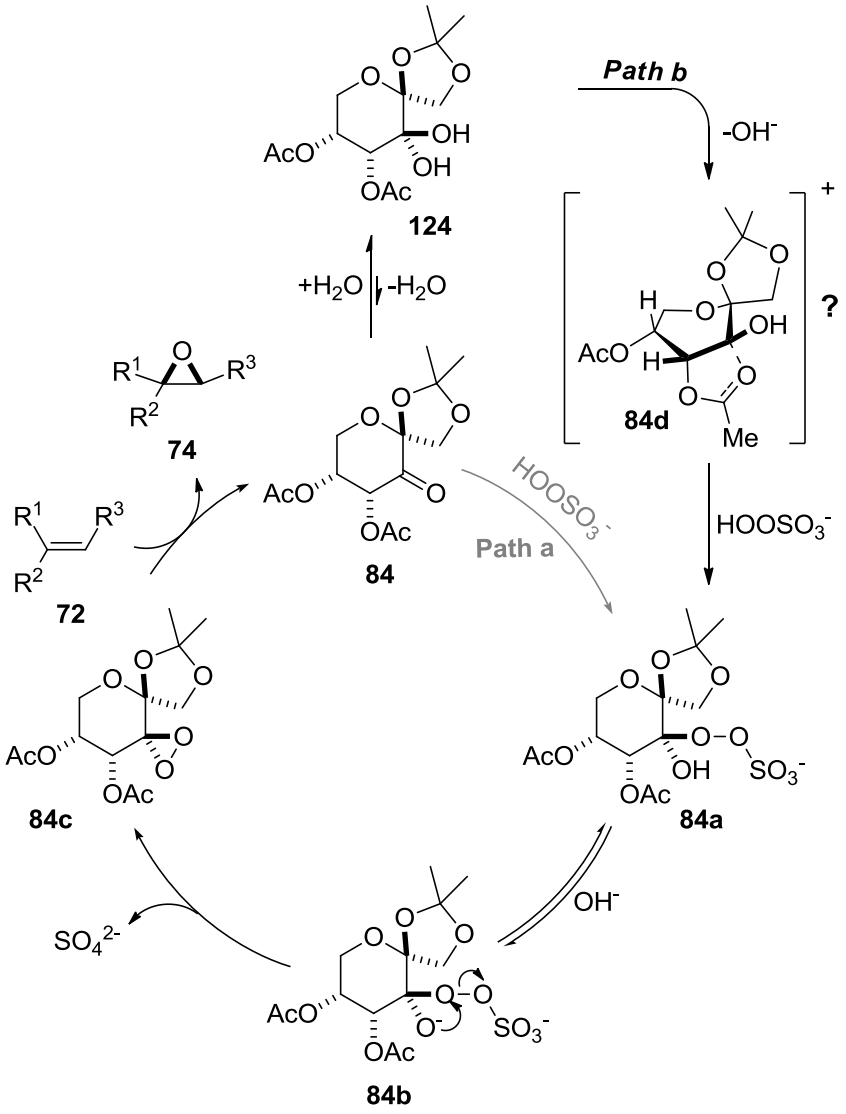
[149] For leading references on this transformation, see: a) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U. S. A*. **2004**, *101*, 5794. b) Yang, D. *Acc. Chem. Res*. **2004**, *37*, 497. c) Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev*. **2005**, *105*, 1603.



Scheme III. 5. Asymmetric epoxidation catalysed by **124**.

Within this mechanistic rationalisation, hydrate **124** would only be acting as a catalyst reservoir, as the reactive dioxirane would be formed from the minor ketone amounts present in the reaction medium. This mechanistic rationalisation is in agreement with the commonly accepted mechanism of the reaction, though it suffers form a weakness: it is assumed that the reaction proceeds from trace catalyst amounts (see Scheme III. 6).

The great tendency of **84** to exist as the hydrated form suggests that the formation of **84a** could also take place through the stable tetrahedral intermediate **84d** by HSO_5^- attack at the dihydroxy substituted carbon of hydrate **124** (path b, see Scheme III. 6).



Scheme III. 6. Possible mechanism for asymmetric epoxidation of olefins catalysed by **124**.

The epoxidation reaction would then proceed as described for path a and hydrate **124** would be regenerated by hydratation of **84**. As can be observed in Scheme III. 6, ketone **84** completely evolves to its hydrate form under the basic reaction conditions. Therefore, the whole process involving **124** could be regarded as a catalytic process.

Unfortunately, we were unable to isolate compound **84d**, nor could it be proved by spectroscopic methods that a hydroxyl group in hydrate **124** is displaced by the peroxomonosulfate anion.[150]

However, in order to establish if nucleophilic displacement onto **124** was possible, other nucleophiles were tested. Methanolysis of **124** at room temperature and in the absence of acid or basic catalysis led to the isolation of methanolate **168**. Crystals of the methanolysis product of **124** were thus isolated and X-ray analysis of these crystals (see Figure III. 7) revealed that methanol stereoselectively displaced the pro-*S* hydroxyl group in **124**.

The neighbouring acetate group might be lending anchimeric assistance to the methanolysis reaction by formation of the stabilised tetrahedral intermediate **84d** (see Scheme III. 6), as has been reported for analogous transformations.[151]

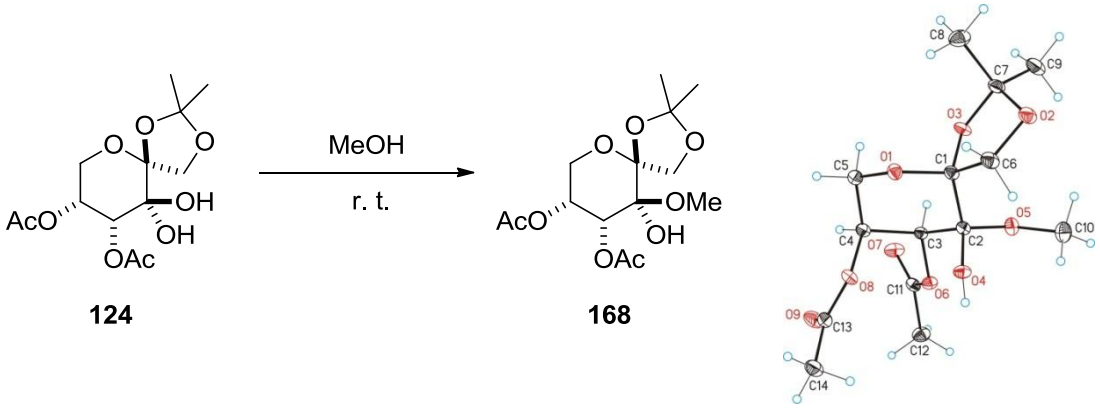


Figure III. 7. ORTEP plot (thermal ellipsoids shown at 50% probability level) of the methanolate **168**.

In an analogous way to our suggestion for the methanolysis reaction, the neighbouring acetate group might be lending anchimeric assistance to the displacement of an OH group from the hydrate by the peroxomonosulfate anion.

[150] ^{13}C NMR analysis after treating hydrate **124** with Oxone® in the usual reaction mixture (CD_3CN/DMM, buffer solution at pH = 9) did not show the characteristic signal of the $C_3(OH)_2$ group from the hydrate. Although it can be assumed that no hydrate is present in the presence of Oxone®, we could not unequivocal establish the structure of the formed product.
[151] Fox, J. M.; Dmitrenko, O.; Liao, L.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317.

While it has been reported that hydrates can potentially shut down the whole epoxidation cycle,[142e,148] results described in this work suggest that hydrates bearing suitable neighbouring groups can catalyse the epoxidation of alkenes by Oxone®. Work is still in progress to definitely prove this assumption.

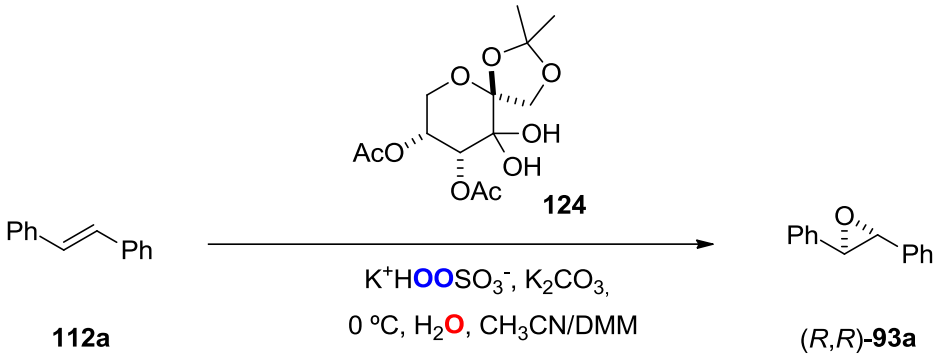
2.1 Study of the stereodifferentiating processes in the epoxidation of alkenes using Oxone® and ketone 84 or hydrate 124 as chiral organocatalysts

This Ph.D. Thesis is also concerned with demostrating the origin of the stereodifferentiating process throughout the epoxidation of alkenes.

We envisaged that a study *via* chemoselective isotopic labeling of the dioxirane species derived from bicyclic chiral catalyst **84** or **124**, could clarify experimentally the origin of the stereodifferentiating processes in the organocatalysed epoxidation of unfunctionalised alkenes mediated by these chiral catalysts. Similar results in terms of conversion and enantioselectivity have been obtained independently of whether ketone **84** or hydrate **124** was used. For this reason, we used enantiomerically pure hydrate **124** in the following studies for the sake of convenience.

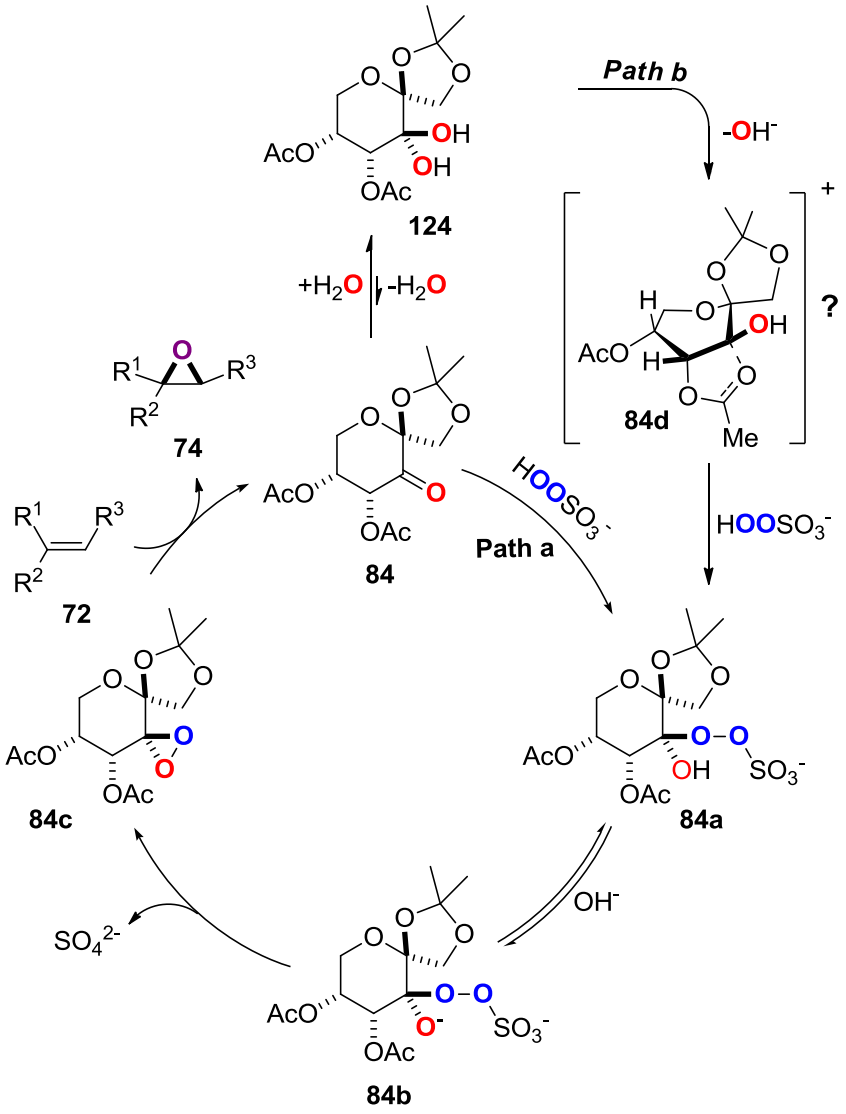
We therefore carried out the epoxidation of the (*E*)-1,2-diphenylethene (**112a**) using labeled species in the optimised reaction conditions. Epoxidations (Scheme III. 7) were carried out in the usual organo-aqueous media and pH value with 10 mol % catalyst at 0 ºC, as this temperature and pH value offer a good balance between conversion and selectivity (see Chapter II).[152]

[152] Higher pH values were not considered since the background reaction could be significant. See: Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577.



Scheme III. 7. Epoxidation of **112a** mediated by hydrate **124** (purple colour has been used to indicate the uncertainty in the source of the epoxide oxygen atom)

According to the literature and to our own results, the reaction pathways believed to be involved in the catalytic cycle are shown in the following scheme:



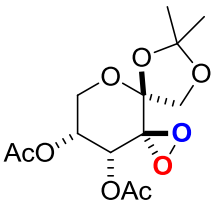
Scheme III. 8. Asymmetric epoxidation catalysed by hydrate **124**.

Equilibrium is established between the ketone and hydrate under the epoxidation conditions.[142e,148c] As also explained previously, chiral dioxirane **84c** can thus be formed in three steps from ketone **84**. First, addition of $KHSO_5$ onto the carbonyl group affords **84a**. This intermediate then evolves to dioxirane **84c** by a base-catalysed intramolecular dioxirane ring-closing reaction. The higher the pH value, the faster the dioxirane ring formation proceeds and therefore the active chiral catalytic species forms. The newly formed dioxirane then transfers an oxygen atom to the olefin to form the corresponding epoxide, whereby ketone **84** is regenerated.

Alternatively, formation of tetrahedral intermediate **84d**, followed by displacement of the pro-*S* hydroxy group by HSO_5^- attack then leads to **84a**.

Epoxidation then proceeds as described for "path a" and hydrate **124** is regenerated by hydration of the ketone **84**. Therefore, the whole process involving **124** could also be regarded as catalytic.

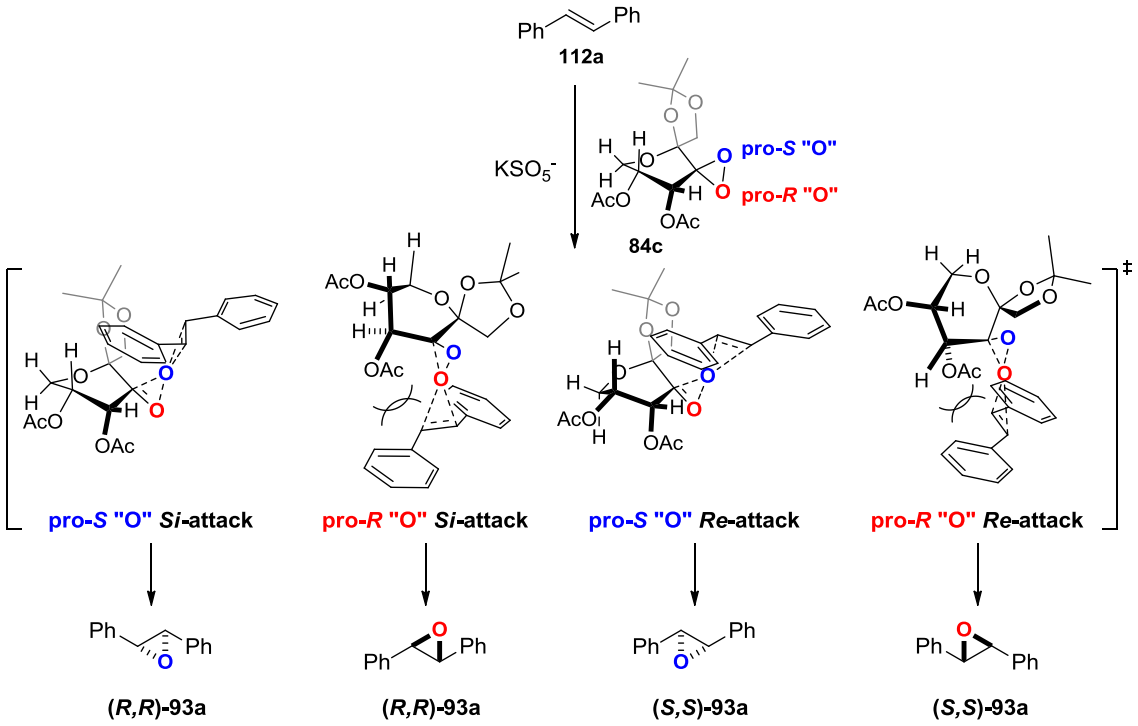
In Scheme III. 8 the two diasterotopic oxygens of the catalyst-derived dioxirane have been drawn in different colour depending on their origin; the one that comes from the oxidising agent is in blue and the one that comes from the initial fructose is marked in red (Figure III. 8). This assumption on the colour codes and origin of the "O" groups implies that there is an attack to the least hindered face of the fructose derivative **84** (β face of the carbohydrate) by HSO_5^- or a substitution of the pro-*S* hydroxyl group in **124** by HSO_5^-.



84c

Figure III. 8. Dioxirane derived from hydrate **124**.

The epoxidation has four possible stereochemical outcomes as each of the two diastereotopic oxygens of the chiral dioxirane **84c** can be delivered onto each of the two enantiotopic faces of the alkene. The four possible diastereomeric transition states for the epoxidation of an alkene are depicted in the following scheme:



Scheme III. 9. Possible stereochemical outcomes of the asymmetric epoxidation of (*E*)-1,2-diphenylethene (**112a**) catalysed by **124**.

Shi *et al.* have postulated that for catalyst **73** the major epoxide enantiomer observed results from the attack of the least-hindered oxygen of the dioxirane by the *Si*-alkene face (pro-*S* "**O**" *Si*-attack). Accordingly, the minor enantiomer could be generated by a pro-*S* "**O**" *Re*-attack. Epoxidation *via* pro-*R* "**O**" attack is thought to be unfeasible because of steric interactions between the alkene and the substituents of the catalyst **73**.

To experimentally clarify the origin of the stereodifferentiating processes, in the case of hydrate **124**, we explored the epoxidation of (*E*)-1,2-diphenylethene (**112a**) with $KSO_3{}^{18}\mathbf{O}{}^{18}\mathbf{O}H$, and then the epoxidation with $H_2{}^{18}\mathbf{O}$, using the previously optimised reaction conditions and 30 mol % of catalyst.

The $^{18}\mathbf{O}$-labeled analogue of Oxone® was prepared from $H_2{}^{18}\mathbf{O}_2$ (90% $^{18}\mathbf{O}$-content) and oleum.[153]. As $H_2{}^{18}\mathbf{O}_2$ was provided by the supplier as a diluted solution (3% H_2O_2 content), the original recipe from Flanagan *et al.* for the synthesis of Oxone® from H_2O_2 had to be slightly modified (see experimental part for details).

[153] Flanagan, J.; Griffith, W. P.; Skapski, A. C *J. Chem. Soc., Chem. Commun.* **1984**, 1574.

With $KSO_3{}^{18}O{}^{18}OH$ in hand, the epoxidation of (*E*)-1,2-diphenylethene using 30 mol % of hydrate **124** was studied. After the usual work-up, (2*R*,3*R*)-2,3-diphenyloxirane **93a** (94% ee) was obtained in low conversion. This was attributed to an inefficient preparation of labelled Oxone® due to experimental difficulties.

The relative abundance of $^{18}O/^{16}O$ isotopologues in the final epoxide was determined by mass spectrometry (see experimental part of this Chapter III; Section 3.2). This analysis showed that the epoxidation product ^{18}O-(2*R*,3*R*)-2,3-diphenyloxirane had the same $^{18}O/^{16}O$ proportion as that of the oxidising agent (89.4 ± 0.4% experimental *vs*. 90.0 ± 0.3% theoretical).[154] These results indicate that the epoxidation involves two stereoselective processes. The first comprises a highly stereoselective attack to the β face of **84** by HSO_5^-. Subsequent dioxirane ring formation by intramolecular cyclisation gives chiral dioxirane **84c**, whereby the oxygen marked in blue in Scheme III. 8 would be ^{18}O. The second step comprises an oxygen transfer through approach of the *Si*-alkene face onto the β face of dioxirane **84c** (pro-*S* "**O**" *Si*- attack). The fact that the final epoxide is fully ^{18}O-labeled can only be accounted for by very high stereoselectivity in both processes. In an analogous way to this doubly stereoselective process, the methanolysis of hydrate **124** takes place in the absence of acidic or basic catalysis with the stereoselective displacement of its pro-*S* hydroxyl group. Crystals of the derivative **168** could be isolated by slow evaporation of the solvent; X-ray analysis (see Figure III. 7) validated the absolute stereochemistry of the methanolate **168**.

Epoxidation of (*E*)-1,2-diphenylethene (**112a**) with standard Oxone® in $H_2{}^{18}O$ (*ca*. 10% ^{18}O content) was then carried out, yielding unlabeled (2*R*,3*R*)-2,3-diphenyloxirane **93a** (^{18}O content < 0.1%).

Mass spectrometry revealed an exchange process between the *gem*-diol group of **124** and the solvent (experimental 9.8 ± 0.5% *vs*. 10.2 ± 0.3% theoretical), thus indicating

[154] For other examples of ^{18}O-labeling in the study of related transformations see: a) Denmark; S. E. Wu. Z. *J. Org. Chem*. **1997**, *62*, 8964. b) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H; Cheung, K. K. *J. Am. Chem. Soc*. **1998**, *120*, 5943; c) González-Núñez, M. E.; Mello, R.; Royo, J.; Ríos, J. V.; Asensio, G. *J. Am. Chem. Soc*. **2002**, *124*, 9154.

that the ^{18}**O**-label is incorporated into the catalyst. Assuming a preference for attack by the oxidant at the β face, this ^{18}**O**-labeled species could evolve to the dioxirane **84c**, whereby the oxygen marked in red in Scheme III. 9 would be ^{18}**O**. Attack of the most hindered face of **84c** (pro-*R* "**O**" attack) by the alkene would thereby yield ^{18}**O**-(2*R*,3*R*)-2,3-diphenyloxirane. As the final epoxide did not incorporate any ^{18}**O**, we conclude that the facial selectivity of the oxygen transfer is also very high.

These results reveal several key aspects about the origin of the stereoinduction and these can be summarised as follows: i) The epoxidation process comprises highly stereoselective attack of the β face of **84** by HSO_5^-; ii) Subsequent dioxirane ring formation renders chiral dioxirane **84c**, whereby the oxygen marked in blue (Scheme III. 9) comes from the oxidant; iii) Oxygen transfer from the dioxirane to the alkene proceeds predominately through approach of the *Si*-alkene face onto the β face of dioxirane **84c** (pro-*S* "**O**" *Si*- attack); iv). Attack of the most hindered face of **84c** (pro-*R* "**O**" attack) by the alkene does not take place to a measurable extent. Although the two acetate groups have more conformational freedom with respect to the dioxirane ring than in the standard Shi´s catalyst, they are bulky enough to prevent the pro-*R* "**O**" attack. Furthermore, while the participation of the pro-*R* "**O**" transition states have been ruled out by computational studies in tricyclic catalysts on the basis of steric grounds, our labeling studies experimentally supports the currently accepted model of dioxirane epoxidations to the chiral bicyclic platform provided by the catalyst. One potential application of this methodology would be to use the labeled dioxiranes as a means of investigating oxygen transfer to some less-than-optimal substrates, with the extent of label transfer providing an efficient marker of α *vs.* β face approach.

3. Experimental section

A. Experimental section organisation

The different compounds synthesised are not presented strictly in the same order of appearance as in the discussion sections of this Thesis.

B. Instrumentation

Please see Chapter I for the instrumentation conditions.

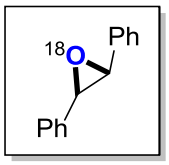
3.1 Asymmetric epoxidation of 93a with ^{18}O-labeled tracers

3.1.1 Preparation of $KSO_3{}^{18}O{}^{18}OH$

$^{18}O_2$-Hydrogen peroxide (Cambridge Isotope Laboratories, 0.93 g, 2.5% H_2O_2 content in water, 23 mg, 0.60 mmol, 90 ± 0.3% ^{18}O-content) was carefully concentrated *in vacuo* (70 ºC, 90 mbar) by eliminating 0.84 g of distillate through a 5 cm Vigreux column. The residue was cooled to –5ºC and fuming sulfuric acid (20% as free SO_3, 0.49 g, 1.22 mmol of SO_3) was carefully added (10 min). The mixture was allowed to reach 0 ºC and was stirred for a further 2 h period. Aqueous K_2CO_3 (0.65 g) in 1 mL water was added dropwise (10 min) to the solution, which was further stirred for 15 min. The suspension which contained $KSO_3{}^{18}O{}^{18}OH$ (0.60 mmol theoretical amount) was stored at 4 ºC and used in the next step without any further work-up or purification.

3.1.2 Epoxidation of (*E*)-1,2-diphenylethene with $KSO_3{}^{18}O{}^{18}OH$

(*E*)-1,2-diphenylethene **112a** (65 mg, 0.35 mmol) and hydrate **124** (34 mg, 0.10 mmol) were dissolved in the solvent mixture acetonitrile/DMM (1:2 v/v, 6 mL). A pH = 6 buffer solution (1.3 mL), tetra-*n*-butylammonium hydrogen sulfate (5 mg, 0.015 mmol) was slowly added with stirring and the mixture was cooled to 0 °C. The flask was equipped with two syringe pumps; one filled with a solution of $KSO_3{}^{18}O{}^{18}OH$ (0.60 mmol theoretical amount, reaction mixture from the previous step) in pH = 6 buffer (2.3 mL) and the other one with a solution of aqueous K_2CO_3 (0.11 g, 0.83 mmol) in H_2O (2.3 mL). The two solutions were added dropwise over a 2 h period. The solution was stirred at 0 ºC for 18 h. The reaction mixture was extracted with hexanes (4 x 6 mL). The combined organic fractions were washed with brine (10 mL) and then dried over anhydrous Na_2SO_4. ^{18}O-(2*R*,3*R*)-2,3-diphenyloxirane **93a** was obtained, together with starting material, after filtration and removal of hexanes *in vacuo*. No isolation of the ^{18}O-(2*R*,3*R*)-2,3-diphenyloxirane was attempted.

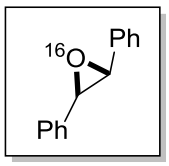


^{18}O-(2*R*,3*R*)-2,3-diphenyloxirane 93a. ^{1}H NMR and MS-CI analysis of the raw material confirmed the conversion of the epoxidation (7 μmol, 2% conv.) and the relative abundance of the ^{16}O/^{18}O isotopologues (89.4 ± 0.4 % experimental *vs.* 90.0 ± 0.3% theoretical), respectively.

HPLC conditions: Column Chiralpak AD-H (Chiral Technologies Inc.), Eluent *n*-hexane/EtOH (90:10); Flow rate: 1 mL/min; Detection: UV 254 nm. (*R*,*R*)-enantiomer (5.4 min); (*S*,*S*)-enantiomer (8.6 min) indicated 94% ee.

3.1.3 Epoxidation of (*E*)-1,2-diphenylethene with $H_2{}^{18}O$

This transformation was carried out at 0 °C as described in the general procedure using: (*E*)-1,2-diphenylethene **112a** (20 mg, 0.11 mmol), hydrate **124** (10 mg, 0.032 mmol), TBAHS (2 mg, 0.005 mmol), pH = 6 buffer (0.4 mL), acetonitrile/DMM (1:2 v/v, 2 mL), Oxone® (0.11 g, 0.17 mmol) in pH = 6 buffer[155] (0.7 mL) and aqueous K_2CO_3 (0.35 g, 0.25 mmol) in $H_2{}^{18}O$ (0.7 mL, 10.2 ± 0.3% ^{18}O-content). The reaction was quenched as described in the general procedure after stirring for 18 h at 0 ºC. ^{16}O-(2*R*,3*R*)-2,3-diphenyloxirane **93a** was obtained after extraction together with starting material. No isolation of the latter compound was attempted: ^{1}H NMR analysis from the raw material confirmed the conversion of the epoxidation and the relative abundance of the ^{16}O/^{18}O isotopologues.



^{16}O-(2*R*,3*R*)-2,3-diphenyloxirane 93a. (0.08 mmol, 72% yield). In the case of recovered catalyst **124** excellent agreement was found using the least squares determined ^{18}O/^{16}O proportion, 9.8 ± 0.5% ^{18}O-content, whilst for compound (2*R*,3*R*)-2,3-diphenyloxirane **93a** the experimental mass spectrum is perfectly reproduced by the pure ^{16}O isotopologue calculated intensities (^{18}O content < 0.1%).

[155] Buffer was also prepared with $H_2{}^{18}O$. Buffer solution (0.05 M potassium dihydrogen phosphate and 1.0 M potassium hydroxide, 5.7 mL/L).

3.2 Mass Spectrometric determination of the relative abundance of $^{16}O/^{18}O$ isotopologues from the epoxidation of (*E*)-1,2-diphenylethene with $KSO_3{}^{18}O{}^{18}OH$

A time-of-flight (TOF) mass spectrometer (Waters GCT) coupled to a gas chromatograph (Agilent 6890N) was used to determine the relative abundance of $^{16}O/^{18}O$ labeled compound ^{18}O-(2*R*,3*R*)-2,3-diphenyloxirane **93a**. The GC conditions were as follows: A DB-XLB (Agilent) column, 30 m × 0.18 mm × 0.18 μm; GC analysis time 30 min (compound ^{18}O-(2*R*,3*R*)-2,3-diphenyloxirane, retention time = 21 min); inlet temperature 250 °C (1 ng of sample injected, split ratio 100:1); oven temperature program, 40 °C held for 3 min, then a 10 °C/min ramp to 340 °C; GC carrier gas He; constant flow 0.6 mL/min. The mass spectrometer was operated in positive ion mode, using CH_4 as the chemical ionisation reagent gas at a source pressure of 2×10^{-4} mbar. The ion source temperature was 165 °C with electron energy of 70 eV and an emission current of 100 μA. Spectra were acquired at 25,000 Hz using an integration time of 0.45 s and a delay of 0.05 s (2 integrated spectra per second).

The $^{16}O/^{18}O$ isotopologues were not separated using the GC method applied in this work. Rather, the GC sample introduction provided an accurate means of background ion subtraction, facilitating subsequent $^{16}O/^{18}O$ determination by comparison with a simulated mixed isotopologue mass spectrum. The simulation is generated by convolution of the respective $^{16}O/^{18}O$ isotopologue *m/z* channel intensities, as determined experimentally using a pure, unlabeled standard (Sigma Aldrich). The relative intensities in each *m/z* channel are assumed to be identical for the two isotopologues. The $^{16}O/^{18}O$ proportion, the only free parameter in the simulation, is obtained from a least squares fit of the observed intensities as a function of the intensities in the calculated spectrum.

After the epoxidation, catalyst **124** was analysed for $^{16}O/^{18}O$ content using a time-of-flight (TOF) mass spectrometer equipped with an electrospray ionisation (ESI) source (Waters LCT premier) applying the following conditions: capillary voltage 3 kV, cone voltage 30 V, desolvation gas temperature 150 °C, source temperature 100 °C. The

sample solution (1 ng/μL in sodium acetate doped CH_3CN) was introduced into the spectrometer by direct infusion at 10 μl/min. Spectra were acquired at 25,000 Hz using an integration time of 0.9 s and a delay of 0.1 s (1 integrated spectrum per second).

Figure III 9 shows the calculated and observed isotopic patterns for compounds ^{18}**O**-(2*R*,3*R*)-2,3-diphenyloxirane **93a** and hydrate **124**. In the case of compound ^{18}**O**-(2*R*,3*R*)-2,3-diphenyloxirane excellent agreement is found using the least squares determined ^{16}O/^{18}**O** proportion, 10.6%, whilst for compound **124** the experimental mass spectrum is perfectly reproduced by the pure ^{16}O isotopologue calculated intensities.

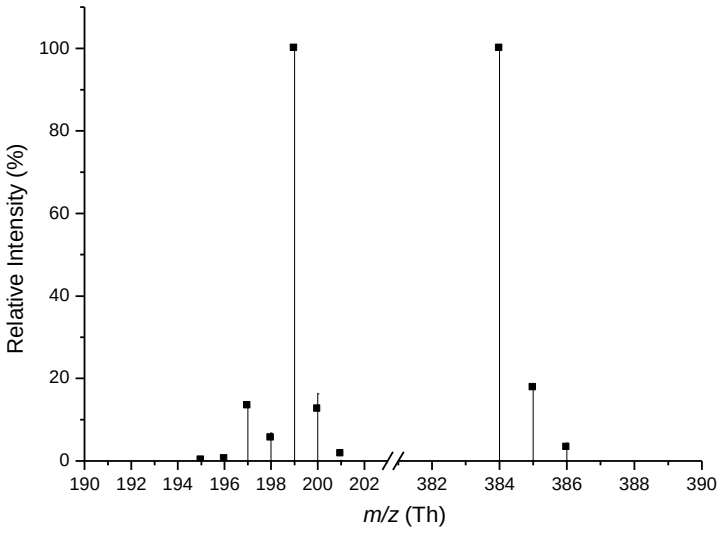


Figure III. 9. Mass spectra and simulated isotopic profiles (squares) of the mixed ^{16}O/^{18}**O** isotopologue $[M+H]^+$ ion of ^{18}**O**-(2*R*,3*R*)-2,3-diphenyloxirane **93a** (monoisotopic masses 197 and 199) and $[M+Na+CH_3CN]^+$ ion of hydrate **124** (monoisotopic masses 384 and 386).

Figure III. 10 demonstrates the reliability of the derived ^{16}O/^{18}O proportion value for compound ^{18}**O**-(2*R*,3*R*)-2,3-diphenyloxirane; a sharp minimum least squares difference is evident at around 10–11% ^{16}O.

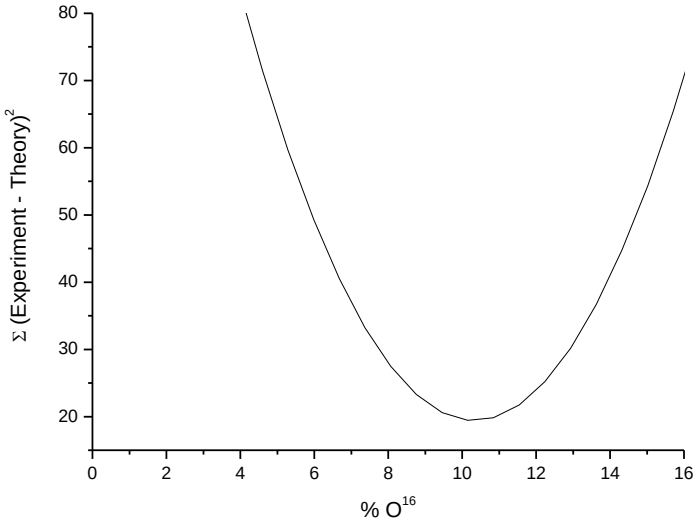


Figure III. 10. Least squares fitting of the observed isotopic profile of ^{18}**O**-(2*R*,3*R*)-2,3-diphenyloxirane **93a** as a function of a simulated mixed ^{16}O/^{18}**O** isotopologue profile.

3.3 ^{13}C NMR determination of the relative abundance of Shi's diester 84/Hydrate 124 derivatives.

Assay 1: A solution of catalyst **84** (20 mg, 0.066 mmol) in CD_3CN (120 μL) was added to buffer pH = 9 (350 μL) and DMM (240 μL). The solution was stirred at room temperature for 10 min and placed in a NMR tube (see Figure III. 4).

Assay 2: A solution of hydrate **124** (20 mg, 0.063 mmol) in D_2O was stirred at room temperature for 10 min and placed in a NMR tube (see Figure III. 5).

Assay 3: A solution of catalyst **84** (20 mg, 0.066 mmol) in CD_3CN was stirred at room temperature for 10 min and placed in a NMR tube (see Figure III. 6).

4. X-Ray data

4.1 X-Ray data for compound 168

Compound **124** (16 mg, 0.05 mmol) was dissolved in methanol (1 mL) and the solution was allowed to stand, while allowing slow solvent evaporation. Single-crystals of the methanolate **168** separated out from the solution. The structure of this newly isolated material could be unambiguously proven by single crystal X-ray diffraction analysis.

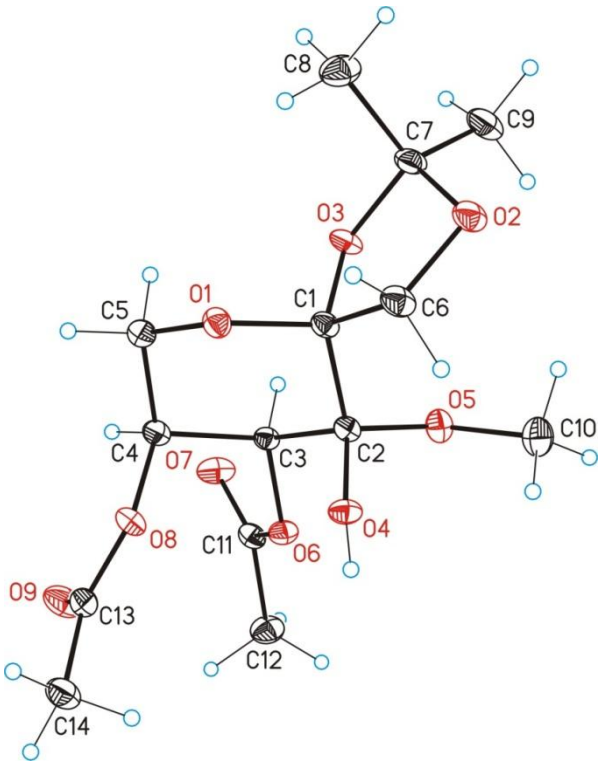


Figure III. 11. ORTEP plot (thermal ellipsoids shown at 50 % probability level) of the methanolate **168**.

Parameter	Crystal Data
Identification code	**Methanolate 168**
Empirical formula	$C_{14}H_{22}O_9$
Formula weight	334.32
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 6.8203(8) Å, α= 90°
	b = 5.5939(7) Å, β= 97.914(3)°
	c = 20.585(3) Å, γ = 90°
Volume	777.89(17) $Å^3$
Z	2
Density (calculated)	1.427 Mg/m^3
Absorption coefficient	0.120 mm^{-1}
F(000)	356
Crystal size	0.30 x 0.01 x 0.01 mm^3
Theta range for data collection	3.00 to 39.71°
Index ranges	$-11 \leq h \leq 9, -7 \leq k \leq 9, -35 \leq l \leq 37$
Reflections collected	13917
Independent reflections	5344 [R(int) = 0.0623]
Completeness to theta = 23.50°	83.9 %
Absorption correction	SADABS (Bruker-Nonius)
Max. and min. transmission	0.9988 and 0.9640
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5344/1/214
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0514, wR2 = 0.1044
R indices (all data)	R1 = 0.0988, wR2 = 0.1226
Absolute structure parameter	–0.3(8)
Largest diff. peak and hole	0.544 and -0.305 $e.Å^{-3}$

Table III. 1. Crystal data and structure refinement for the methanolate **168**.

Bond	Bond lengths [Å]	Bond	Bond lengths [Å]
C(1)-O(3)	1.411(2)	O(4)-C(2)-O(5)	112.40(13)
C(1)-O(1)	1.417(2)	O(4)-C(2)-C(3)	113.95(16)
C(1)-C(6)	1.535(2)	O(5)-C(2)-C(3)	104.06(13)
C(1)-C(2)	1.559(2)	O(4)-C(2)-C(1)	105.18(12)
O(1)-C(5)	1.434(2)	O(5)-C(2)-C(1)	113.21(16)
C(2)-O(4)	1.398(2)	C(3)-C(2)-C(1)	108.18(13)
C(2)-O(5)	1.407(2)	C(6)-O(2)-C(7)	106.68(15)
C(2)-C(3)	1.531(2)	O(6)-C(3)-C(4)	109.86(15)
O(2)-C(6)	1.425(3)	O(6)-C(3)-C(2)	107.37(12)
O(2)-C(7)	1.427(2)	C(4)-C(3)-C(2)	113.22(13)
C(3)-O(6)	1.4529(19)	C(1)-O(3)-C(7)	109.32(13)
C(3)-C(4)	1.528(3)	O(8)-C(4)-C(5)	108.01(13)
O(3)-C(7)	1.444(2)	O(8)-C(4)-C(3)	110.07(13)
C(4)-O(8)	1.444(2)	C(5)-C(4)-C(3)	108.46(15)
C(4)-C(5)	1.518(2)	O(1)-C(5)-C(4)	112.16(14)
O(5)-C(10)	1.451(2)	C(2)-O(5)-C(10)	117.65(13)
O(6)-C(11)	1.348(2)	O(2)-C(6)-C(1)	104.62(15)
C(7)-C(9)	1.498(3)	C(11)-O(6)-C(3)	116.28(13)
C(7)-C(8)	1.526(2)	O(2)-C(7)-O(3)	104.32(14)
O(7)-C(11)	1.210(2)	O(2)-C(7)-C(9)	109.22(17)
O(8)-C(13)	1.348(2)	O(3)-C(7)-C(9)	108.46(15)
O(9)-C(13)	1.213(2)	O(2)-C(7)-C(8)	110.82(15)
C(11)-C(12)	1.495(2)	O(3)-C(7)-C(8)	110.14(17)
C(13)-C(14)	1.498(3)	C(9)-C(7)-C(8)	113.45(17)
O(3)-C(1)-O(1)	112.24(13)	C(13)-O(8)-C(4)	118.61(14)
O(3)-C(1)-C(6)	104.59(15)	O(7)-C(11)-O(6)	123.71(15)
O(1)-C(1)-C(6)	105.47(13)	O(7)-C(11)-C(12)	123.81(16)
O(3)-C(1)-C(2)	108.19(13)	O(6)-C(11)-C(12)	112.48(15)
O(1)-C(1)-C(2)	110.45(15)	O(9)-C(13)-O(8)	123.95(19)
C(6)-C(1)-C(2)	115.85(14)	O(9)-C(13)-C(14)	126.01(19)
C(1)-O(1)-C(5)	114.96(12)	O(8)-C(13)-C(14)	110.04(16)

Table III. 2. Bond lengths [Å] and angles [°] for the methanolate **168**.

Bond	Torsion angles [°]	Bond	Torsion angles [°]
O(3)-C(1)-O(1)-C(5)	61.96(18)	C(1)-O(1)-C(5)-C(4)	59.2(2)
C(6)-C(1)-O(1)-C(5)	175.26(14)	O(8)-C(4)-C(5)-O(1)	65.93(19)
C(2)-C(1)-O(1)-C(5)	-58.87(17)	C(3)-C(4)-C(5)-O(1)	-53.34(19)
O(3)-C(1)-C(2)-O(4)	168.85(14)	O(4)-C(2)-O(5)-C(10)	-44.6(2)
O(1)-C(1)-C(2)-O(4)	-67.95(17)	C(3)-C(2)-O(5)-C(10)	-168.36(15)
C(6)-C(1)-C(2)-O(4)	51.9(2)	C(1)-C(2)-O(5)-C(10)	74.4(2)
O(3)-C(1)-C(2)-O(5)	45.75(18)	C(7)-O(2)-C(6)-C(1)	27.86(17)
O(1)-C(1)-C(2)-O(5)	168.96(13)	O(3)-C(1)-C(6)-O(2)	-11.75(17)
C(6)-C(1)-C(2)-O(5)	-71.24(19)	O(1)-C(1)-C(6)-O(2)	-130.29(14)
O(3)-C(1)-C(2)-C(3)	-69.02(18)	C(2)-C(1)-C(6)-O(2)	107.24(17)
O(1)-C(1)-C(2)-C(3)	54.19(17)	C(4)-C(3)-O(6)-C(11)	80.39(17)
C(6)-C(1)-C(2)-C(3)	173.99(16)	C(2)-C(3)-O(6)-C(11)	-156.09(16)
O(4)-C(2)-C(3)-O(6)	-58.50(17)	C(6)-O(2)-C(7)-O(3)	-33.22(18)
O(5)-C(2)-C(3)-O(6)	64.26(17)	C(6)-O(2)-C(7)-C(9)	-149.01(14)
C(1)-C(2)-C(3)-O(6)	-175.09(14)	C(6)-O(2)-C(7)-C(8)	85.29(19)
O(4)-C(2)-C(3)-C(4)	62.93(17)	C(1)-O(3)-C(7)-O(2)	25.69(18)
O(5)-C(2)-C(3)-C(4)	-174.31(14)	C(1)-O(3)-C(7)-C(9)	142.02(15)
C(1)-C(2)-C(3)-C(4)	-53.65(18)	C(1)-O(3)-C(7)-C(8)	-93.28(17)
O(1)-C(1)-O(3)-C(7)	105.33(16)	C(5)-C(4)-O(8)-C(13)	143.88(16)
C(6)-C(1)-O(3)-C(7)	-8.51(17)	C(3)-C(4)-O(8)-C(13)	-97.88(17)
C(2)-C(1)-O(3)-C(7)	-132.56(15)	C(3)-O(6)-C(11)-O(7)	2.0(3)
O(6)-C(3)-C(4)-O(8)	55.32(16)	C(3)-O(6)-C(11)-C(12)	-177.23(16)
C(2)-C(3)-C(4)-O(8)	-64.70(18)	C(4)-O(8)-C(13)-O(9)	-0.7(3)
O(6)-C(3)-C(4)-C(5)	173.29(13)	C(4)-O(8)-C(13)-C(14)	178.97(14)
C(2)-C(3)-C(4)-C(5)	53.26(18)		

Table III. 3. Torsion angles [°] for the methanolate **168**.

Conclusions

The conclusions of the work presented in this Thesis are as follows:

- A practical synthesis of diester **84**, previously described in the literature by Shi et *al*., has been developed, in which the efficiency, cost, selectivity and environmental aspects of the reagents involved for its preparation have been considered. Diester **84** was prepared in four steps (D-Fructose double ketalisation, oxidation of the free hydroxyl group to the corresponding ketone, selective deketalisation and diacetylation) using easy work-up procedures and with no purification steps until the end of the synthetic sequence (a chromatographic purification) with an overall 35% isolated yield in multigram quantities. Environmentally friendlier reagents to those originally used by Shi *et al.* were used in the synthetic procedure developed in the present Ph.D. Thesis (ruthenium-mediated oxidation of a secondary alcohol with sodium (meta)periodate instead of pyridinium chlorochromate (PCC) as oxidant, and aqueous acetic acid as selective deketalisation agent instead of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)). The last step in the synthesis of diester **84** (*i.e.* diacetylation) proved to be critical, as Shi's results could not be reproduced: variable amounts of the α to carbonyl acetate elimination product were obtained when acetic anhydride as the acetylating agent and 4-(dimethylamino)pyridine (DMAP) as the catalyst were used. We found that the same acetylating agent gave high yield (66 %) and selectivity (99%) in the acetylation reaction when anhydrous zinc(II) chloride was used as catalyst. The work-up conditions (use of neutral silica gel and temperature control during work-up) also turned out to be critical in order to avoid the elimination side product derived from **84**.

- The hydrate derived from **84** (compound **124**), which was an unknown compound not previously described in the literature, was also isolated. Its structure was unambiguously proven by single crystal X-ray diffraction analysis. This new compound was also prepared with the same synthetic sequence as that for **84** but using a different purification step at the end of the synthetic sequence (precipitation and filtration) with an overall 22% isolated yield in multigram quantities.

- The catalytic properties of diester **84** and hydrate **124** were assessed in the enantioselective organocatalysed epoxidation of unfunctionalised alkenes. Interestingly, hydrate **124** showed the same catalytic activity as its parent compound **84** in epoxidation studies of an array of differently substituted alkenes using Oxone® as the oxidant. The chiral platform provided by the catalysts **84** and **124** tolerates a wide range of substituents giving high yields and enantioselectivities (transfer of the pro-*S* "O" of the related dioxirane species) in the epoxidation of a number of (*E*)-di- and trisubtituted olefins. Yields ranged from 41% to 95% and enantioselectivities from 60% to 96% ee (24 examples). The epoxidation of terminal olefins by **84** or **124** showed poor enantioselectivities, though conversions remained high under all tested conditions.

- In order to demonstrate the origin of the stereodifferentiating processes throughout the asymmetric epoxidation, we conducted different studies *via* chemoselective isotopic labeling of the dioxirane species derived from bicyclic chiral organocatalyst **124**. The results obtained revealed that: i) The epoxidation process comprises highly stereoselective attack of the β face of catalyst **84** by HSO_5^-; ii) Subsequent dioxirane ring formation renders the corresponding chiral dioxirane, whereby the pro-*S*-oxygen comes from the oxidant; iii) Oxygen transfer from the dioxirane to the alkene proceeds predominately through approach of the *Si*-alkene face onto the β face of the chiral dioxirane (pro-*S* "**O**" *Si*- attack); iv) Attack of the most hindered face of the chiral dioxirane (pro-*R* "**O**" attack) by the alkene does not take place to a measurable extent. Although the two acetate groups have more conformational freedom with respect to the dioxirane ring in the standard Shi´s catalyst, they are bulky enough to prevent the pro-*R* "**O**" attack.

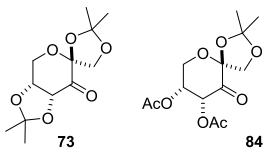
Annex I

Resumen de la tesis: Epoxidación asimétrica de alquenos no funcionalizados catalizada por derivados de la D-Fructosa

RESUMEN TESIS

Esta tesis se centra en la síntesis de epóxidos enantiopuros utilizando derivados de la D-fructosa como organocatalizadores para la epoxidación enantioselectiva de alquenos no funcionalizados.

Shi y colaboradores describen la cetona **73** (compuesto derivado de la D-fructosa) como catalizador y Oxone® como agente oxidante para la síntesis de epóxidos enantiopuros a partir de los alquenos correspondientes.[1] Sin embargo, la cetona **73** presenta inestabilidad bajo las condiciones de reacción de oxidación, dado que se ha postulado que descompone en las lactonas que derivan por reacción de Baeyer-Villiger, lo que implica que se requiera alta carga de catalizador (típicamente 20–30 mol %). Otro de los catalizadores derivados de la D-fructosa es la cetona **84**, cuya estabilidad en el medio básico de epoxidación es mayor y cuya utilización en reacciones de epoxidación se había descrito sólo para ésteres α,β-insaturados.



73 **84**

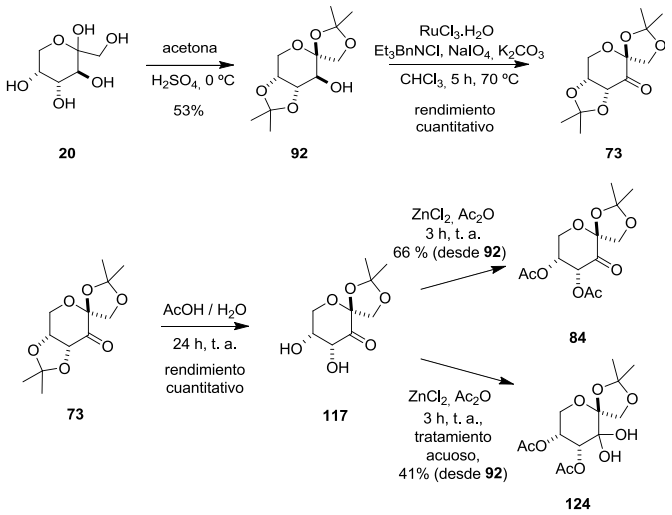
Esquema 1

Se debe mencionar que al inicio de este trabajo no había precedentes sobre el uso de **84** como catalizador para la epoxidación asimétrica de alquenos no funcionalizados. Shi sólo estudió la actividad catalítica de **84** para la epoxidación de una familia de alquenos α, β–insaturados. Esta Tesis se centra en la síntesis de epóxidos enantiopuros a partir de alquenos ricos electrónicamente y no funcionalizados utilizando derivados de la D-fructosa como catalizadores y Oxone® como agente oxidante.

Inicialmente se optimizaron las condiciones de síntesis del derivado **84**, previamente descritas por Shi y colaboradores.[2] Se desarrolló una síntesis eficiente del diéster **84** en la que se tuvieron en cuenta aspectos como la selectividad, eficiencia, y coste de los reactivos usados.

El compuesto **84** se obtuvo en cuatro pasos de síntesis, que consisten en la protección de la D-fructosa (**20**), oxidación de **92**, desprotección selectiva de **73**, y la diacetilación final de **117**, conduciendo al derivado deseado con un 35% de rendimiento global (Esquema 2). Curiosamente, un cambio en el método de purificación de la última etapa sintética permitió aislar e identificar el dihidrato derivado del diéster **124** con un rendimiento del 41%, ambos en cantidades multigramo (compuesto no descrito en la bibliografía anteriormente).[3]

[1] Véase por ejemplo: a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. b) Shi, Y. *Acc. Chem. Res*. **2004,** *37*, 488. c) Wong, O. A.; Shi, Y. *Chem. Rev*. **2008**, *108*, 3958. d) Shi, Y., *Modern Oxidation Methods (Chapter 3)*, Ed. by J.-E. Bäckvall, Wiley-VCH Verlag GmbH & Co. KGaA, Germany, 2010. e) Wong, O. A, Shi, Y. *Curr. Chem*. **2010**, 201. d) *Catalysts for Fine Chemical Synthesis, Regio- and Stereo-Controlled*, edited by Roberts, S. M.; Whittal, J.,Wiley, England, 2007.
[2] Wu, X. Y.; She, X.; Shi, Y. *J. Am. Chem. Soc*. **2002**, 124, 8792.
[3] a) Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem*. **2005**, *70*, 10143. b) Nieto, N.; Munslow, I. J.; Fernández-Pérez, H.; Vidal-Ferran, A. *Synlett* **2008**, 2856.



Esquema. 2

Una vez desarrollada una síntesis práctica del diéster **84** y del hidrato **124**, se optimizaron las condiciones de epoxidación para un alqueno modelo. Éstas se llevaron a cabo con ambos catalizadores **84** ó **124**, con cantidad suficiente de disolvente para solubilizar el sustrato (CH_3CN-DMM,[4] 1:2 v/v), en la presencia de un catalizador de transferencia de fase (TBHAS)[5] y una disolución tampón, ambos previamente usados por Shi y colaboradores.[2] Posteriormente, se añadieron simultáneamente disoluciones de Oxone® en una disolución tamponada y K_2CO_3 en agua durante 2 horas, (manteniendo el valor de pH constante). Finalmente, la mezcla de reacción se mantuvo bajo agitación a 0 ºC durante 16 h.

Ambos catalizadores fueron ensayados en la epoxidación asimétrica de un conjunto de alquenos no funcionalizados obteniendo altas actividades catalíticas y enantioselectividades.[3] Algunos de los ejemplos se muestran en la Tabla 1. Se observó que el diéster **84**, y más interesantemente, el hidrato **124** fueron muy eficaces como catalizadores de epoxidación hacia una variedad de olefinas *trans*-aril-sustituidas (por ejemplo, *trans*-estilbeno (entrada 1)), alcoholes alílicos y homoalílicos disustituidos (entradas 2 y 3) y olefinas trisustituidas tales como por ejemplo el trifeniletileno (entrada 4). Por otro lado, los dos catalizadores derivados de la D-fructosa **84** y **124** (diéster **84** y su hidrato **124**) muestran una menor selectividad para los alquenos *cis*-sustituidos como el indeno (entrada 5), lo que sugiere que tanto el diéster **84** como su hidrato **124** tienen un comportamiento similar al de la cetona de Shi **73** hacia este tipo de epóxidos. Por último, el hidrato **124** catalizó la epoxidación de olefinas terminales con bajas selectividades (entrada 6), aunque las conversiones se mantuvieron altas en todas las condiciones ensayadas.

[4] DMM = dimetoximetano.
[5] TBHAS = Hidrógeno sulfato de tetra-*n*-butilamonio.

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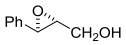
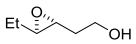
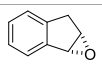
En todos los casos, las configuraciones absolutas de los productos obtenidos estuvieron de acuerdo con las obtenidas con el catalizador **73**.

Entrada	Cat.	Cat. (mol %)	pH final	Producto	Rend. (%)[a]	ee (%)[b]	Enriquecimiento óptico[c]
1	**84**	10	9	 **93a**	53[d]	90[d]	Hexano, 46% >99% ee
	84	30	9		75	94	-
	124	10	9		55	89	-
2	**84**	10	9	 **93c**	68	96	-
	124	10	10		89	86	-
3	**84**	8	9	 **154b**	*f*	62	-
	84	24	9			76	-
	84	24	10			83	-
	124	10	9			60	-
	124	30	9			75	-
	124	30	10			80	-
4	**84**	8	9	 **98c**	58	87	Hexano, 45%, 90% ee
	124	10	19		52	92	-
5	**84**	10	9	 **162a**	96	46	-
	124	10	9		98	48	-
6	**124**	30	9	 **97a**	90[e]	26	-

[a] Rendimiento aislado. [b] Exceso enantiomérico. [c] Se recristaliza el epóxido con el fin de aumentar la pureza óptica. [d] Valor promedio de 4 experimentos. [e] En este caso la reacción se llevó a cabo a –10 ºC. [f] No determinado, puesto que el epóxido destila junto con el disolvente durante el proceso de purificación.

Tabla 1

Finalmente, se intentaron identificar y entender los mecanismos de esteroinducción implicados en el proceso de epoxidación mediante estudios de marcaje isotópico. La epoxidación del *trans*-estilbeno utilizando el hidrato **124** como catalizador y Oxone® ($K_2SO_2{}^{18}O^{18}OH$) como agente oxidante (previamente sintetizado por reacción de $H_2{}^{18}O_2$ con ácido sulfúrico fumante y K_2CO_3) condujo al ^{18}O-(*R*,*R*)-óxido de estilbeno con incorporación total de ^{18}O en el producto final. Posteriormente, se realizó la epoxidación del *trans*-estilbeno usando **124** como catalizador y Oxone® como agente oxidante en $H_2{}^{18}O$, lo que condujo al ^{16}O-(*R*,*R*)-óxido de estilbeno sin incorporación de ^{18}O en el epóxido final (contenido en ^{18}O < 0.1%).

Por otro lado, mediante ensayos de ^{13}C RMN se observó que el diéster **84** se transformaba en el hidrato **124** en las condiciones de reacción (CD_3CN, dimetoximetano y disolución tamponada a pH = 9) y que el hidrato **124** no mostraba la señal característica del carbono dihidroxílico después de adicionar Oxone® sobre la mezcla de reacción. Por último, la metanólisis del hidrato **124** a temperatura ambiente y en ausencia de catalizadores ácidos o básicos condujo a un derivado en el que el metanol desplazaba al grupo hidroxilo pro-*S* de **124**.

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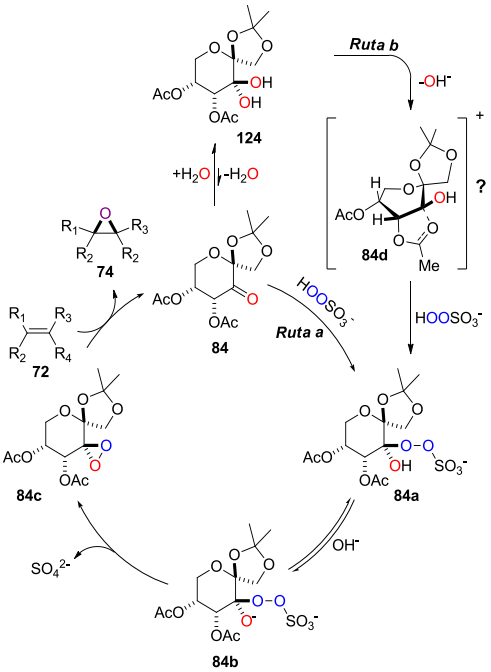
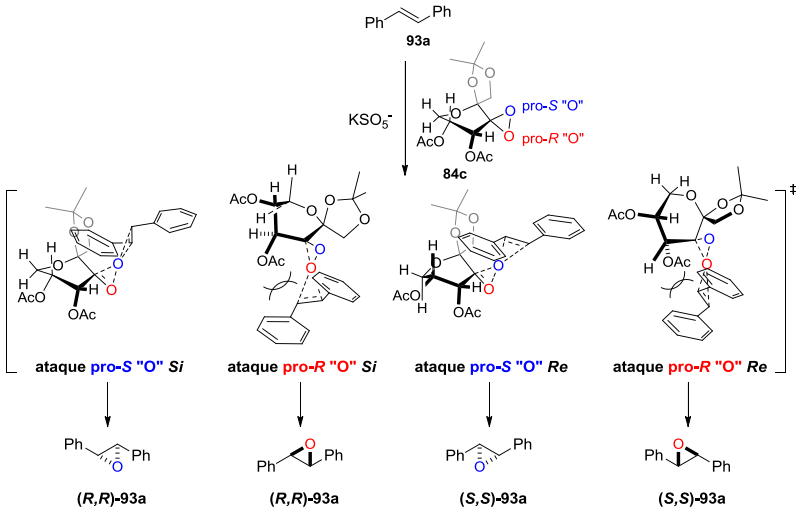
Por todo ello y de acuerdo con el mecanismo postulado por Shi y colaboradores[6,7] proponemos el siguiente ciclo catalítico para la epoxidación de *trans*-olefinas (Esquema 3):



Esquema 3

Por otro lado, concluimos que de los cuatro posibles caminos estereoquímicos, de acuerdo con resultados obtenidos para la epoxidación de *trans*-alquenos no funcionalizados utilizando **84** y **124** como catalizadores (ver Tabla 1), que el enantiómero mayoritario que se observa se forma mediante ataque pro-*S* ”O” *Si* (ver Esquema 4).[8]



Esquema. 4

[6] Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224.
[7] Para referencias generales sobre el mecanismo de la epoxidación asimétrica de **73**, véase: a) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. c) Shi, Y. *Acc. Chem. Res*. **2004,** *37*, 488. d) Wong, O. A.; Shi, Y. *Chem. Rev*. **2008**, *108*, 3958. e) Wang, B.; Wu, X. W.; Wong, O. A.; Nettles, B.; Zhao, M. X.; Chen, D.; Shi. Y. *J. Org. Chem*. **2009**, *74*, 398.
[8] Nieto, N.; Munslow, I. J.; Barr, J.; Benet-Buchholz, J.; Vidal-Ferran, A. *Org. Biomol. Chem.* **2008**, *6*, 2276.

Tarragona, 2013