THESIS ON NATURAL AND EXACT SCIENCES B8

Asymmetric Oxidation of Prochiral and Racemic Ketones By Using Sharpless Catalyst

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Abstract

The Sharpless complex was discovered in the beginning of the 1980s to provide epoxides with a high enantioselectivity from allylic alcohols. Due to its high efficiency the process soon became an important tool for obtaining enantiomeric compounds in many laboratories and industrial enterprises. The unique structural properties of the complex were also successfully used also in other processes, e.g., in the enantioselective oxidation of sulfides.

In this thesis, the possibility for further extension of the synthetic utility of the Sharpless complex was investigated. The investigation was focused on the possibility of the direct asymmetric oxidation of ketones. Different types of racemic and prochiral ketones were used as the substrates of the reaction. Thus, prochiral and racemic cyclobutanones, alicyclic and aliphatic β-hydroxy ketones and 3-alkyl-1,2-cyclopentanediones were oxidized under different conditions using the Sharpless complex. The wide choice of the ketone structures enables establishment of the scope of and limitations to the method with respect to the substrates. Several types of ketones were found to give different oxidation products with a very high enantiomeric purity.

We found that cyclobutanones undergo the asymmetric Baeyer-Villiger oxidation resulting in enantiomeric lactones. The enantioselectivity of oxidation of bicyclic ketones varied from moderate to good (53-75% *ee*), while that of 2- and 3-monosubstituted cyclobutanones was lower (37-40% *ee*). The racemic α-branched ketones with a hydroxy group in the molecule are converted into lactones in a good yield (30-40%) by the kinetic resolution.

We found that different α-hydroxymethyl ketones (substituted alicyclic ketones with 5- and 6-membered ring and aliphatic ketones) undergo the direct asymmetric α-hydroxylation at the branched carbon resulting in α,β-dihydroxy ketones with a high enantiomeric purity (86-97% *ee*) and in a satisfactory yield (37-58%). These results were rationalized by the assumption that the reaction proceeds *via* the asymmetric epoxidation of the allylic enolate formed from β-hydroxyketone.

We found that 3-alkyl-1,2-cyclopentanediones undergo the direct asymmetric oxidation resulting in two major types of enantiomeric compounds: primary hydroxylation products (3-hydroxylated diketones) and more oxygenated ring cleaved hydroxylation products (lactones and esters). With a proper choice of the reaction conditions it is possible to obtain preparatively both of these compounds (either 3-hydroxylated products or ring cleaved products). Thus *via* primary hydroxylation the corresponding α-hydroxylated diketones with an isolated yield of up to 40% and enantiomeric purity >95% *ee* can be obtained. The use of the excess of the oxidizing reagent results in the oxidative ring cleavage leading to the corresponding lactones and esters in up to 75% isolated yield with an excellent enantiopurity (>95% *ee*). In the case of 3-(2-hydroxyethyl)-1,2-cyclopentanedione the lactone-acid obtained can be converted into the chiral spirodilactone.

The new asymmetric oxidation methods developed enable various oxygenated compounds to be obtained directly from ketones, in most cases, with a high enantioselectivity.

Prokiraalsete ja ratseemiliste ketoonide asümmeetriline oksüdatsioon Sharplessi katalüsaatori manulusel

Kokkuvõte

Titaani ja viinhappe estri kompleks *tert*-butüülhüdroperoksiidiga (Sharplessi kompleks), mis avastati kaheksakümnendate aastate alguses, oksüdeerib stereoselektiivselt allüülseid alkohole vastavateks epoksiidideks. Protsessi kõrge efektiivsus tagas tema laialdase kasutuselevõtu laboratooriumides ja ettevõtetes enantiomeersete ühendite saamisel. Sharplessi kompleksi unikaalsed struktuursed omadused võimaldasid teda kasutada ka teistes asümmeetrilise sünteesi protsessides nagu näiteks sulfiidide stereoselektiivne oksüdatsioon.

Käesolevas töös käsitletakse võimalusi Sharplessi kompleksi kasutusalade edasiseks laiendamiseks. Et selgitada välja oksüdatsioonimeetodi kasutuspiirid ning võimalused sõltuvalt ketoonide tüübist, uuriti eri tüüpi ketoonide - prokiraalsete ja ratseemiliste tsüklobutanoonide, alitsükliliste ja alifaatsete β-hüdroksüketoonide ning 3-alküül-1,2-tsüklopentaandioonide - oksüdatsiooni kiraalse Sharplessi katalüsaatori manulusel.

Leiti, et tsüklobutanoonid oksüdeeruvad Baeyer-Villiger'i järgi, andes enantiomeerseid laktoone. Bitsükliliste tsüklobutanoonide korral on oksüdatsiooni enantioselektiivsus hea (*ee* 53-75%), 2-ja 3-monoasendatud tsüklobutanoonide korral on enantioselektiivsus madalam (*ee* 37-40%). α-hargnemise ja hüdroksügrupi esinemine ketooni molekulis parandab protsessi parameetreid ning võimaldab enantiomeersete laktoonide kineetilise lahutamise.

Erinevalt tsüklobutanoonidest 5- ja 6-lülilise tsükliga ning alifaatsed α-hüdroksümetüül-asendatud ketoonid α-hüdroksüleeruvad, andes Sharplessi katalüsaaatori manulusel kõrge enantiomeerse puhtusega (*ee* 86-97%) ja rahuldava saagisega (37-58%) α,β-dihüdroksüketoone. Töös oletatakse, et reaktsioon toimub β-hüdroksüketoonist moodustuva allüülse enolaadi epoksüdeerumise ja sellele järgneva ümbergrupeerumise kaudu.

3-alküül-1,2-tsüklopentaandioonid on omapärased selle poolest, et sõltuvalt reaktsiooni tingimustest nad kas α-hüdroksüleeruvad või edasisel oksüdatsioonil lõhustuvad. Nii on võimalik saada kahte põhitüüpi enantiomeerseid ühendeid: α-hüdroksüleerimisel 3-hüdroksüleeritud diketoone (*ee* >95%, saagisega kuni 40%) või tsükli oksüdatiivsel lõhustumisel laktoone ning estreid (*ee* > 95%, saagisega kuni 75%). Saadud lõppühendite head eraldatud saagised ja kõrge enantiomeerne puhtus lubab eeldada meetodi edukat kasutuselevõttu preparatiivseteks eesmärkideks. 3-(2-hüdroksüetüül)-1,2-tsüklopentaandiooni korral saadud laktoon-hape tsükliseerub kiraalseks spiro-dilaktooniks.

Töös on leitud võimalused ketoonide otseseks asümmeetriliseks oksüdatsiooniks ja laiendatud Sharplessi kompleksi kasutuspiiri. Real juhtudel on ketoonide otsese asümmeetrilise oksüdatsiooni meetod kasutatav enantiomeersete oksüdeeritud ühendite preparatiivseks saamiseks.

CONTENTS

1. LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred by their Roman numerals.

I. Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. Asymmetric Baeyer−Villiger oxidation of cyclobutanones. *Tetrahedron Lett.* **1996,** *37,* 7583−7586.

II. Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. Direct Asymmetric α-Hydroxylation of β-Hydroxyketones. *Tetrahedron Lett.* **1997,** *38,* 5051−5054.

III. Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. Asymmetric oxidation of 1,2-cyclopentanediones. *Tetrahedron Lett.* **2000,** *41,* 6883−6887.

IV. Lopp, M.; Paju, A.; Kanger, T.; Kriis, K.; Ilmarinen, K.; Pehk, T. Asymmetric Oxidation of Ketones. *Proc. Est. Acad. Sci., Chem.* **2001,** *50,* 124−137.

2. ABBREVIATIONS

AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
CHP	cymene hydroperoxide
DAT	dialkyl tartrate
DCC	*N,N'*-dicyclohexylcarbodiimide
DET	diethyl tartrate
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethyformamide
DMSO	dimethylsulfoxide
DMT	dimethyl tartrate
ee	enantiomeric excess
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
MCPBA	*m*-chloroperbenzoic acid
MPA	α-methoxyphenylacetic acid
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
TBDMS	*t*-butyldimethylsilyl
TBHP	*t*-butyl hydroperoxide
$Ti(O\textit{i}Pr)_4$	titanium tetraisopropoxide
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	toluenesulfonyl

3. INTRODUCTION

The need for asymmetric synthesis comes from the importance of enantiomerically pure compounds that are broadly used in drugs, agrochemicals, food additives, etc. Most of the important building blocks, which make up the biological macromolecules of living systems, exist in one enantiomeric form only. When a biologically active compound such as a drug interacts with its receptor site in a chiral biological system, two enantiomers of a chiral drug interact differently and may lead to different effects. In the drugs tested for therapeutical use very often only one enantiomer possesses the desired biological activity, whereas the other enantiomer is either inactive or possesses even an antagonistic activity and causes toxic effects. Even if the other enantiomer is inert, it is still necessary to synthesise and use only the active enantiomer in its pure form for economic, toxicity hazard and environmental reasons.[1] Nowadays, the asymmetric synthesis is one of the most important areas of research and development in modern organic chemistry− most chemical reactions have an asymmetric version. In the present work, we will concentrate on the asymmetric oxidation methods.

Enantiomerically pure compounds can be obtained in three different ways:[2]

(1) by transformation of chiral natural products;

(2) by optical resolution of racemates;

(3) by direct asymmetric synthesis.

The most effective approach to enantiomeric compounds is their asymmetric synthesis from prochiral or racemic compounds. The advantages of the asymmetric synthesis over the other methods of synthesis are well recognized. First, the asymmetric synthesis provides a wider choice of starting materials since they do not come from the “chiral pool”. Although resolution methods provide sometimes the most cost-effective way of obtaining enantiomerically pure compounds in a large scale, the development of reliable resolution procedures for a given compound is still a matter of trial and error. Moreover, not all necessary starting chiral compounds can be found in the “chiral pool”.

The asymmetric synthesis may be defined as the act of generating stereogenic units of necessary configuration – a prochiral substrate or a functional group is directly converted to the chiral product or a new stereogenic centre by using a chiral reagent or a chiral catalyst. The initial source of chirality may be in the substrate itself, in the chiral reagent used or in the chiral catalyst. If optically pure starting material is used, the asymmetric synthesis is a reaction that generates a new stereogenic

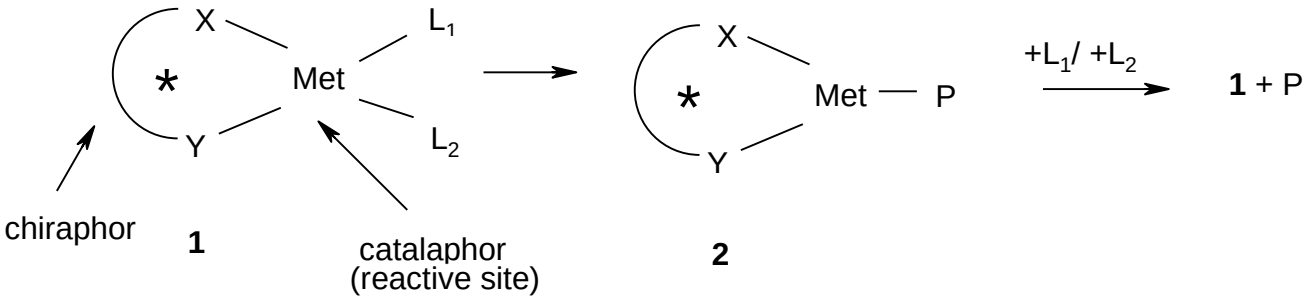
centre by the intramolecular induction of the existing chirality centres. This type of process is called "asymmetric synthesis with chirality relay". In several cases it is possible to attach a stoichiometric chiral auxiliary to the achiral substrate to achieve the asymmetric induction and realize the chirality relay. The auxiliary will be removed once it has served its purpose.[1] When the chiral catalyst affects the asymmetric induction, the achiral substrate is directly converted into a chiral product with an achiral reagent.

4. LITERATURE SURVEY

4.1. Titanium-tartrate catalyzed asymmetric oxidation

4.1.1. Chiral catalysis

The chiral catalysts work, in general, in a homogeneous medium in which small molecules are mostly monomeric and contain one (mononuclear) or sometimes two (binuclear) metal atoms in a chelate complex with chiral organic ligands. In chiral catalysts the common Lewis acids like Ti(IV), B, Al or Cr(III) are most frequently used. The characteristic coordination numbers for them are 4 and 6 with tetrahedral, planar squared or octahedral complex geometries.



Scheme 1. A general scheme of the chiral catalysis (Met = Lewis acid, metal; X, Y = donor atoms of the chiral ligand; L_1 = substrate; L_2 = reagent; P = product).

The binding forces of metal Met to donor atoms X, Y of the ligand are relatively strong and have to be maintained throughout the catalytic cycles. The variable parts of catalyst **1** are ligands L_1 and L_2 which should be rapidly exchanged in the course of the process. L_1 is the substrate (e. g., an allylic

alcohol in the case of the metal-catalyzed epoxidation) and L_2, the reagent (in the case of the asymmetric epoxidation TBHP). By the non-covalent attachment to Met

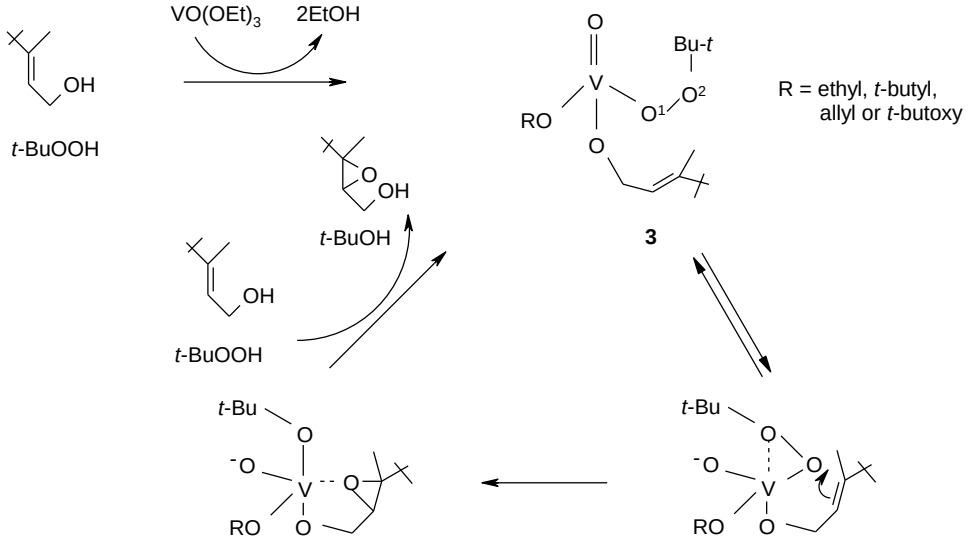
- L_1 and L_2 are activated to react with each other;
- L_1 and L_2 are brought into close proximity (entropy effect);
- L_1 and L_2 are immersed into a chiral environment, so that one of the several diastereomorphous transition states should be greatly favoured.

By the combination of these different effects the desired reaction is accelerated and proceeds with an asymmetric induction. After the reaction product P in **2** must have a much lower binding constant to Met and will be immediately replaced by another L_1, L_2 pair to regenerate species **1**.

There are two essential parts in the chiral catalyst: The "*chiraphor*"- a chiral ligand which bears chiral information, and the "*catalaphor*"- the metal attenuated by donors X and Y plus ligands L_1 and L_2 to serve as the reactive site. Typically, the catalyst in its storable form contains the chiraphor part, whereas the reactive ligands L_1 and L_2 are introduced *in situ* by the ligand exchange.[2]

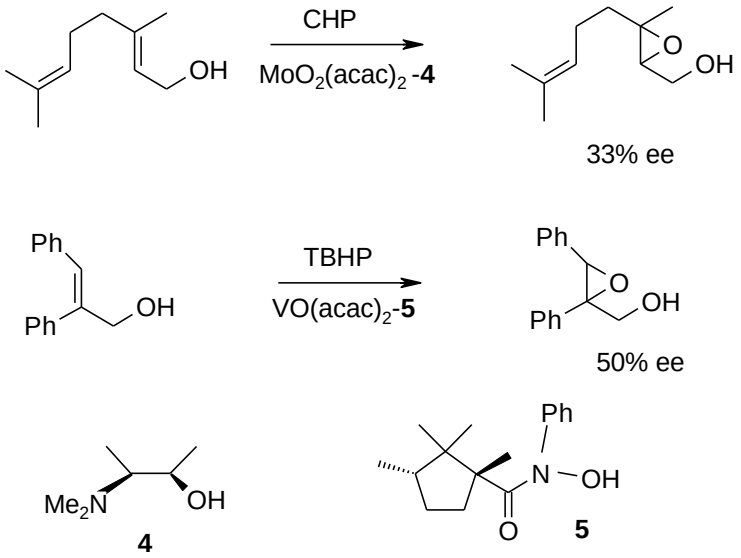
4.1.2. Metal-catalyzed epoxidation of allylic alcohols

The metal-catalyzed epoxidation of allylic alcohols by alkyl hydroperoxides is a method of high synthetic value because of the availability of allylic alcohols, mild reaction conditions and the formation of synthetically useful epoxyalcohols. A metal alkoxide having more than two alkoxy ligands can be a catalyst for the epoxidation of allylic alcohols (Scheme 2).[3]



Scheme 2. Vanadium-catalysed epoxidation of allylic alcohols.

The exchange of the ligand of metal alkoxides with alcohol occurs smoothly and gives an intermediate species **3** loaded with an allylic alcohol and TBHP (TBHP may also be considered an alcohol). The coordination of the distal oxygen (O^2) in **3** to metal activates peroxide and promotes the intramolecular epoxidation. Finally, the exchange of the resulting epoxy alkoxide and *tert*-butyl alkoxide with allylic alcohol and TBHP completes the catalytic cycle, giving epoxy alcohol as the product. In this cycle, the alkoxide ligand (RO) does not participate in the oxygen transfer reaction although it is located close to the reaction site. If this bystander ligand is replaced by an optically active ligand, the metal species are expected to catalyze the enantioselective epoxidation process. The first studies on the asymmetric epoxidation of allylic alcohols with alkyl hydroperoxides using the molybdenium[4] or vanadium[5] catalyst with chiral ligands indicated the potential of this method although the enantioselectivity of these reactions was modest (Scheme 3).

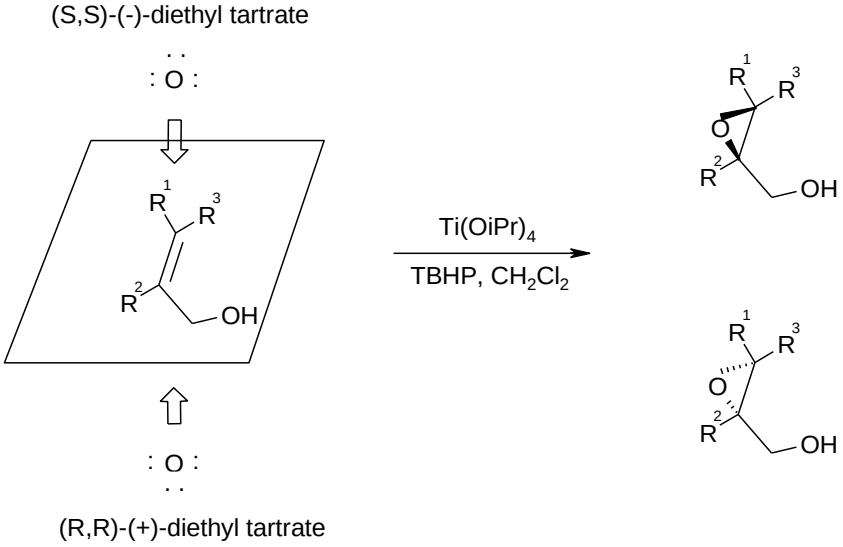


Scheme 3. Asymmetric metal-catalyzed epoxidation of allylic alcohols.

4.1.3. General aspects of titanium-catalyzed asymmetric epoxidation of allylic alcohols

One of the most fundamental achievements in the asymmetric oxidation is the enantioselective epoxidation of allylic alcohols developed by Sharpless and co-workers in the beginning of the 1980s. They found that in the presence of the titanium(IV) catalyst, *tert*-butylhydroperoxide and a chiral

tartrate ligand allylic alcohols are converted into the corresponding epoxides in good yield and with excellent enantioselectivity.[6] This method has become a routine reaction in chemical syntheses because of its generality, broad scope of use, high enantioselectivity and predictability of configurations of the target epoxyalcohols.[7] The epoxidation of primary allylic alcohols using the titanium tetraisopropoxide, (+) or (−) diethyl tartrate and TBHP system gives uniformly high asymmetric inductions throughout a range of substitution patterns (greater than 90% *ee*, except for some substrates only). In addition, an excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. The enantioface selection is determined by the chirality of the DET used (Scheme 4).

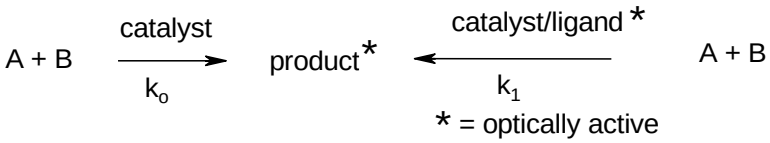


Scheme 4. AE of allylic alcohols with (*S*,*S*)-(−)-and (*R*,*R*)-(+)-DET.

When the olefinic unit is in the plane of the drawing with the hydroxymethyl group at the lower right, the use of (+)-DET leads to the addition of the epoxide oxygen from the bottom side and when (−)-DET is employed, then *vice versa*. In the reactions of achiral allylic alcohols there is no exception to this empirical rule [6].

The source of metal in these complexes is titanium tetraalkoxide ($Ti(OiPr)_4$) which is known to form stable chelate complexes with electron donors. In the present case it forms a complex with optically active diols (tartaric acid derivatives). The formation of the stable chelate was expected to suppress the formation of undesired metal species which might catalyze the non-selective

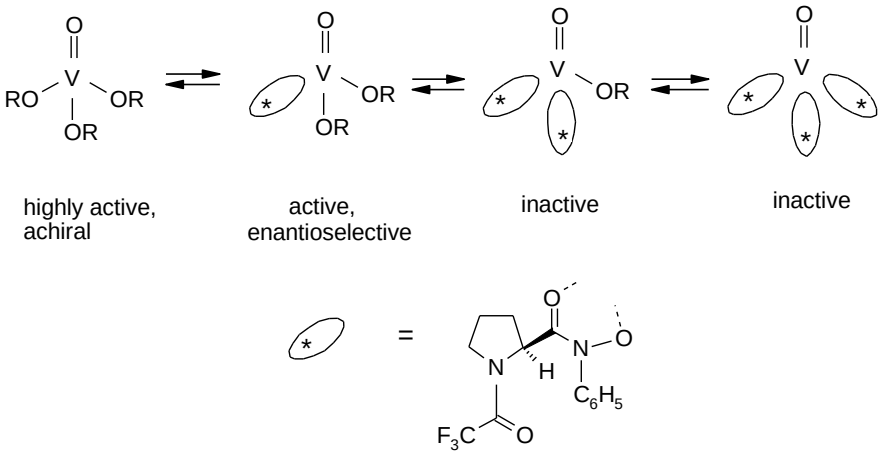
epoxidation process. The titanium complex bearing a multidentate ligand such as dialkyl tartrate was found to show a higher catalytic activity than the parent titanium tetraalkoxide in preliminary experiments. This is the first example of enhancement of the catalytic activity of a metal complex by the ligand exchange. This phenomenon is called the ligand acceleration.[8]



Scheme 5. The ligand-accelerated catalysis.

In the ligand-accelerated catalysis the addition of the ligand increases the rate of the already existing catalytic transformation (Scheme 5). The nature of the ligands bound to the metal almost always affects the selectivity and rate of the reactions. When the rate of product formation slowed down, the ligand deceleration is observed.

In the asymmetric epoxidation reactions catalyzed by chiral vanadium complexes[5] (Scheme 3) a significant deactivation of the catalyst upon binding of the chiral ligand to the metal, i. e., ligand deceleration, takes place. In the absence of the chiral ligand the reaction completes in less than one day, the enantioselective reaction under the optimized conditions takes four days. As shown in Scheme 6, a progressive replacement of the three alkoxide groups by the chiral ligand first reduces and then destroys the activity of the complexes.



Scheme 6. Activity of vanadium alkoxide complexes in the epoxidation.

The exchange of more than one alkoxide group to the chiral ligand leads to inactive complexes. To avoid the racemic pathway, an excess of the chiral ligand to vanadium is necessary. In this case, however, chiral but inactive complexes are generated. Consequently, with increasing ligand concentration the enantiomeric excess increases, whereas the reaction rate decreases steadily.[8]

In the asymmetric epoxidation catalyzed by titanium complexes the rapid exchange between the monoalkoxide ligands (allylic alkoxide, isopropoxide, epoxy alkoxide and alkyl hydroperoxide) attached to titanium *via* oligomeric intermediates and the corresponding free alcohols in the solution leads to a complex mixture of equilibrium titanium alkoxides. These different aggregates have non-equivalent amounts of the metal and tartrate ligand. Many of these act as epoxidation catalysts, each operating at a different rate, enantioselectivity and facial selectivity.[9] For example, the solution-phase structures of Ti-tartrate mixtures indicate that one major species of 1:1 stoichiometry is present in the reaction mixture together with at least two minor non-equimolar components. Kinetic experiments using different ratios of $Ti(O\textit{i}Pr)_4$ to (+)-diisopropyltartrate revealed that the major species (a dimeric complex, 2:2) is the catalyst that dominates in the determination of epoxidation activity of the mixture.[10] The addition of 2 equivs of the tartrate to titanium results in considerably decreased reaction rate if compared to that of a 2:2 mixture, indicating that the epoxidation activity of the complexes having more tartrate than titanium is negligible. The ratio less than that value (the Ti amount higher than the chiral ligand amount) lowers the rate of epoxidation (Table 1).

Table 1. Estimated fractions of the three main epoxidation catalysts present in a 1:1 mixture of $Ti(O\textit{i}Pr)_4$ and DIPT, approximate relative rates of epoxidation, and the enantioselectivity of epoxidation of (*E*)-2-hexen-1-ol in CH_2Cl_2.

	$Ti(O\textit{i}Pr)_4$	$Ti_2(DIPT)(O\textit{i}Pr)_6$	$[Ti(DIPT)(O\textit{i}Pr)_2]_2$
Fraction in solution, (%)	ca. 10	ca. 10	ca. 80
Relative epoxidation rate	1.4	1.0	3.6
Enantioselectivity	None	Low	high

The use of a 2:1 ratio of $Ti(O\textit{i}Pr)_4$ to tartrate (forming the $Ti_2(DIPT)(O\textit{i}Pr)_6$ complex as a major species) under standard conditions results in the epoxidation of the "predicted" olefinic face in the

reduced enantiomeric excess. For example, the epoxidation of (*E*)-α-phenylcinnamyl alcohol yields a (2*S*)-epoxy alcohol in 80% ee, compared to >98% ee at a 1.0:1.2 Ti:DIPT ratio.

The fact that the Ti-tartrate complex with a stoichiometry of 2:2 is the most reactive and enantioselective among the species presented in Table 1 is extremely fortunate (and necessary) for the successful operation of the AE reaction. This dimeric complex, $[Ti(DIPT)(O\textit{i}Pr)_2]_2$, is much more active than $Ti(O\textit{i}Pr)_4$ alone or Ti-tartrates of stoichiometry other than 1:1, and thus exhibits a selective ligand-accelerated effect. The high activity of the 2:2 system avoids the deleterious effects of any 2:1 complex or free $Ti(O\textit{i}Pr)_4$ that might be present in the solution. Additionally, the recommended Ti/tartrate ratio for the standard AE reaction is 1.0:1.2 to ensure the formation of the 2:2 Ti-tartrate complex only. If the most selective "2:2 catalyst" was not the most active particle, compared to the 2:1 complex or free $Ti(O\textit{i}Pr)_4$, a much higher tartrate/titanium ratio would be required to obtain high *ee* and the rate would suffer. This is exactly that unfortunate case which was observed in earlier metal-catalyzed asymmetric epoxidations.[8]

The first reported titanium-catalyzed asymmetric epoxidation was a stoichiometric reaction because of the high water sensitivity of the titanium-tartrate complex. The catalytic modification of the original procedure was realized when the reaction was performed in the presence of 3Å or 4Å molecular sieves.[11,12] The use of molecular sieves enables the reaction to be carried out by using only 5-10 mol% of $Ti(O\textit{i}Pr)_4$ and 6-13 mol% of tartrate ester, giving products of high enantioselectivity (90−95% ee) at rates similar to those of the stoichiometric system. However, the stoichiometric reaction is still used in many cases because of the low price of all the reagents used. Furthermore, in most cases,[3] the catalytic reaction is slightly less selective (1−5% lower enantioselectivity) than the stoichiometric reaction.

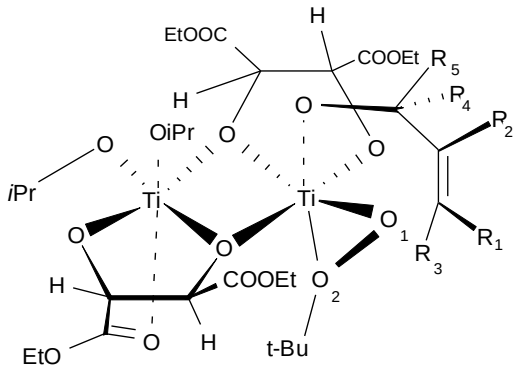
4.1.4. Mechanism of the asymmetric epoxidation and the structure of the catalyst

The mechanism of the asymmetric epoxidation reaction has been studied extensively. The dimeric structure has been declared to be an active form of the catalyst in the solution.[9] This conclusion has been made on the basis of the following considerations:

1. The average molecular mass of the titanium complex in the solution corresponds to the formula $[Ti(tartrate)(OR)_2]_2$.

2. NMR measurements in different solvents show that a single structure comprises at least 80% of the total mixture in the solution.
3. The pseudo-first-order reaction rate constant of epoxidation varies linearly from the Ti-tartrate concentration over a 10-fold range, suggesting that neither the dissociation to monomers nor the association to higher aggregates of the active catalyst occurs.

The dimeric structure of the titanium-tartrate complex was also proved by X-ray analysis of closely related complexes.[13] Based mainly on the above data Sharpless proposed the transition state model **6** for the epoxidation of allylic alcohols (Figure 1).



6

Figure 1. Transition state model for the Sharpless epoxidation.

In this model both allylic alcohol and TBHP ligands are bound to the same titanium atom in the oxygen transfer step. The allylic alcohol (a substrate), the source of oxygen (TBHP) and the chiral auxiliary (a tartrate ester) are all coordinated to titanium *via* the Ti−O bonds. The alkene moiety is never bound to the metal, and the facial selectivity of oxygen transfer is a consequence of the geometrical features of the complex and the tight association of reactants and the chiral auxiliary in the coordination sphere of titanium.[14] The bound substrate takes a conformation having a small dihedral angle (O−C−C=C, ca. 30^{o}) to supply its olefinic moiety in an appropriate place in space for epoxidation. The coordination of the distal oxygen (O_2) in the TBHP activates the peroxy bond and olefin performs a nucleophilic attack to the activated peroxide. The reactivity of the substrate increases with increasing electron density of olefin. For example, the epoxidation of *p*-methoxycinnamyl alcohol occurs ten times faster than that of *p*-nitrocinnamyl alcohol.[3]

The labile titanium(IV) alkoxides exchange rapidly ligands that enables these species to catalyze epoxidation reactions.[10]

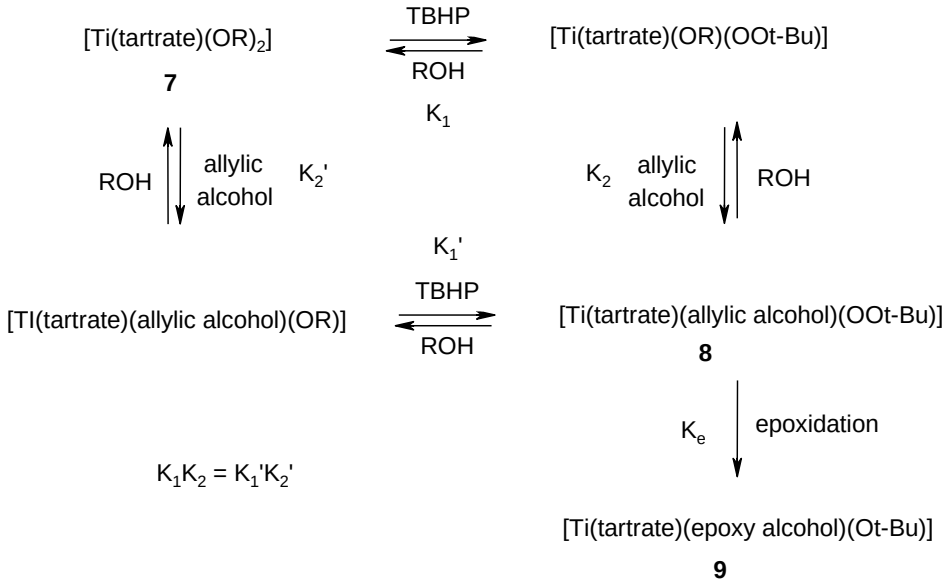
$$Ti(OR)_4 + \text{tartrate} \rightleftharpoons [Ti(\text{tartrate})(OR)_2] + 2ROH \qquad (1)$$

When 1 equiv of dialkyl tartrate is mixed with 1 equiv of titanium tetraalkoxide, the equilibrium represented by eq (1) is shifted far to the right because the diols such as tartrates exhibit a much higher binding to the titanium atom than monodentate alcohols. The binding of tartrate is also enhanced by the increased acidity of its hydroxy groups due to the inductive effects of the esters.[7] The amount of alcohols released after the addition of tartrate was measured by NMR and vapor-phase gas chromatography and was found to be exactly 2 equiv per tartrate.

A rapid ligand exchange continues after hydroperoxide and allylic alcohol have been added to the reaction medium. The pseudo-first-order kinetics experiments show a first order rate dependence on the titanium-tartrate complex, hydroperoxide and allylic alcohol, and an inverse second order dependence on the non-reactive alcohol ligand (inhibitor alcohol, i.e. isopropyl alcohol). The rate law derived from these results is expressed in eq (2) and the full ligand exchange pathway is outlined in Scheme 7.

$$\text{Rate} = k \frac{[\text{allylic alcohol}]\,[Ti(\text{tartrate})(OR)_2]\,[ROOH]}{[\text{inhibitor alcohol}]^2} \qquad (2)$$

After the formation of the Ti-tartrate complex **7,** the two remaining alkoxide ligands are replaced in reversible exchange reactions with the TBHP and allylic alcohol resulting in the loaded complex **8**. The reaction does not depend on the way of which complex **8** is reached. The rate-controlling step of the process is the oxygen transfer from TBHP to the double bond that gives the coordinated complex **9**. The product alkoxides are replaced again by allylic alcohol and TBHP to regenerate complex **8** and complete the catalytic cycle. The inverse-squared dependence on the nonreactive alcohol is due to the necessary replacement of the two alkoxide ligands in 7 with hydroperoxide and allylic alcohol.[10]



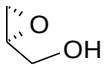
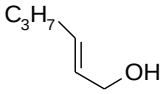
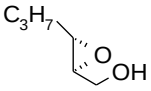
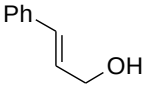
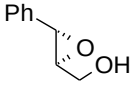
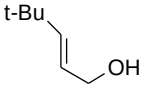
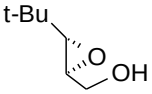
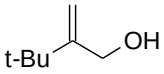
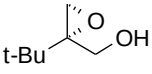
Scheme 7. Ligand exchange pathway in the asymmetric epoxidation.

4.1.5 Asymmetric epoxidations of the substrates with different structures

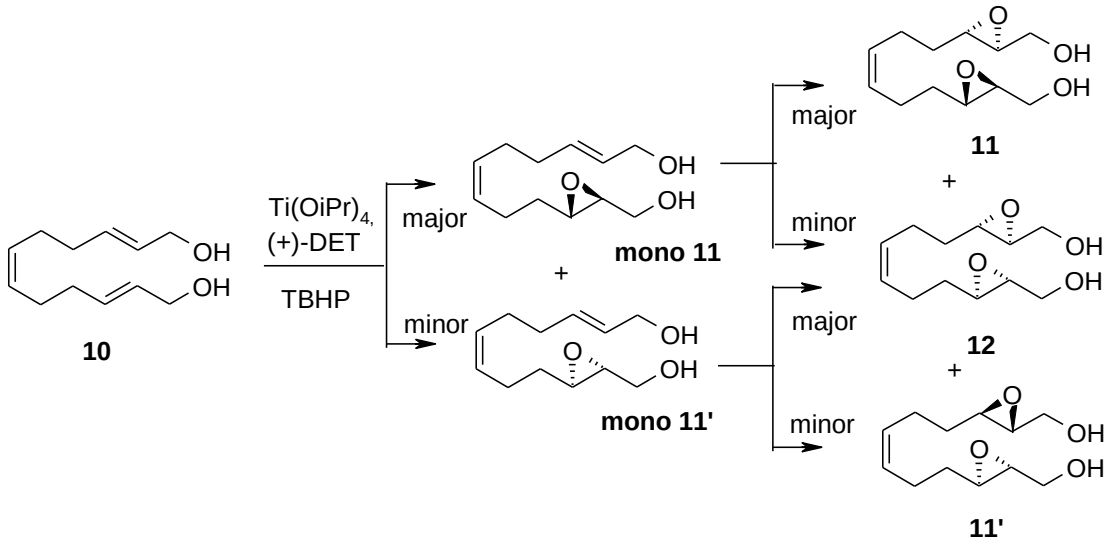
Primary allylic alcohols

The major advantage of the Sharpless epoxidation is that allylic alcohols of widely varying structure can be used as substrates (Table 2). Both the stereochemistry and substrate reactivity in this reaction can be reasonably explained by model **6.**[7,13] The *E*-substituent (R_1) of the allylic alcohol protrudes into an open quadrant and *trans*-allylic alcohols always show a high enantioselectivity, irrespective of the bulkiness of the *E*-substituent (entries 2-4 *vs* allyl alcohol, entry 1). On the other hand, the C2-substituent (R_2) exists in the vicinity of the tartrate ligand and the bulky C2-substituent affects the enantioselectivity to some extent (entry 5). The *Z*-substituent (R_3) is directed toward the ligand. Thus, the presence of a bulky *Z*-substituent makes it difficult for the substrate to take the desired conformation, decreasing the enantioselectivity to a considerable extent (entry 6 *vs* entry 4).

Table 2. Asymmetric epoxidation of primary allylic alcohols.[12,15]

Entry	Substrate	$Ti(OR)_4$	Tartrate	Product	% ee	% yield
1		$Ti(OiPr)_4$	(+)-DIPT		90	65
2		$Ti(OiPr)_4$	(+)-DET		94	85
3		$Ti(OiPr)_4$	(+)-DIPT		>98	89
4		$Ti(OiPr)_4$	(+)-DET		95	52
5		$Ti(OtBu)_4$	(+)-DET		85	42
6		$Ti(OiPr)_4$	(+)-DET		25	77

The epoxidation of the bis-allylic alcohols possessing a C_S- or C_2-symmetry gives the corresponding diepoxy compounds of extremely high enantiopurity.[3] In the epoxidation of triene **10** of a C_S-symmetry a mixture of *d,l*-and *meso*-diepoxides **11**/**11'** and **12** were obtained (Scheme 8).

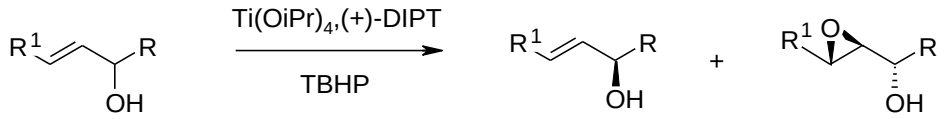


Scheme 8. Double Sharpless epoxidation of C_S-bis-allylic alcohol.

First, monoepoxides **mono 11** and **mono 11'** are formed. In the subsequent epoxidation the minor enantiomer **mono 11'** gives the *meso*-diepoxide **12** as the major product, while the major monoepoxide **mono 11** forms the major chiral diepoxide **11** and minor *meso*-diepoxide **12**. As a result, the amount of the minor enantiomer **mono 11'** is very small. Thus, the symmetry of triene **10** provides two paths to the *meso*-compound **12** and the enantiomeric excess of the chiral di-epoxide **11** will be extremely high. For example, if the single epoxidation reaction proceeds with an enantiofacial selectivity of 19:1 (90% *ee*) and assuming that there are no end effects in this double Sharpless reaction (i.e. 11/12=12/11'), a reasonable expectation for the **11:12:11'** ratio was deduced: (19+1)(19+1) or 361:38:1. According to that calculation the *ee* of the chiral diepoxide **11** should be 99.45%. Indeed, the experiment revealed a significantly higher enantiopurity for diepoxide **11** than for the corresponding monoepoxide **mono 11.**[16,17]

Secondary allylic alcohols

Shortly after the discovery of the highly efficient asymmetric epoxidation reaction of primary allylic alcohols, Sharpless and co-workers have demonstrated that the same system may be used to resolve kinetically racemic secondary alcohols[18] (Scheme 9).



Scheme 9. Kinetic resolution of secondary allylic alcohols.

In this kinetic resolution, in which one enantiomer reacts considerably faster than the other one, it is possible to resolve enantiomers. If the relative rate constant, $k_{rel} = k_{fast}/k_{slow}$, is about 50, then starting already from a 55% conversion of the starting material the enantiomeric purity of an unreacted substrate is higher than 99% *ee* (Figure 2).

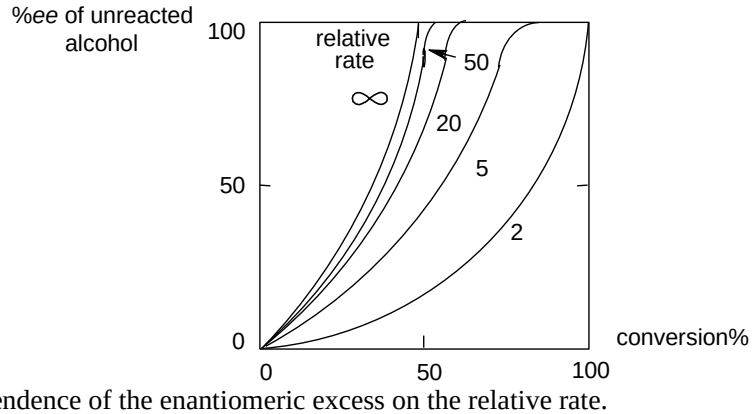


Figure 2. Dependence of the enantiomeric excess on the relative rate.

However, it should be mentioned that even small differences in relative rate (k_{rel} =5-10) can provide useful amounts of a substance with a high enantiomeric purity when appropriate conversion extents are used.

The efficiency of the kinetic resolution can be rationalized by model **6** (Fig. 1). The loaded substrate suffers from steric hindrance when $R_4 \neq H$, and the epoxidation of such a substrate is strongly retarded. The enantiomer ($R_4 \neq H$, $R_5 = H$) reacts much slower than the other enantiomer ($R_5 \neq H$, $R_4 = H$).

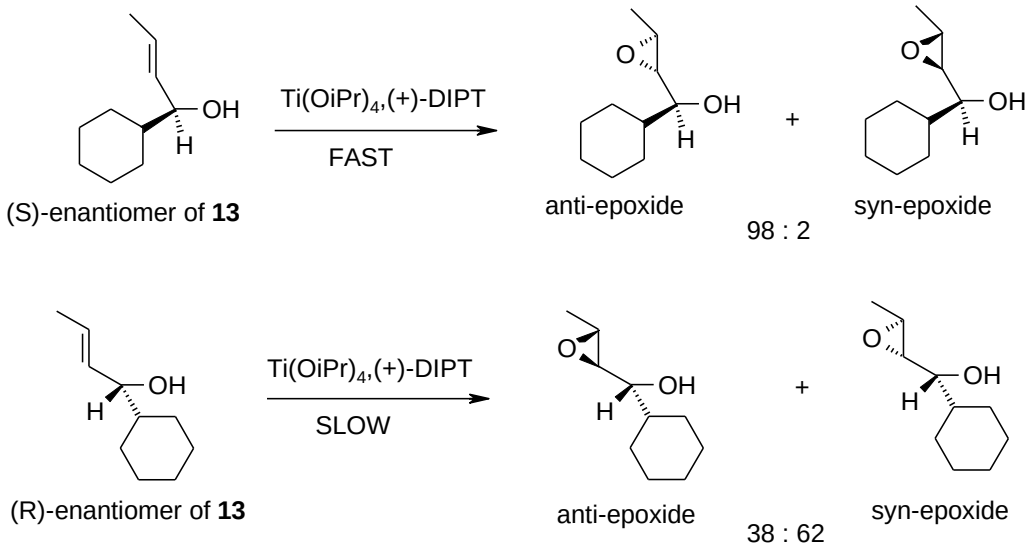
For the kinetic resolution the choice of tartrate ester is also important: the relative rate differences increase with increasing ester alkyl moiety increases (DMT<DET<DIPT). For this reason, DIPT is generally used in kinetic resolutions. At the same time, the catalytic procedure with DIPT has a slightly lower selectivity than the stoichiometric reaction. The use of more bulky dicyclohexyl and dicyclododecyl tartrates leads to a higher selectivity in the catalytic applications.[12]

In the epoxidation of racemic secondary allylic alcohols two stereochemical problems arise:

(1) differentiation of enantiomers (kinetic resolution);

(2) diastereoface selection in epoxidation.

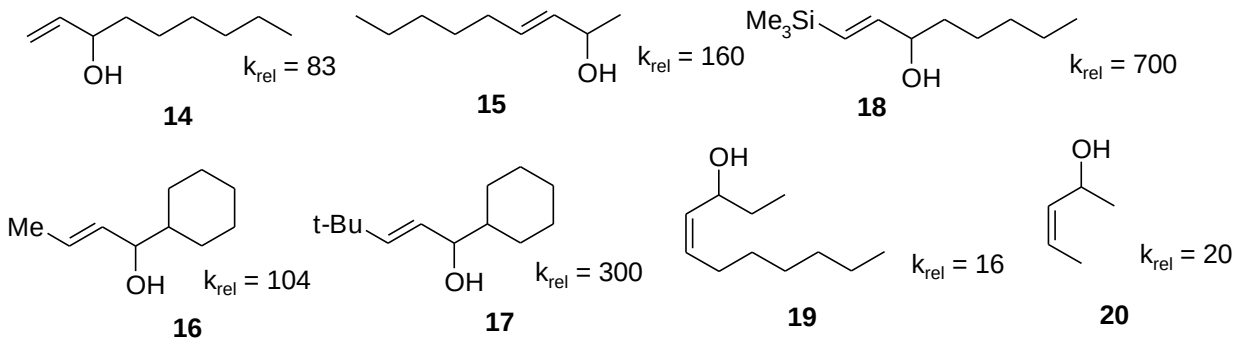
The epoxidation of most substrates follows the empirical rule of stereochemistry: when using *R*,*R*-(+)-tartrates, the *S*-enantiomer of the alcohol reacts faster than the *R*-enantiomer, while the *R*-enantiomer reacts faster when *S*,*S*-(−)-tartrates are used. The faster reacting enantiomer gives the *anti*-epoxy alcohol with a high stereoselectivity, while the slower reacting enantiomer shows a lower



Scheme 10. Differential *syn-anti* selectivity of enantiomers **13**.

diastereoselectivity, giving a mixture of *syn*- and *anti*-epoxy alcohols (Scheme 10).[18]

By analogy with primary allylic alcohols, the secondary allylic alcohols bearing a bulky *E*-substituent (R_1, fig. 1) are good substrates for kinetic resolution. Increasing the steric hindrance at the olefinic terminus (to a certain limit) increases the rate of epoxidation of the faster reacting enantiomer and decreases the rate of epoxidation of the slower reacting enantiomer. Thus, the relative rate constant (k_{rel}) increases[19] (Scheme 11, **14** *vs.* **15**, **16** *vs.* **17**).

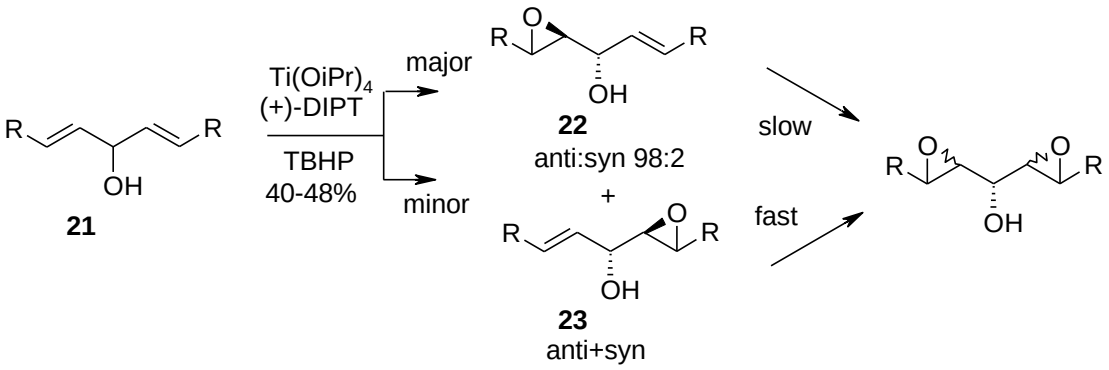


Scheme 11. Relative rates of epoxidation.

The substrates bearing a *Z*-substituent ($R_3 \neq H$, fig 1) have a considerably lower k_{rel} value and reveal a modest diastereoselectivity (**19** and **20**). In contradiction to the empirical rule, the substrates bearing a bulky *Z*-substituent often give *syn*-epoxy alcohols even in the epoxidation of the faster reacting isomers. The most efficiently resolved substrates are those which have the trimethylsilyl, trimethylstannyl or iodo *E*-substituent. In these cases it is possible to obtain both, unreacted allylic alcohols and epoxy alcohols, with more than 99% *ee*, simultaneously at ~50% conversion.[20,21]

The efficiency of the kinetic resolution of cyclic allylic alcohols depends on ring size. Cyclohexenol is one of the poorest kinetic resolution substrates – in the asymmetric oxidation of cyclohexenol the enantiomeric purity of an unreacted substrate is 30% *ee*, while that of cycloheptenol is 80% *ee*. The low selectivity could be attributed to the fixed dihedral angles of C=C-C-O in these substrates.[18] The efficiency of the kinetic resolution is related to the steric factors between the tartrate ligand and the C1 alkyl group (R_4, Fig. 1) in the slower reacting isomers. Therefore, when C1-substituents are aryl or secondary alkyl, kinetic resolutions proceed very efficiently. However, the resolution is not effective for allylic alcohols with tertial alkyl C1-substituents resulting in the enantiomeric excess of the recovered allylic alcohols of only 5-10% *ee*.[15]

The epoxidation of prochiral dialkenyl carbinols **21** proceeds with a combination of the enantiotopic group and diastereotopic face selectivity and results in the formation of products with a very high optical purity. In this reaction the kinetic resolution is coupled with the asymmetric synthesis to increase the *ee* of primary products with time.[22]

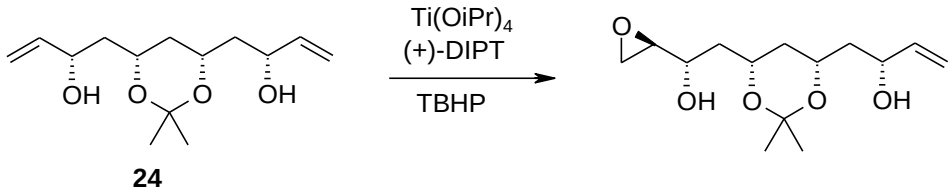


Scheme 12. Asymmetric epoxidation of prochiral dialkenyl carbinols.

The first epoxidation occurs in an enantiotopic selective manner while the second one proceeds in an enantio-differentiating manner (kinetic resolution). In the second step, the minor *R*-monoepoxides **23** are consumed faster than the major *S*-monoepoxides **22** and the *ee* of the major product increases as the reaction proceeds (Scheme 12). For example, in the epoxidation of 1,4-pentadien-3-ol the minor enantiomer is removed through the second epoxidation reaction and the *ee* of the major *anti*-epoxide **22** (R = H) improves as the reaction proceeds toward completion:[22]

3 h ─ 84% *ee*, 92% *de*; 24 h ─ 93% *ee* , 99.7% *de* and 140 h ─ >97% *ee*, >99.7% *de*. At the same time, the catalytic version of the reaction gave *anti*-epoxide **22** (R=H) with high *ee* (97%) and *de* (98%) in 65% yield after 10 days at –20 ^{o}C.[23]

Like simple divinyl carbinols, the *meso*-secondary diallylic alcohols also undergo a group and face selective asymmetric epoxidation reaction to provide products with enhanced enantiomeric purity. For example, the epoxidation of *meso*-tetraol derivative **24** gives the desired *anti*-epoxide of high *ee* in 69% yield (Scheme 13).[24]



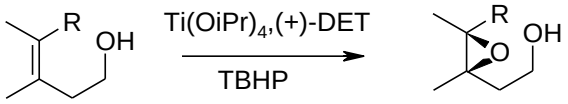
24

Scheme 13. Asymmetric epoxidation of *meso*-secondary diallylic alcohols.

The minor enantiomer produced in this reaction is selectively "destroyed" by a fast second epoxidation and the *ee* of the product increases as the reaction proceeds to completion.

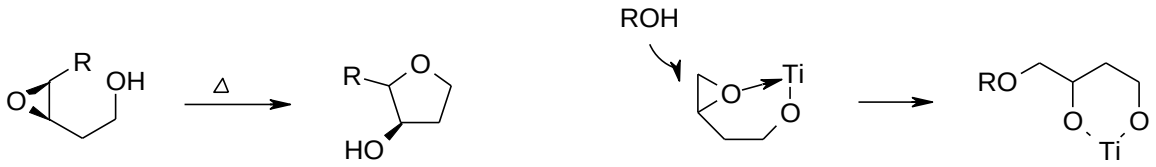
Homoallylic alcohols

Titanium-tartrate complexes also catalyze the epoxidation of homoallylic alcohols but the enantioselectivity of these reactions is considerably lower than that of allylic alcohols.[25] Enantiomeric purity of the 3,4-epoxy alcohols obtained range from 23 to 55% *ee*. Besides, the epoxidation with (+)-DET always gives products enriched in the 3*R* enantiomer (epoxidation of allylic alcohols with (+)-DET gives almost exclusively the 2*S* enantiomer). Thus, the enantiofacial selection is opposite to that observed in the case of allylic alcohols (Scheme 14).



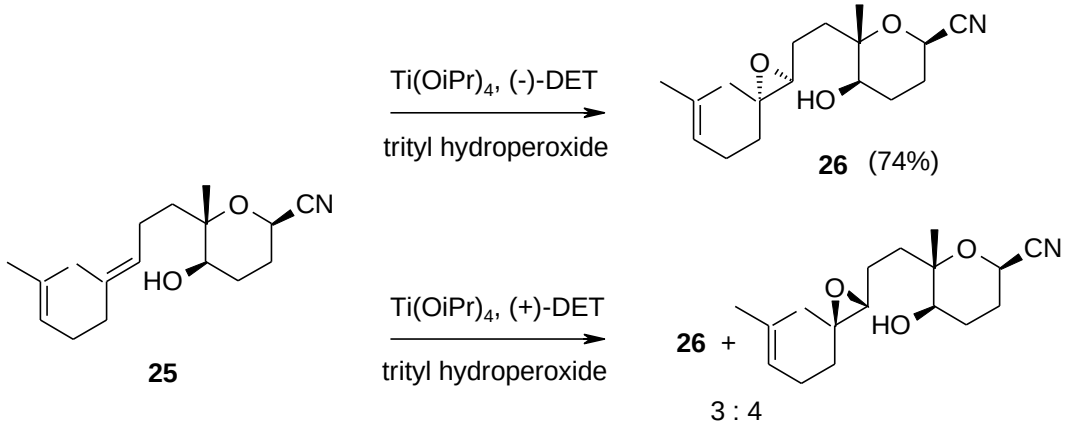
Scheme 14. Asymmetric epoxidation of homoallylic alcohols.

The epoxidation reaction is relatively slow and several side reactions occur: the rearrangement of the epoxide resulting in tetrahydrofuran derivatives; the titanium-assisted epoxide opening resulting in diols (Scheme 15).



Scheme 15. Formation of the by-products in the epoxidation of homoallylic alcohols.

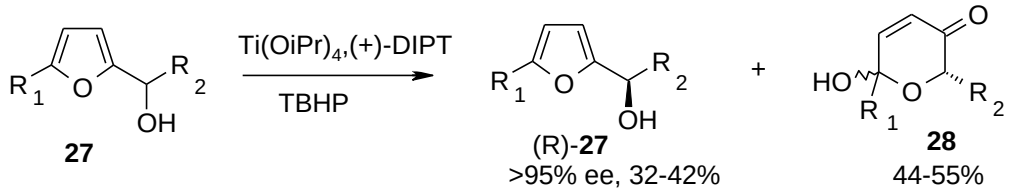
The high stereoselectivity can only be realized when the substrate is chiral and the substrate's stereocontrol matches with that of the chiral titanium-tartrate catalyst. For example, the epoxidation of trishomoallylic alcohol **25** proceeds with a high diastereoselectivity when *S,S*-(−)-DET is used as a chiral inducer resulting in single **26**. With the *R,R*-(+)-DET-derived catalyst from **25** a mixture of diastereomeric 6,7-epoxides is obtained. This stereoselective epoxidation requires also more bulky oxidant - trityl hydroperoxide (Scheme 16).[26]



Scheme 16. Stereoselective epoxidation of trishomoallylic alcohol.

Furyl and thienyl alcohols

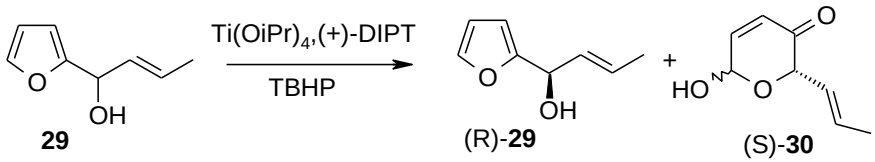
The titanium-tartrate catalyst can be used for the oxidation of heterocyclic compouns such as furan, pyrrole and thiophene. The kinetic resolution of 2-furyl alcohol **27 (**R_2 is a primary, secondary or aryl group) using 0.6 equiv of TBHP provides *R*-furyl alcohol **27** in >95% *ee* and pyranones **28** (Scheme 17).[27]



Scheme 17. Kinetic resolution of racemic furyl alcohols.

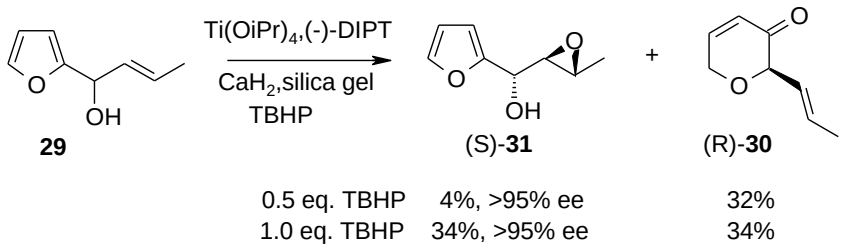
The stereochemisty of these resolutions is consistent with the parent process in the kinetic resolution of secondary allylic alcohols. When R_2 is a tertiary alkyl group, the enantioselectivity drops remarkably (to 6% *ee* for R_2 = *t*-Bu). In the case of a bis-allylic system under standard

conditions only the furyl ring is oxidized and the double bond in the side chain is not oxidized. (Scheme 18).



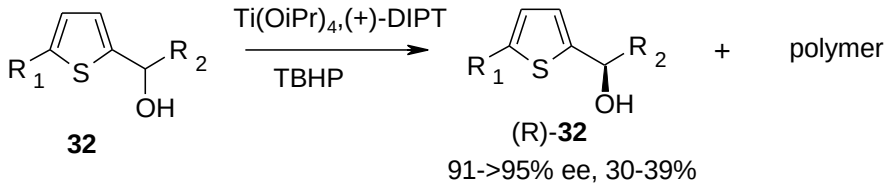
Scheme 18. Oxidation of 2-furylmethanol **29** under standard conditions.

However, when 2-furylmethanol **29** is oxidized by a modified titanium-tartrate system (with calcium hydride and silica gel) two oxidation products, epoxy alcohol **31** and pyranone **30**, are formed (Scheme 19).[28]



Scheme 19. Oxidation of 2-furylmethanol **29** using a modified Ti-tartrate system.

The kinetic resolution of 2-thienyl alcohols **32** by the asymmetric epoxidation proceeds effectively as well. Differing from the oxidation of 2-furyl alcohols, the oxidation of the thienyl compound **32** gives not the corresponding 2-mercaptopyranones but a mixture of unidentified polymeric compounds (Scheme 20).[29]

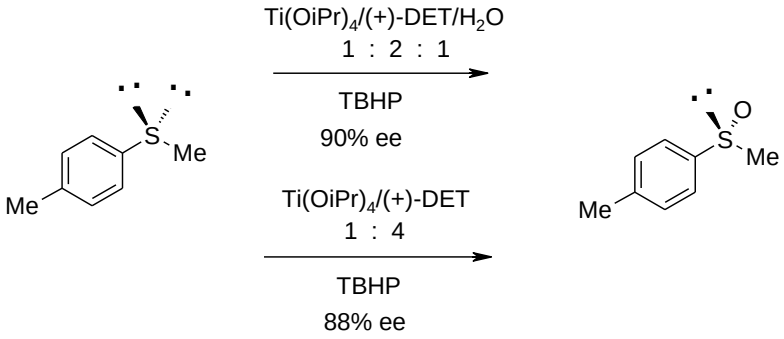


Scheme 20. Kinetic resolution of racemic thienyl alcohols.

The stereochemistry of this oxidation is also consistent with the AE face-selection rule. The kinetic resolution of various thienyl alcohols **32** by using 3 equivs of TBHP enables a highly efficient resolution when R_2 is a primary alkyl or an aromatic group; resolution in the case of R_2 = *t*-Bu results in the alcohol with only 47% *ee*.

4.1.6. Asymmetric oxidation of sulfides

In 1984, two groups (see Kagan[30] and Modena[31]) developed independently a method for the efficient oxidation of sulfides. Both the procedures involve a modification of the standard Sharpless catalyst, as the standard asymmetric epoxidation procedure leads to almost racemic sulfoxides. Only the addition of 1 mol equiv of water or increasing the DET/Ti(O*i*Pr)$_4$ ratio afforded sulfoxides with *ee* values of up to 90% (Scheme 21).

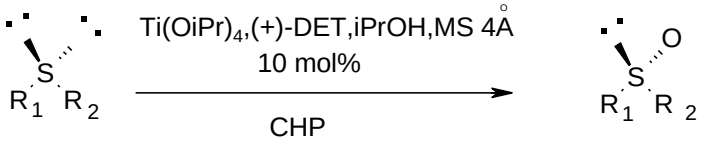


Scheme 21. Asymmetric oxidation of *p*-tolyl methyl sulfide.

It is worth to mention that prochiral sulfides which are not able to chelate on titanium lead to a very high enantioselectivitiy. The chemical yield is satisfactory and the sulfone formation is always negligible in these reactions. In the oxidation of sulfides the nature (structure) of the substrate plays a more significant role than in the case of epoxidation of allylic alcohols. While alkyl aryl sulfides usually give sulfoxides with *ee* in the range of 75-90% in a predictable manner, dialkyl sulfides provide rather modest optical yields (50−70% *ee*). The optimum water content in respect of enantioselestivity was found to be 1 mol equivalent of water to 1 mol equivalent of titanium. It is critical to avoid the excess of water.[32] The use of cumene hydroperoxide instead of TBHP results in a significant increase in the *ee* of many sulfoxides, without any decrease in chemical yield. A careful

control of generation of a water-modified titanium complex $Ti(OiPr)_4$/(+)-DET/H_2O = 1:2:1 allows to achieve *ee* >99% with CHP as an oxidant.[33]

In 1987 a catalytic sulfide oxidation based on the combination of $Ti(O\textit{i}Pr)_4$/(+)-DET/H_2O = 1:2:1 and molecular sieves was reported.[34] Under the catalytic conditions the amounts of water present in the reaction media may be sufficient to destroy the most selective titanium catalyst structure leading to a lower enantioselectivity in oxidation. In order to protect the desired titanium catalyst structure $Ti(O\textit{i}Pr)_4$/(+)-DET/H_2O = 1:2:1 against the excess of water, 4Å molecular sieves were added before the catalyst formation. The molecular sieves regulate the amount of water in the reaction mixture and the formation of any undesired titanium species in the reaction media is diminished. Using this technique, the *ee* values of up to 90% (20 mol% of the catalyst) were obtained. Nevertheless, the use of lower proportions of this catalyst result in a decrease in enantioselectivity. A further decrease in the amount of the catalyst to 10 mol% was achieved when replacing water with isopropanol in the catalytic complex (Scheme 22).[35]



Scheme 22. Catalytic asymmetric oxidation of sulfides.

The enantioselective catalytic system based on the use of 10 mol% of $Ti(O\textit{i}Pr)_4$, 40 mol% of (+)-DET and 40 mol% of isopropanol in the presence of 1 weight equivalent of 4Å molecular sieves and 2 equivalents of CHP as an oxidant affords high *ee* values (70-95%) in many cases.

Concerning the structure of the catalyst it was found that the IR-spectra of the complexes $Ti(O\textit{i}Pr)_4$/DET = 1:2 and $Ti(O\textit{i}Pr)_4$/DET/H_2O = 1:1:1 are almost superimposable indicating that similar species have been obtained. Indeed, both catalysts are stereoselective: e.g., in the oxidation of *p*-tolyl methyl sulfide the enantiomeric excess of 70 and 84% *ee* have been obtained, respectively. It can be suggested that the classical epoxidation catalyst Ti/DET = 2:2 is transformed into a new species by the modification process. The structure of the complex with a stoichiometry of 1:1:1 (Ti/DET/H_2O) seems to be close to that of the complex with a stoichiometry of 1:2:0. A common feature of these two complexes is the higher OH/Ti ratio compared with the stoichiometry of the

classical Sharpless catalyst (2OH/Ti). For the oxidation of sulfides, no vacant exchangeable sites on titanium are necessary.[32] The catalytically active titanium species for the oxidation reaction is supposed to be dimeric with two titaniums being connected via the η-oxo bridge (**33**, Figure 3).

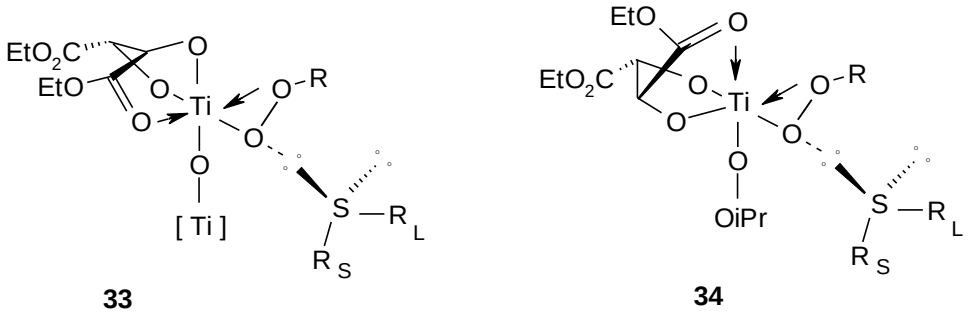
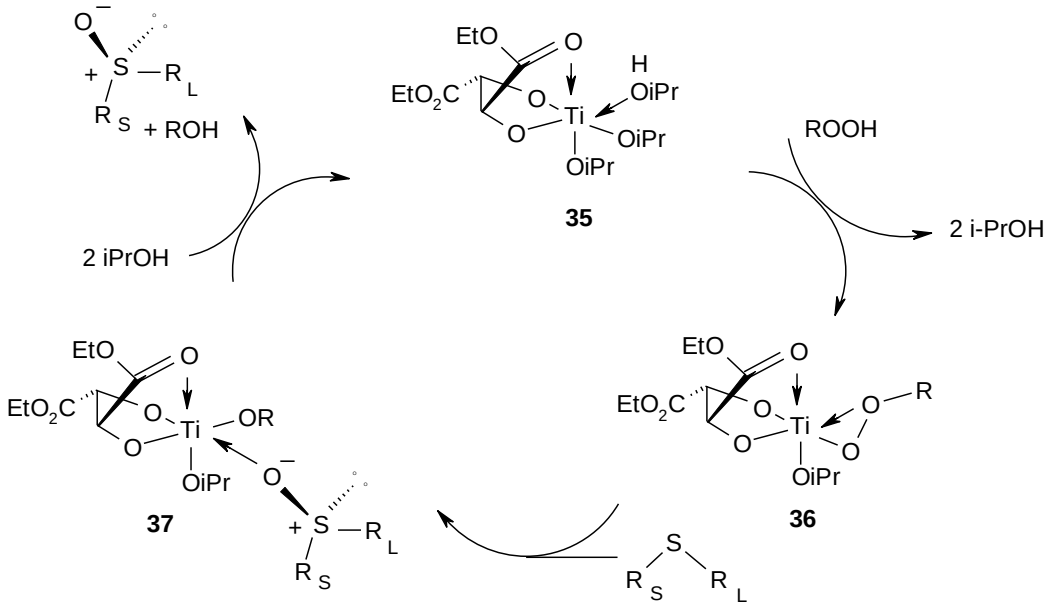


Figure 3. Titanium species in sulfide oxidation.

In the reaction medium different titanium species exist. The presence of a monomeric titanium compound of type **34** bearing a simple isopropoxide instead of the η-oxo group is also possible. In both intermediates tartrate is bound in a tridentate fashion and the peroxide in the oxidant reagent can substitute for one alkoxy ligand and stay in a η^2-coordination. This model ensures that the approach of the incoming sulfide is determined by a distinction between the steric bulkiness of the groups

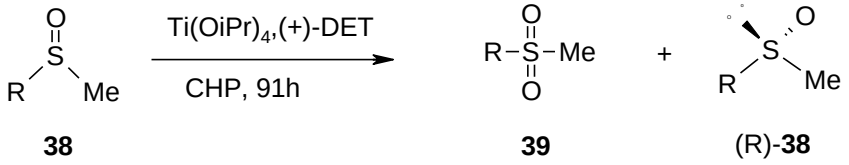


Scheme 33. Enantioselective sulfide oxidation with Ti/DET complexes in the presence of i-PrOH.

present in the substrate. As a consequence, the high enantiotopic discrimination generally occurs when two substituents in sulfide are significantly different in size (R_L and R_S, respectively).[36]

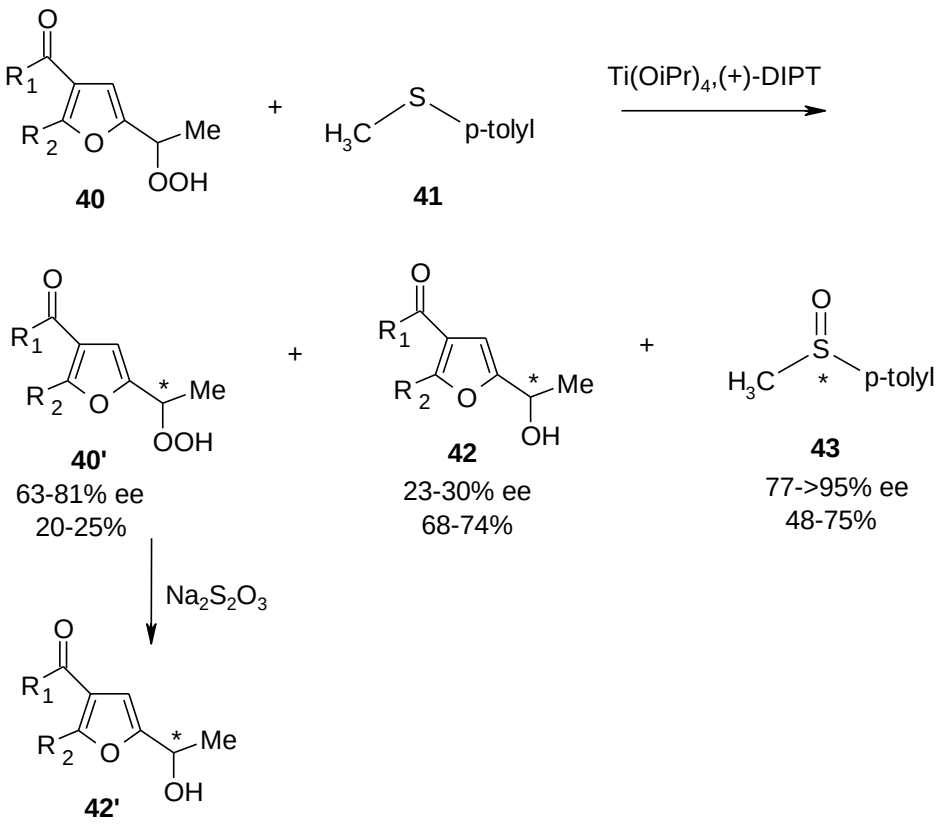
The overall catalytic cycle is believed to involve various titanium complexes which all have at least one isopropoxy ligand attached to the metal (Scheme 33). It is evident that the kind and structure of alkoxide can influence the catalysis, in particular, the chirality transfer step from **36** to **37** via **34** and the displacement of sulfoxide from **37** to regenerate **35**. The use of other titanium alkoxides and alcohols such as methanol lead to less efficient catalyst systems.[36]

The kinetic resolution of racemic sulfoxides has been reported to proceed via the enantioselestive oxidation to sulfones under Modena's conditions using CHP as an oxidant (Scheme 34).[37]



Scheme 34. Kinetic resolution of racemic sulfoxides.

In the enantioselective oxidation of racemic sulfoxides **38** the preferential oxidation of the *S*-enantiomer takes place resulting in sulfone **39** and the enantiomerically enriched sulfoxides *R*-**38** are recovered. Although this procedure is almost completely unsuccessful in the case of dialkyl sulfoxides, chiral methylaryl sulfoxides are obtained in a satisfactory yield (31−40%) and with a very good enantiomeric excess (83−94%). The kinetic resolution of racemic sulfoxides represents a different approach to chiral sulfoxides. In both ways, by the asymmetric oxidation and by the kinetic resolution, *R*-sulfoxides are obtained when *R*,*R*-tatrates are used as asymmetric inducers. When furyl hydroperoxides are used instead of CHP the enatioselectivity of the process increases even in the case of diakyl sulfides (for example, methyl *n*-octyl sulfoxide is obtained in 78% *ee*). The racemic secondary hydroperoxides are found to undergo a kinetic resolution in the course of the asymmetric oxidation. Although tertiary hydroperoxides have usually afforded the best results, both in terms of yield and enantiomeric excess, chiral sulfoxides **43** are obtained in high *ee* values by the oxidation with the oxidant containing a stereogenic centre. In that case the asymmetric oxidation involves also a kinetic resolution of racemic hydroperoxides **40** (Scheme 35).[38]



Scheme 35. Asymmetric oxidation of methyl *p*-tolyl sulfide **41** with secondary furylhydroperoxides.

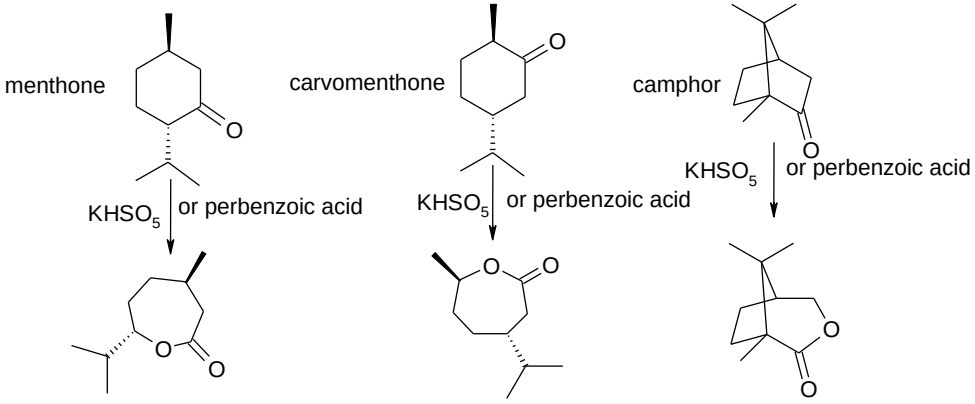
These results are indicative of the opportunity of obtaining optically active hydroperoxides **40'** which are useful stereoselective oxidizing reagents in the other processes. Moreover, this route also gives access to the enantiomerically enriched 2-furylcarbinols since the unreacted hydroperoxide **40'** can easily be reduced to the corresponding alcohol **42'**. Altogether four optically active compounds can be obtained simultaneously in the course of this reaction.

4.2. Asymmetric oxidation of ketones

4.2.1. Asymmetric Baeyer-Villiger oxidation

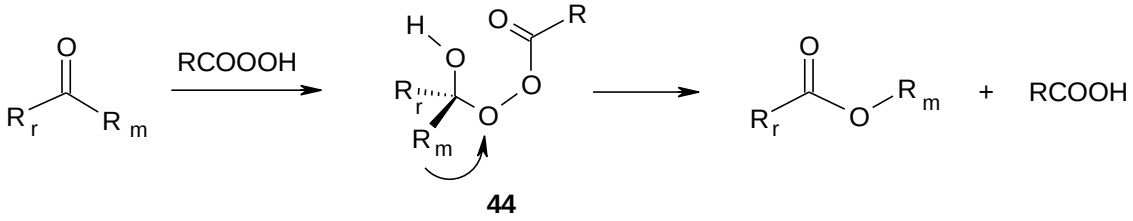
The Baeyer-Villiger oxidation of cyclic ketones is a highly valuable method for the synthesis of lactones in a very straightforward manner. The reaction was discovered by Alfred Baeyer and Victor Villiger more than a hundred years ago.[39,40] Although natural chiral ketones were the first compounds

which were oxidized by these chemists, their work cannot be considered the beginning of the asymmetric Baeyer−Villiger reaction (Scheme 36).



Scheme 36. The first transformation of cyclic ketones into lactones.

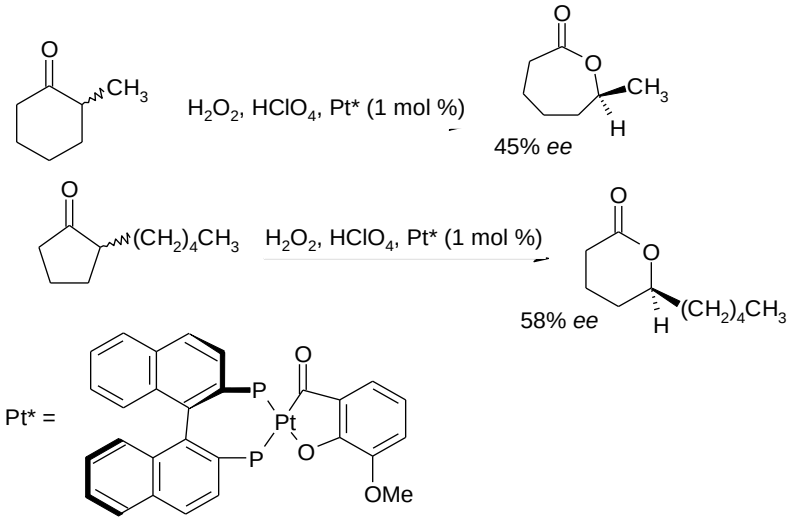
Concerning the mechanism of the Baeyer-Villiger oxidation Griegee proposed a two-step mechanism for that.[41] The first step is an acid-catalyzed addition of a peroxide to carbonyl function resulting in a tetrahedral peroxyhemiketal **44** known as the Griegee intermediate (Scheme 37). The next step comprises the migration of the substituent R_m from the carbonyl carbon to the next oxygen atom of the peroxy bridge and, simultaneously, the cleavage of the O−O-bond along with the release of the acid moiety.



Scheme 37. Mechanism of the Baeyer-Villiger oxidation of ketones.

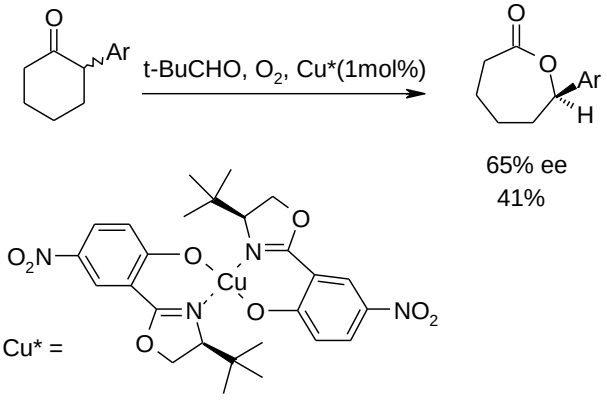
The migration of the substituent R_m is important in determining the selectivity and rate of the reaction. A more substituted carbon atom migrates better because it is able to stabilize the partially positive charge that is formed in the transition state. There are cases demonstrating the influence of other electronic and steric effects or the structure of peroxide on the regioselectivity of the oxygen insertion. The configuration of the migrating substituent is preserved in all cases.[45] Usually, the oxidation is performed using organic peroxyacids or other peroxy compounds, including hydrogen peroxide and alkyl hydroperoxides as a reagent.

The development of efficient metal-catalyzed oxidation procedures[42,43,44] allowed the reaction to be performed in an enantioselective manner by employing appropriate ligands. Since 1994, there have been some reports on the enantioselective Baeyer−Villiger oxidation[45,46]. The first two examples of the asymmetric metal-catalyzed Baeyer−Villiger oxidation were published almost simultaneously by Strukul[47] and Bolm.[48] In both cases the reaction under study was a kinetic resolution of racemic ketones through enantiospecific conversion them into chiral lactones. Strukul and co-workers oxidized 2-alkylcycloalkanones using hydrogen peroxide in the presence of chiral platinum complexes to chiral lactones up to 58% *ee* (Scheme 38).[47]



Scheme 38. Asymmetric oxidation of ketones catalyzed by chiral Pt-complexes.

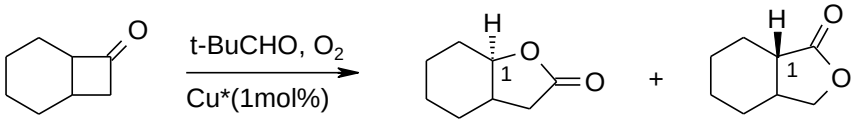
Bolm and co-workers published data about using a chiral modified Mukaiyama system with a copper and nickel complexes. The best yields and enantioselectivities of the oxidation were obtained with the copper complex bearing two bidentate oxazoline-type ligands in the presence of



Scheme 39. Asymmetric oxidation of ketones catalyzed by chiral Cu-complexes.

pivaldehyde. The racemic aryl-substituted cyclohexanones could be oxidized to the corresponding enantiomerically enriched lactones up to 69% *ee* (Scheme 39).[47] The catalytic system described is limited to 2-arylcycloalkanones only, the positional isomers and 2-alkyl-substituted cycloalkanones are not reactive.

The same oxidizing system was used to oxidise racemic substituted cyclobutanones which give rise to two isomeric lactones (Scheme 40).[49] The reaction proceeds in an enantiodivergent manner, i.e., the chiral catalyst Cu* transforms the enantiomers of ketones into different regioisomeric lactones (1*R*)-**46a** and (1*S*)-**46b** with different *ee* values. The recovered starting ketone was found to be almost racemic (≤ 6% ee).



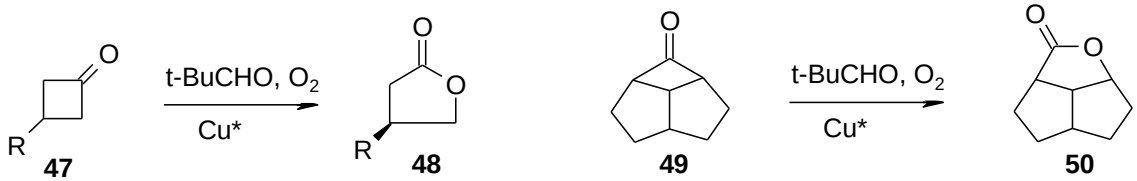
rac-**45** (1R)-**46a** 67% ee (1S)-**46b** 92% ee

61% (3 : 1)

Scheme 40. Transformation of a racemic mixture into two chiral regioisomeric products.

The oxidation of unsaturated bicyclic ketone **57** led to a complex product mixture consisting of the desired lactones and the products derived from the oxidation of the double bond.

The prochiral 3-substituted cyclobutanones **47** were oxidized under the same conditions with a moderate enantioselectivity – the corresponding lactones **48** with *ee* values of up to 47% were obtained.[50] Tricyclic ketone **49** was found to be the only prochiral substrate which afforded a highly enantioselective reaction. So, the corresponding lactone **50** was obtained with the enantiomeric excess >90% (Scheme 41).



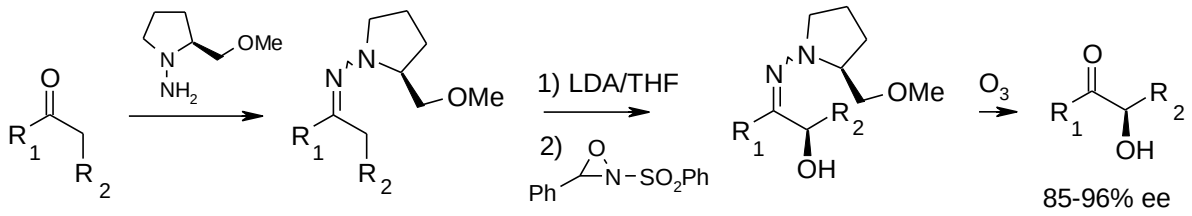
47 **48** 23-47% ee 77-92% **49** **50** 91% ee 62%

Scheme 41. Asymmetric oxidation of prochiral cyclobutanones catalyzed by chiral Cu-complexes.

Very recently, a zirconium-based asymmetric oxidation system was developed by Bolm and co-workers.[51] So, using a combination of Zr(*t*-Bu)/ *S*-BINOL/BIPOL/TBHP in the oxidation of bicyclic and monosubstituted cyclobutanones they obtained two regioisomeric lactones with *ee* values of up to 84%. However, higher *ee* values are observed for minor regioisomers. In the zirconium-mediated oxidation the metal was used in stoichiometric amounts.

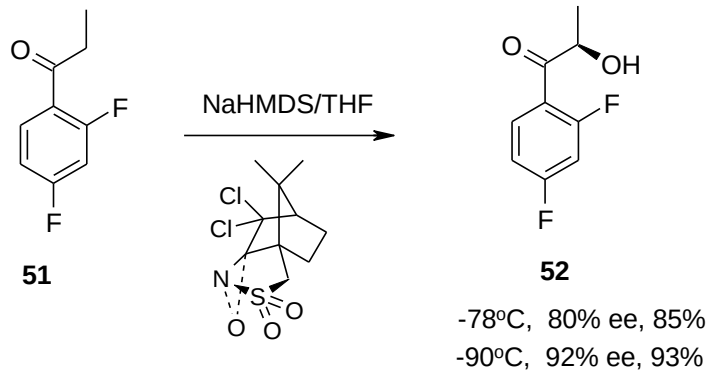
4.2.2. Asymmetric α-hydroxylation of ketones

One of the earliest oxidative methods used for the synthesis of optically active α-hydroxy ketones is the stereoselective hydroxylation of enolates in which the chiral organic or organometallic auxiliary is covalently bound to the enol functionality. α-Hydroxy ketones of high *ee* and good overall yield are achieved by the hydroxylation of azaenolates derived from chiral SAMP hydrazones with phenylsulfonyl oxaziridines as oxidants (Scheme 42).[52]



Scheme 42. Diastereoselective hydroxylation of chiral enolates.

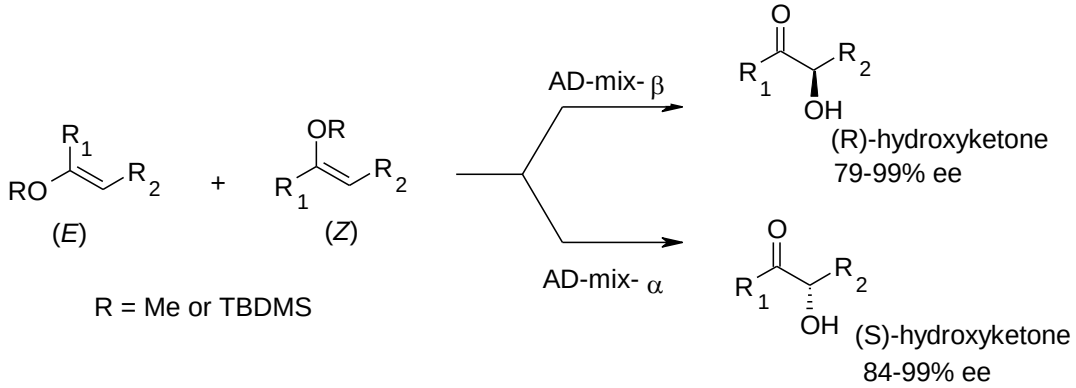
However, the disadvantage of any chiral auxiliary based asymmetric synthesis is the necessity to prepare a compound with the auxiliary (usually an expensive chemical substance) and, eventually, later remove the auxiliary reagent. This problem can be avoided by using the enantiomerically pure oxaziridines as oxidizing reagents for induction of chirality into the substrate molecule.[53] The hydroxylation of prochiral enolates using the enantiopure N-sulfonyloxaziridines has been widely employed in the synthesis of natural products.[54] For example, an optically active α-hydroxy ketone **52** required for the total synthesis of azole antifungals was prepared *via* an asymmetric oxidation of sodium enolate of ketone **51** with chiral camphorsulfonyl oxaziridines (Scheme 43).[55]



Scheme 43. Enantioselective hydroxylation of prochiral ketone enolates.

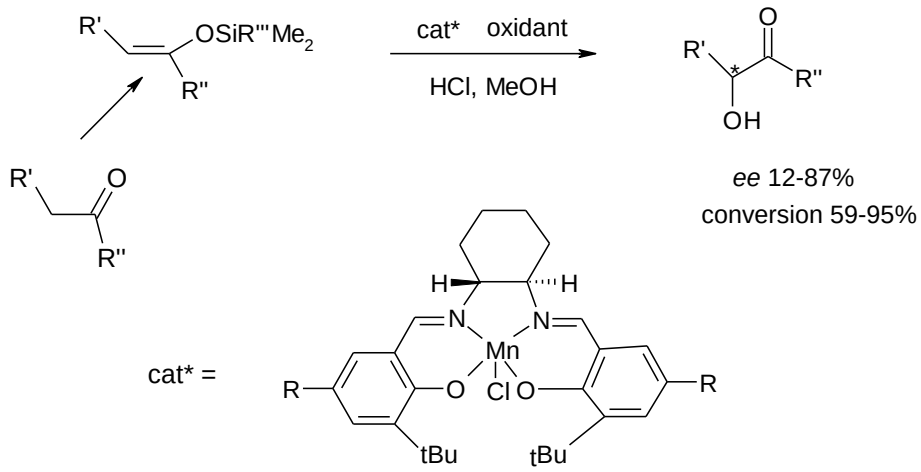
The disadvantage of the method is its strong dependence on reaction conditions, reagent and substrate structure. So, the enantioselectivity of the asymmetric enolate oxidation is highly dependent on the structure of the oxaziridine, the enolate and the reaction conditions. In some cases, the addition of HMPA improves the enantioselectivity of oxidation and, in other cases, reduces it. Similarly, it has been observed that in some cases potassium enolate gives better results than the corresponding lithium enolate.[54]

In the efforts to extend the scope of an asymmetric dihydroxylation (AD) method, Sharpless and co-workers found that enol ethers are excellent substrates for the dihydroxylation complex, giving rise to α-hydroxy ketones with a high enantiomeric purity[56] (Scheme 44). It is noteworthy that the poor *Z/E* ratio has no deleterious effect on the enantioselectivity realized upon AD of the *E/Z* mixture. The results obtained reveal that the *E*-isomer gives the same ketol enantiomer as the *Z*-isomer, albeit with somewhat lower *ee*. In addition, the AD of tetrasubstituted acyclic and cyclic enol ethers give the corresponding α-hydroxy ketones in fair to good yields and with moderate to good *ee* values.[57]



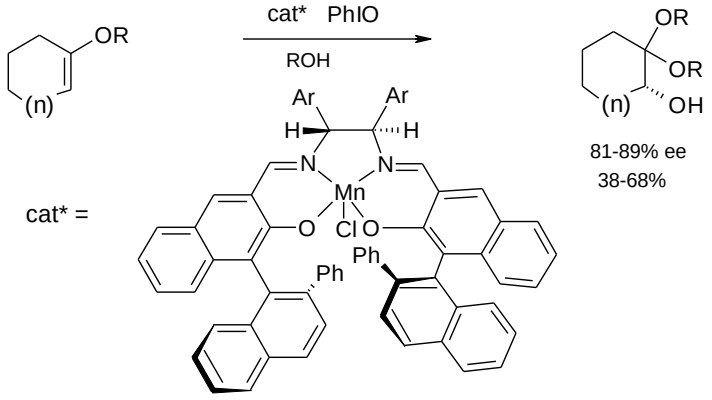
Scheme 44. Catalytic asymmetric dihydroxylation of enol ethers.

The asymmetric generation of α-hydroxy ketones has been achieved by the oxidation of silyl enol ethers and ketene acetals using (salen)manganese(III)-complexes and oxidants such as NaOCl in the presence of N-oxides (Scheme 45).[58,59]



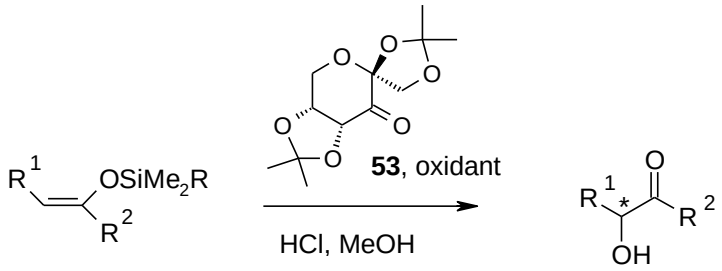
Scheme 45. Enantioselective oxidation of silyl enol ethers and ketene acetals by (salen)Mn(III)-complexes.

Similarly, alkyl and acetyl enol ethers have been successfully oxidized to α-hydroxy acetals using the hindered Mn-salen complexes, iodosylbenzene as an oxidant and alcoholic reaction media (Scheme 46).[60] The reaction in the other solvents showed irregular and lower enantioselectivity, partly due to the racemization of the resulting α-hydroxy ketones.



Scheme 46. Asymmetric oxidation of enol derivatives using the Mn-salen catalyst.

Recently, some metal-free asymmetric oxidation methods were reported.[61,62] The optically active α-hydroxy ketones have been prepared with a moderate to high enantioselectivity by the oxidation of silyl enol ethers with *in situ* generated dioxirane from the fructose-derived chiral ketone **53** (Scheme 47).



Scheme 47. Asymmetric oxidation of enol ethers by the dioxirane generated *in situ* from ketone **53**.

5. AIMS OF THE PRESENT STUDY

The above short literature overview demonstrates the difficulties in realising an asymmetric version of direct oxidation of ketones – there is a certain shortage of efficient oxygenation methods, especially those mild methods that enable to get α-hydroxy ketones, lactones, etc. At the same time, the unique features of the Sharpless complex – its structural specificity − that in many cases enables a very high enantioselectivity and good yields of the products is clearly evident. However, the scope of this method is limited to allylic (homoallylic) alcohols and sulfides (sulfoxides). Our laboratory has traditionally been interested in the synthesis of natural bioactive compounds. Therefore, the need for new methods of synthesis of enantiomeric oxygenated compounds (e.g., lactones, α-hydroxy compounds, etc.) has become very urgent for us. The optically active α-hydroxy ketones, lactones and hydroxy acids are widely represented among biologically active natural products. Some oxygenated species have become very important only recently (monosaccharide carba-analogues, components for anti-AIDS medicals, etc.). Consequently, efficient methods for the synthesis of these compounds in a chiral nonracemic form are in demand. An attractive route to the enantiomerically enriched derivatives of ketones is the direct asymmetric oxidation of the parent carbonyl compounds. When performing the asymmetric oxidation reaction the nature of the substrate, the enantio- as well as regio- and chemoselectivity have to be considered.

The main goals of the present investigation were:

- to extend the synthetic utility of the Sharpless titanium-tartrate catalyst to compounds other than allylic alcohols and sulfides
- to find out some suitable substrates for oxidation among ketones and diketones (the scope of this method)
- to elucidate the reaction conditions necessary to achieve a high enantioselectivity and yield of the oxygenated compounds
- to find possible reaction pathways and limitations to the process
- to identify, isolate and characterize the products
- to determine the enantiomeric purity the reaction products obtained

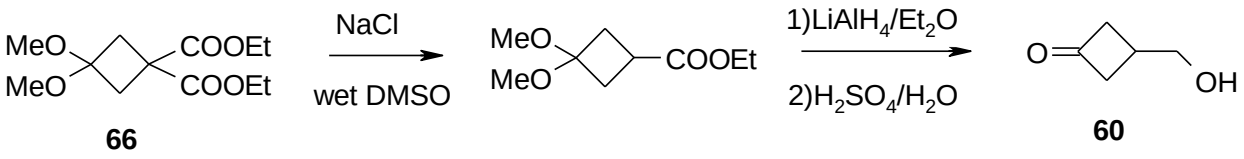
Three different types of prochiral and racemic ketones were investigated: cyclobutanones, cyclic- and acyclic β-hydroxyketones and 3-alkyl-1,2-cycloalkanediones.

6. RESULTS AND DISCUSSION

6.1. Asymmetric Baeyer-Villiger oxidation of cyclobutanones using Sharpless complex (I)

In order to develop an enantioselective method for the synthesis of optically active γ-butyrolactones, we assumed that the Sharpless oxidation catalyst may oxidize the strained cyclic ketones (cyclobutanones) into lactones. Indeed, our preliminary experiments showed that from cyclobuanone **54** lactone **55** with a certain enantiopreference was formed. Starting from this finding we decided to investigate this oxidation method in more detail. The study involved the oxidation of different racemic (compounds **56**–**59**) and prochiral ketone (**60**) under the Sharpless oxidation conditions [18].

The substrates for oxidation were prepared according to known procedures[63,64,65,66] (**54**, **56**, **57** and **58** respectively). Iodohydrin **59** was synthesised analogously to bromohydrin **54**, using NIS instead of NBS. Cyclobutanone **60** was prepared from diethyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate **66**[67] (Scheme 48).



66 **60**

Scheme 48. Synthesis of cyclobutanone **60**.

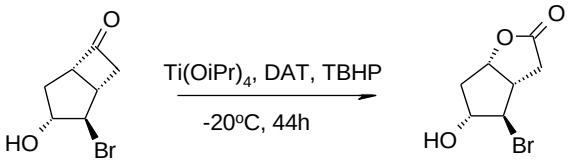
Cyclobutanone **54** was chosen as a model compound due to its availability in a racemic form in our laboratory. The oxidation of **54** with the Sharpless complex under different reaction conditions and at different Ti/DAT/TBHP ratios was preformed. Also, the tartaric acid ester in the Sharpless complex was varied (Me, Et, and *i*Pr esters were used). Depending on these conditions, i.e. the presence of molecular sieves, the amount of the catalyst, the kind of tartrate ester and oxidant, lactone **55** was obtained with an *ee* varying from 34 to 75% (Table 3).

We found that the combination of the substrate/Ti(O*i*Pr)$_4$/DIPT/TBHP ratio of 1:1.5:1.8:1.5 gives the best *ee* and yield. Further increasing the amount of the catalyst did not improve the enantioselectivity (entries 4,5). Also, the higher substrate and catalyst concentrations did not influence the selectivity or did not lead to side reactions (which may arise from the large amount of Ti-tartrate species and isopropyl alcohol in the solution). An excess of the oxidant with respect to the catalyst led to a lower *ee* value (entry 1). This may be the result of competition between catalytic and uncatalytic reaction pathways[49] leading to the formation of the racemic product to some extent. The order of addition of TBHP and ketone did not influence the optical and chemical yields (entries 2 and 3). It is consistent with the model of the ligand exchange pathway in the epoxidation of allylic alcohols[10] (Scheme 7).

The effect of variation of tartrate ester upon selectivity was also examined (entries 2, 6, 9). The highest enantioselectivity was obtained with DET, while the catalyst with DIPT was slightly and with DMT considerably less selective. At the same time, the reaction rate increased with decreasing bulkiness of the ester alkyl group: DMT>DET>DIPT. The high sensitivity of water to the titanium-tartrate complex is well-known[12, 34]. In our experiment, the addition of 1 equiv of water to the catalyst resulted in a lower selectivity and very slow reaction (entry 8). At the same time, the addition of molecular sieves to the reaction mixture in order to completely avoid the presence of water slightly improved the selectivity of oxidation (entry 7). The more common Baeyer−Villiger oxidant ─ *m*-chloroperbenzoic acid (MCPBA) instead of TBHP in the oxidation gave a product with a moderate *ee*

and low yield (entry 10) indicating that MCPBA is not suitable (does not fit properly in) for the Sharpless complex.

Table 3. Asymmetric oxidation of racemic ketone **54** at different Ti/DAT/TBHP ratios



54 **55**

Entry	Ti(O*i*Pr)$_4$(eq)	DAT	eq	TBHP	Yield (%)	ee (%)
1	1	(+)-DIPT	1.5	1.5	24.5	62
2	1.5	(+)-DIPT	1.8	1.5	28	67
3	1.5	(+)-DIPT	1.8	1.5	29	67[a]
4	2	(+)-DIPT	2.4	1.5	28	67
5	2	(+)-DIPT	2.4	1.0	21	67[b]
6	1.5	(+)-DET	1.8	1.5	41	73
7	1.5	(+)-DET	1.8	1.5	40	75[c]
8	1.5	(+)-DET	1.8	1.5	4	41[d]
9	1.5	(+)-DMT	1.8	1.5	49	34
10	1.8	(+)-DIPT	1.8	0.6[e]	20	38

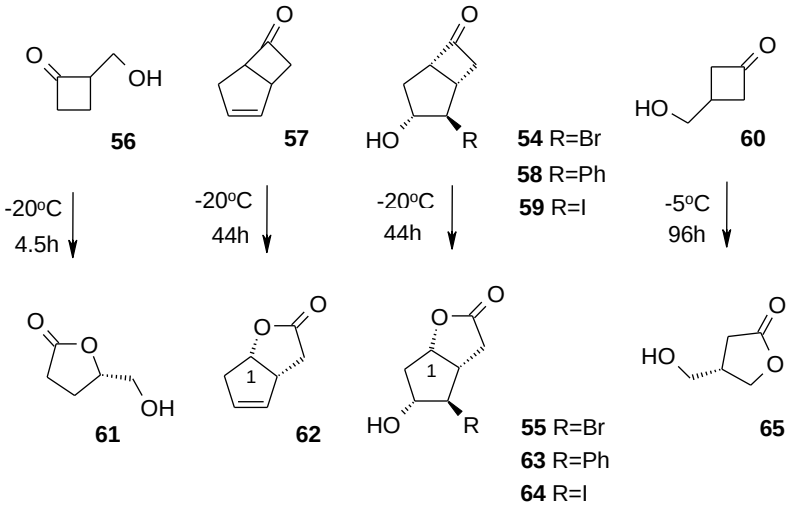
[a] TBHP was added before ketone.
[b] 1.5 times more concentrated catalyst solution was used.
[c] 4Å molecular sieves was added.
[d] 1 eq of water was added.
[e] MCPBA was used instead of TBHP.

Following the optimal conditions found by us (entry 7), we carried out the oxidation of various cyclobutanones (Table 4). The best enantioselectivity (up to 75% *ee*) was obtained for the sterically more hindered ketones (entries 2−5), while the sterically accessible monosubstituted cyclobutanones **56** and **60** resulted in lactones **61** and **65** only in a moderate enantiomeric excess (entries 1 and 6). It should be noted that the enantioselective oxidation of prochiral ketone **60** and the kinetic resolution of racemic cyclobutanone **56** resulted in a similar selectivity.

It is noteworthy that the existence of a pendant hydroxy group in the molecule is not essential for determining the enantioselectivity (e. g., ketone **57** was oxidized into lactone **62** also with rather

high enantioselectivity ─ 53% *ee*). However, the reactivity of the substrates depends strongly on the presence of the hydroxy group. Thus, the reaction with substrate **57** proceeded very slowly (7% yield under standard conditions), while α-hydroxymethyl cyclobutanone **56** was the fastest oxidized substrate in the series investigated.

Table 4. Enantioselective Baeyer-Villiger oxidation of cyclobutanones



Entry	Ketone	Lactone	Yield (%)	ee (%)[a]	$[\alpha]_D$[b]	Abs. conf.
1	56	61	35[c]	37	+15	*S*
2	57	62	7	53[d]	-60°	1*S*
3	54	55	40	75	-14°	1*S*
4	58	63	31	59	-30°	1*S*
5	59	64	30	62	-16°	
6	60	65	14	40	-11°	*S*

[a] Determined from the ratio of diastereoisomers of the corresponding (*S*)-(+)-α-methoxyphenylacetic acid esters by HPLC and/or NMR spectroscopy.
[b] Measured in 96% ethanol.
[c] 1.5 times more diluted catalyst solution was used.
[d] Based on optical rotation of the reference sample $[\alpha]_D^{20} = -113°$.

Substrates **54**, **58** and **59** bearing a hydroxy group remote from the reaction centre were also readily converted into the corresponding lactones. This is probably due to the coordination of the hydroxy group to the titanium that enhances the reaction rate (brings the reaction centre close to the reagent,

both are bound to the same tiatnium atom[14]). On the other hand, such a coordination seems to affect not the enantioselection but only reactivity: the α-unbranched β-hydroxymethyl cyclobutanone **60** has a considerably lower reactivity; the oxidation occurred only at an elevated temperature (–5 °C) and with a prolonged reaction time (96 h). Even so, a still remarkable enantioselectivity of oxidation (40% *ee*) was observed.

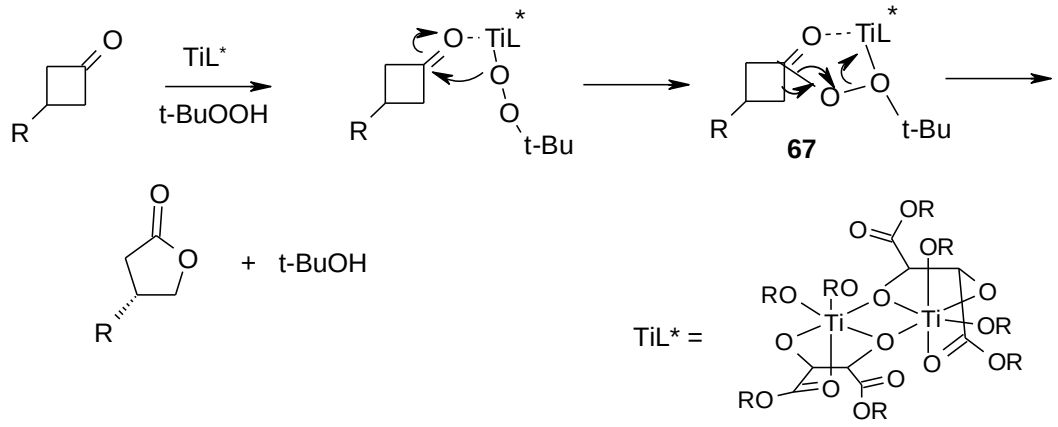
The oxidation of branched cyclobutanones occurs exclusively at the branched carbon atom (no regioisomers were detected). As expected, the isolated double bond in ketone **57** did not epoxidize under the reaction conditions.

The kinetic resolution of racemic cyclobutanones gave predominantly lactones having an *S*-configuration at the branched carbon atom connected with oxygen. It should be mentioned that in the kinetic resolution of secondary allylic alcohols by using (+)-tartrate ester as a chiral source , the *S*-enantiomer of alcohol also reacts faster than the *R*-enantiomer.[18] Lactone **65** that was obtained from the oxidation of prochiral cyclobutanone **60** was also dominantly in the *S*-configuration.

The absolute configurations of lactones **61**, **62** and **65** were established by comparison of the sign of $[\alpha]_D$ of the compounds with the corresponding literature data.[68,69,70] The absolute configuration of lactone **63** was determined by our group separately.[66] The absolute configuration of lactone **55** was established by the (–)-sign of the optical rotation of unreacted ketone **54** which reveals the excess of the 1*R*-enantiomer.[71] Consequently, lactone **55** should have a 1*S*-configuration. The absolute configuration of lactone **64** was not established.

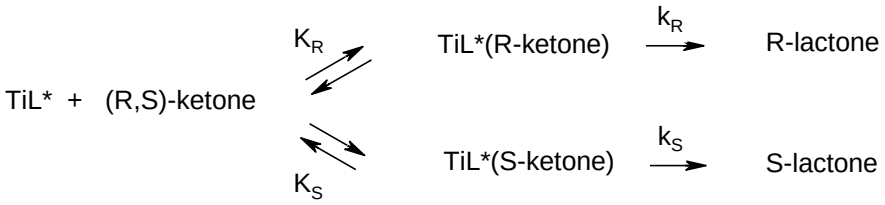
Our results presented above are the first examples of the asymmetric Baeyer-Villiger oxidation of ketones by the Sharpless catalytic complex. On the basis of a classical imagination about the mechanism of the metal-catalyzed oxidation[46] we may propose the following mechanism for the titanium-tartrate catalyzed oxidation of cyclobutanones (Scheme 49).

In analogy with the platinum-catalyzed Baeyer-Villiger oxidation,[47] the titanium catalyst is assumed to behave like the Lewis acid capable to bound the carbonyl oxygen. The simultaneous coordination of TBHP to titanium promotes the formation of a peroxometallacyclic intermediate which bears strong similarities with the Griegee intermediate.[41] The similarity of mechanism of the Baeyer-Villiger oxidation and the rearrangement of intermediate **67** is supported by the exclusive migration of the most substituted species in the case of α-branched cyclobutanones (no regioisomers were detected in our case).



Scheme 49. Mechanistic pathway for the Baeyer-Villiger reaction catalyzed by the Ti-tartrate complex.

The mechanistic interpretation of the asymmetric induction in the metal catalyzed oxidation systems where both the chiral ligand and the substrate are simultaneously coordinated to the metal has been presented by Strukul in an article.[46] In the kinetic resolution of racemic ketones the asymmetric transformation occurs by the formation of diastereomeric cat* (ketone) intermediates followed by a stereoselective oxygen transfer step. A similar interpretation could well apply to the titanium-tartrate catalyzed enantiospecific oxidation (Scheme 50).



Scheme 50. Principal scheme of the kinetic resolution process with chiral Ti complexes.

As described above, the structure of the substrate and the choice of tartrate ester have a significant influence on the selectivity of oxidation. Consequently, the enantioselectivity may depend on the steric properties of the ligand and the substrate. In the oxidation of cyclobutanones, using the combination of (+)-DET/bicyclic cyclobutanone gave the best results. The enantiomeric purity of the bicyclic lactones obtained ranges from 53 to 75% *ee*. Also, the yield of the kinetic resolution (50% is maximum) for compounds having a hydroxy group is good (30–40%). The results obtained show the

usefulness of the method for the synthesis of some enantiomeric lactones since the functionalized bicyclic lactones are valuable intermediates in the synthesis of many organic compounds.[72,73,74]

The use of the titanium catalytic complex in a little higher than the stoichiometric amount is needed to achieve the best optical and chemical yield. The inhibition of the Ti catalytic activity during the reaction may occur due to the stronger coordination of the products formed to the metal centre than that of the substrates.[32] That type of difference in the complexation ability may retard the substrate/product exchange and, therefore, the catalyst activity.

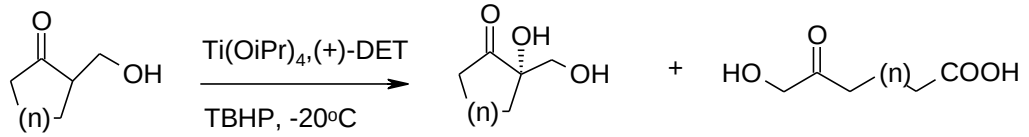
6.2. Direct α-hydroxylation of ketones (II)

In order to broaden the scope of the use of the direct asymmetric oxidation of ketones we investigated the oxidation of ketones other than cyclobutanones. After we have found that the above α-hydroxymetyl cyclobutanone is the most readily oxidized substrate (I), we performed the oxidation of α-hydroxymethyl cyclopentanone **68a**. Surprisingly enough, we found that the oxidation of **68a** under the Sharpless oxidation conditions leads to a completely different compound, a α-hydroxy compound (α,β-dihydroxy cyclopentanone **69a**) with a high enantiomeric purity instead of the Baeyer–Villiger oxidation product, a lactone. Based on this preliminary result, we investigated the oxidation of α-hydroxymethyl alkanones in more detail. First, we observed that together with an α-hydroxy compound, which was the main product, a certain amount of ω-hydroxy ketoacids **70** was formed.

To establish the scope of the reaction, optimal reaction conditions and the product profile β-hydroxy ketones **68** were synthesized. Substrates **68a** and **68b** were prepared according to a reported procedure[75] (from commercially available ethyl 2-oxocyclopentanecarboxylate and methyl 2-oxocyclohexanecarboxylate[76], respectively). The substrates were oxidized using the Sharpless complex under various conditions (Table 5). We found that the oxidation conditions that were optimal for cyclobutanone lactonization gave hydroxy ketones **69a** and **69b** in low yield (Table 5, entries 1 and 8). The use of the prolonged reaction time caused only a slight increase in chemical yield. Also, a slight improvement in yield was observed when the quantity of the catalyst was increased (Table 5, entries 3 and 4). Nevertheless, in all cases a considerable amount of the substrate remained unchanged. The addition of more of the oxidant to the system (a higher excess of TBHP)

diminished the yield (Table 5, entry 5). The reaction rate accelerated, just on the contrary, when the amount of the oxidant was decreased (Table 5, entries 6 and 7). As seen in the Table 5, the best yield was obtained at a ratio of the substrate/Ti(O*i*Pr)$_4$/(+)-DET/TBHP of 1/3/3.6/1.2 (Table 5, entry 7).

Table 5. Oxidation of cyclic α-hydroxymethyl ketones under various conditions



68a n=1
68b n=2

69a n=1
69b n=2

70

No	Ketone	Ti(OiPr)$_4$/DET ratio (eq)	TBHP eq	Time h	Hydroxyketone **69**			Acid **70**	Recovered **68**		
					Yield %	$[\alpha]_D$[a]	ee[b]%	yield %	yield %	$[\alpha]_D$[c]	ee[d] %
1	68b	1.5/1.8	1.5	46	20	+101°	86	5	54	0	
2	68b	1.5/1.8[e]	1.5	46	15	+94°		4	56		
3	68b	1.5/1.8	1.5	160	24	+95°		8	35	0	0
4	68b	2/2.4	1.5	46	24	+105°	87	7	35	0	
5	68b	3/3.6	3	46	15	+96°	85	9	37		
6	68b	2.3/2.8	1.15	46	55	+101°	86	8	15		
7	68b	3/3.6	1.2	46	58	+101°	86	8	3		
8	68a	1.5/1.8	1.5	48	11	+53°	75	9	56	+21°	10
9	68a	2.4/2.9	1.2	46	32	+81°	97	12	33	+40°	24
10	68a	3/3.6	1.2	46	37	+79°	97	12	23	+32°	21

[a] Measured in 96% ethanol.
[b] Determined by HPLC and/or NMR spectroscopy of the primary *R*-(-)-α-methoxyphenylacetic acid mono esters (Sheme 51).
[c] Measured in CH_2Cl_2.
[d] Determined by HPLC from the *R*-(-)-α-methoxyphenylacetic acid esters.
[e] (+)-DIPT was used instead of (+)-DET.

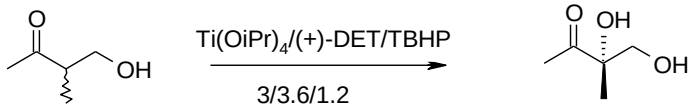
The reaction conditions had little or no effect on the enantioselectivity. On the other hand, the selectivity of hydroxylation depended considerably on the substrate. The highest *ee* value was obtained in the case of cyclopentanone **68a** (Table 5, entries 9 and 10), while the oxidation of

cyclohexanone **68b** proceeded with a slightly lower enentioselectivity. Analogously with the oxidation of cyclobutanones, the use of (+)-DIPT instead of (+)-DET effected the oxidation in a similar way.

Thus, cyclohexanone **68b** was oxidized with (+)-DIPT to a lower extent than with (+)-DET (Table 5, entries 2 and 1, respectively) resulting in a lower yield of hydroxyketone **69b** under identical reaction conditions.

Remarkable was the finding that also open-chain ketones are oxidized under the proposed reaction conditions. Thus, the α-branched aliphatic β-hydroxyketone **71** (1-hydroxy-2-methyl-3-butanone **71** was purchased from Aldrich) was also oxidized resulting in the corresponding hydroxyketone **72** with a high enantioselectivity (Table 6).

Table 6. Asymmetric α-hydroxylation of open-chain ketone **71**



71 **72**

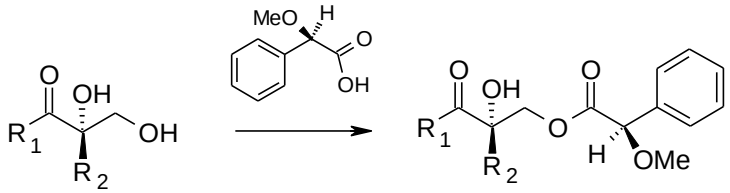
No	Time	Hydroxyketone **72**			Recovered **71**		
	h	yield %	$[\alpha]_D$	*ee* %	yield %	$[\alpha]_D$	*ee* %
1	46	29	−10°	95	49	+5°	15
2	92	47	−10°	93	30	+10°	29
3	168	54	−10°	91	21	+13°	35

Increasing the reaction time resulted in a higher chemical yield of the product without a significant loss in the enantiomeric purity of the resulting α-hydroxyketone. The *ee*% of the unreacted starting ketone **71** also increased steadily in time. The total sum of the recovered and transformed product (78% vs. 75%) slightly decreases with increasing reaction time. This indicates of a possible formation of a certain amount of other by-products (~22−25%) that were not discovered and separated from the reaction mixture.

The conversions of the starting ketone over 50% without a considerable loss in stereoselectivity hint at a possible formation of an achiral intermediate from the racemic starting ketone *prior* to

oxidation. Consequently, in that case an enantioface selection rather than a kinetic resolution of the racemate takes place.

The enantiomeric purity of the α-hydroxy ketones obtained was determined by HPLC from the diastereomeric ratio of their mono-*R*-(−)-α-methoxyphenylacetic acid esters (see Scheme 51).



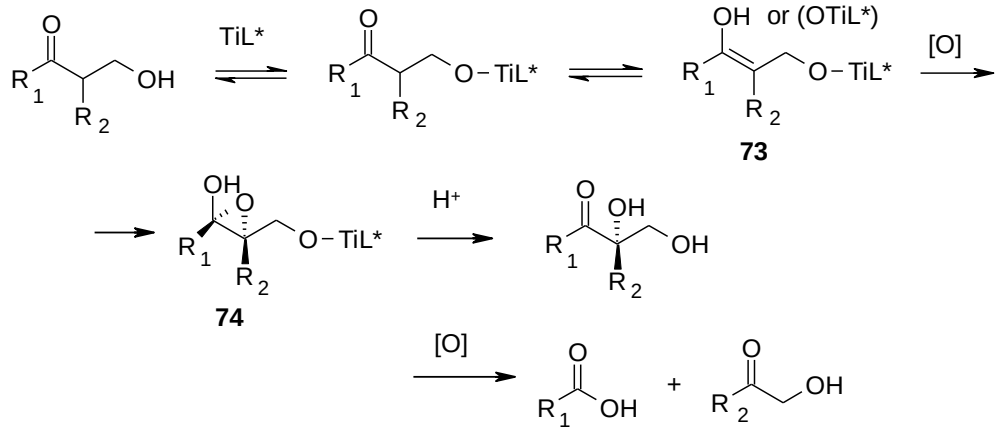
69a $R_1 = R_2 = -(CH_2)_3-$

69b $R_1 = R_2 = -(CH_2)_4-$

72 $R_1 = R_2 = -CH_3-$

Scheme 51. Preparation of primary *R*-methoxyphenylacetic acid monoesters.

The presented above results can be explained by an assumption that the reaction proceeds *via* the Sharpless asymmetric epoxidation of an allylic intermediate that is formed from substrates under the influence of the titanium-tartrate complex (the reactive form of the starting ketone should be achiral) (Scheme 52).



Scheme 52. Mechanistic pathway for the asymmetric oxidation of β-hydroxy ketones by Ti-tartrate complex.

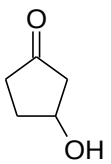
The presence of the β-hydroxy group and the branching of the substrate in the α-position favour the formation of the allylic enolate **73**. Such an allylic system oxidizes according to an ordinary Sharpless oxidation process leading to epoxide **74**. This epoxide rearranges in acidic media in α,β-dihydroxy ketone. The assumption that allylic intermediates are formed in the oxidation process is supported by the fact that the existence of the OH-group is essential for oxidation. Thus, α-branched ketones such as 1-methylcyclopentanone and 1-methylcyclohexanone were not oxidized under our reaction conditions (see II).

The formation of an allylic achiral intermediate always causes the racemization of the substrate. Indeed, we found that the unreacted substrate **68b** was racemic. However, the recovered ketones **68a** and **71** revealed a low optical activity (*ee* up to 35%). This indicates that enantioselection does exist also in the enolate formation step. In the case of **68a** and **71** the ketone/enolate equilibrium is shifted towards the ketone reducing the influence of the kinetic racemization. The enolate formation step may be considered more important in determining the rate of the reaction as evidenced by the higher conversion of substrate **68b** compared with the other substrates.

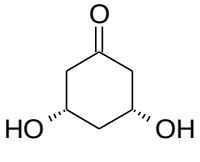
As described above, the excess of TBHP diminishes the yield of ketone diol **69b**. At the same time, any substantial increase in the amount of the oxidative cleavage product **70** was not observed. Thus, it may be assumed that the excess of TBHP suppresses the formation of enolate **73** and, therefore, the subsequent oxidation.

This novel α-hydroxylation method provides a valuable way to important 1,2-ketodiols that are known and frequently found as structural units in biologically active natural products.[77,78,79] The method enables to obtain chiral α,β-dihydroxy ketones from cyclic and acyclic β-hydroxy ketones with a very high enantioselectivity (86−97% *ee*) and in satisfactory yield (37−58%) in a straightforward manner.

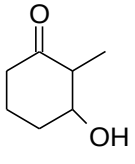
The method is limited to the α-hydroxymethyl substituted ketones. Our attempts to extend the scope of the asymmetric α-hydroxylation to other cyclic carbonyl compounds having the OH-group(s) in the β-position in the ring (compounds **75**−**77)** failed – these compounds were not oxidized.



75

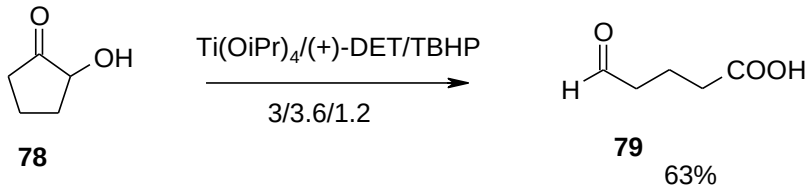


76



77

We assume that α-unbranched ketones **75** and **76** do not oxidize under the reaction conditions usual for β-hydroxyketones probably due to the inability of these compounds to form the intermediate enolate with the titanium complex (Ti in this complex is the Lewis acid rather than a base that catalyses the enolate formation). However, the more easily enolizable ketone − α-methyl-β-hydroxycyclohexanone **77** was not oxidized under our reaction conditions either. This may be accounted for that cyclohexenol is known as one of the poorest substrates in the kinetic resolution of allylic secondary alcohols in the ordinary Sharpless oxidation[18] reaction and that may be the case also in our example. On the other hand, α-hydroxy cyclopentanone **78** was completely converted to the oxidative cleavage product **79** by the Sharpless complex (Scheme 53).



78 **79** 63%

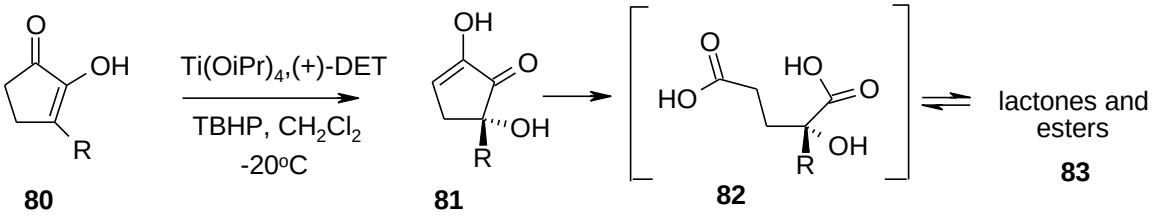
Scheme 53. Titanium-tartrate catalyzed oxidation of 1-hydroxycyclopentanone.

Although α,ω-oxocarboxylic acids are useful starting materials in organic synthesis, this example cannot be considered an important possibility of obtaining this compound because the racemic substrate is converted into an achiral product.

6.3. Asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones (III, IV)

The nonasymmetric version of oxidation of 1,2-diones resulting in ring cleavage products, diacids or keto acids, is known in the literature.[80] Only few examples describe the formation of 2-hydroxy-diacids when oxidizing 1,2-cyclopentanediones. Thus, the formation of 2-hydroxy-2-methyl-pentanediacid was observed when 3-methyl-1,2-cyclopentanedione was oxidized by the Re catalyst[81] or by photooxygenation.[82,83] The asymmetric version of the reaction in any form has not yet been cited in the literature.

As an extension of our studies, we investigated the oxidation of 3-alkyl-1,2-cyclopentanediones **80** with the Sharpless complex and found that these compounds may be considered good asymmetric oxidation substrates leading to enantiomeric products (Scheme 54).

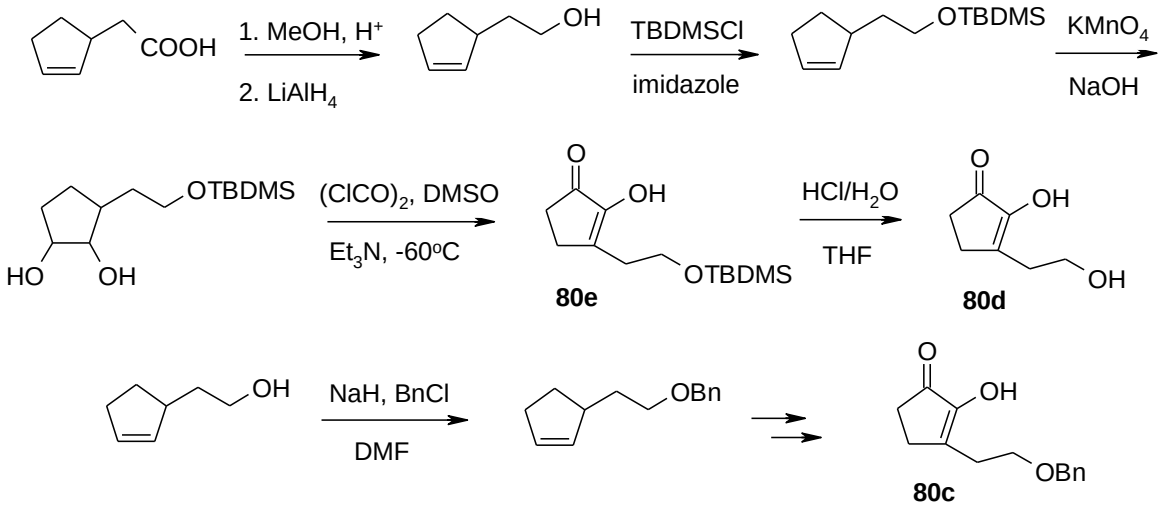


Scheme 54. Oxidation of cyclopentanediones under the Sharpless conditions.

We have observed the formation of two different types of products, chiral monooxygenated products (3-alkyl-3-hydroxy compounds **81)** and chiral ring cleavage products (higher order oxygenated compounds in the form of diacids **82**, esters and lactones **83)**. As the asymmetric synthesis of both types of compounds has not been described in the literature and in order to find optimal conditions for the synthesis of both types of compounds, we investigated the oxidation from the point of view of product formation separately for mono- and polyoxygenated products.

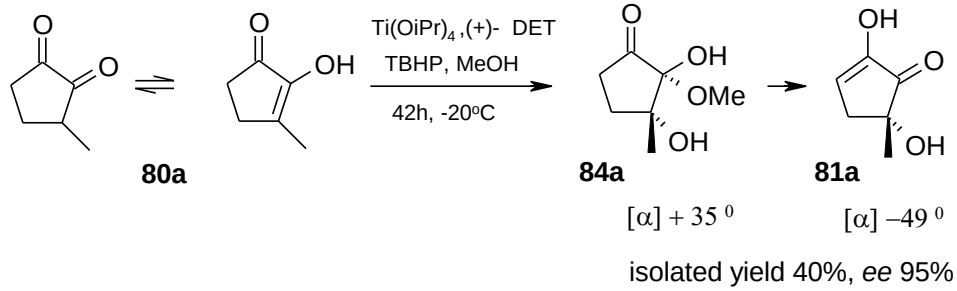
6.3.1. Asymmetric 3-hydroxylation of 3-alkyl-1,2-cyclopentanediones

Substrates 3-methyl- and 3-ethyl-1,2-cyclopentanediones **80a** and **80b** were purchased from Aldrich and compounds **80c**, **80d** and **80e** were prepared from 2-cyclopentene-1-acetic acid according to the procedures presented in Scheme 55.



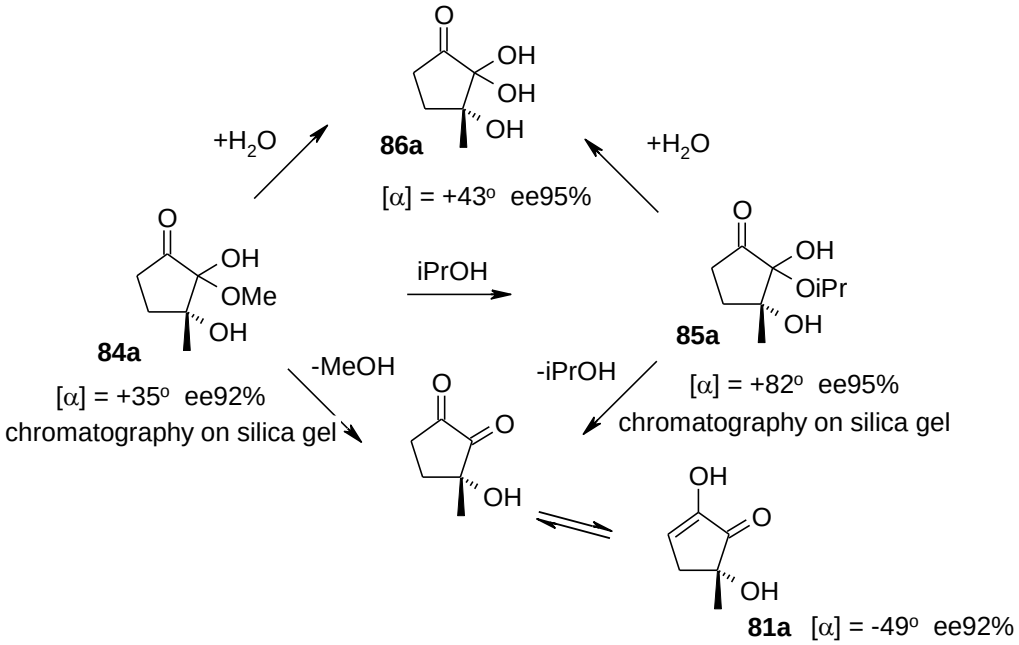
Scheme 55. Synthesis of cyclopentanediones **80c**, **80d** and **80e**.

These compounds were subjected to the oxidation with the Sharpless complex. When oxidizing dione **80a** in the presence of the Sharpless catalyst the direct oxidation resulting in 3-hydroxylated products with a high enantioselectivity occurs. Quenching the reaction by the addition of methanol led to the formation of **84a** (one diastereomer only) as main reaction product in up to 40% isolated yield. After purification on silica gel we always got a certain amount of the deacetalized dione **81a** (Scheme 56).



Scheme 56. Asymmetric 3-hydroxylation of 3-methyl-1,2-cyclopentanedione.

We observed that the initially formed methyl hemiacetal **84a** undergoes reacetalization in isopropanol resulting in a crystalline isopropyl acetal **85a**. These acetals hydrolyze in water into a relatively stable hydrate **86a**. Under anhydrous conditions (e.g. chromatography on silica gel) acetals **84a** and **85a** rearrange into α-hydroxy-1,2-diketone **81a** (in the enol form) (Scheme 57).



Scheme 57. Reacetalization, hydration and enolization of hydroxylated diketone.

It is well known and we have also observed in our studies on other substrates that the asymmetric chemical transformations by the Sharpless complex are sensitive to the reagent/substrate ratio. In the present case the oxidation does not require the excess of the catalyst (as observed by us in the asymmetric oxidation of β-hydroxyketones (II)). The best enantioselectivity was observed when up to 1 eq of Ti was used at the Ti/DET ratio of 1:1.2 to 1:2. The result obtained is very similar to that known for the Sharpless oxidation of allylic alcohols,[12] and lower than that obtained by us in the α-hydroxylation of β-hydroxy ketones. With a proper choice of the reaction conditions it is possible to obtain enantiomeric 3-hydroxylated products in up to 40% isolated yield. It means that the use of the method on a preparative scale may be considered (Table 7).

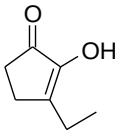
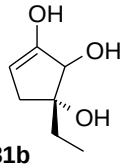
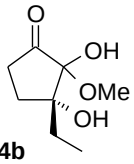
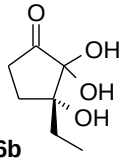
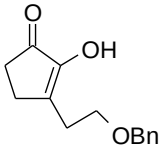
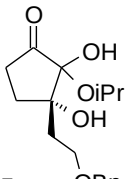
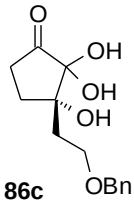
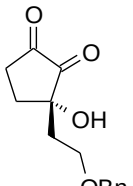
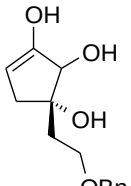
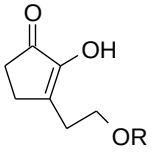
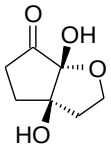
Table 7. Dependence of enantioselectivity and yield on the reagent components ratio in the oxidation of 3-methyl 1,2-cyclopentanedione

Molar ratio $Ti(OiPr)_4$/(+)-DET/TBHP	Yield, %[a]	*ee*%[b]
0.5/1.0/1.5	28	94.7
0.8/1.6/1.5	37	95.5
1.0/1.5/1.2	37	94.8
1.0/1.6/1.5	40	94.3
1.5/1.8/1.5	37	92.4
2/2.4/1.5	32	89.6
2/2.4/2	30	88.8
3/3.6/2	25	87.7

[a] Isolated yields after column chromatography.
[b] Determined by HPLC on chiral column (Daicel Chiralcel OD-H) of the corresponding isopropyl acetals **85a**.

Other 3-alkyl-1,2-cyclopentanediones such as 3-ethyl-1,2-cyclopentanedione **80b**, 3-hydroxyethyl-1,2-cyclopentanedione **80d** and OH-protected 3-hydroxyethyl-1,2-cyclo-pentanediones (the benzyl-protected substrate **80c** and the silyl-protected substrate **80e**) also oxidized readily affording the 3-hydroxy compounds (in different forms, like **81**, **84**, **85** and **86**). In all cases, except for the silyl protected substrate **80e**, the oxidation with the titanium-tartrate complex was highly enantioselective (Table 8).

Table 8. Asymmetric 3-hydroxylation of cyclopentanediones[a]

Cyclic dione	Hydroxylation products ee[b]%, yield%	Sum of ring cleavage products %
 **80b**	 **81b** $[\alpha]_{546}= -180^{o}$  **84b** >95% ee[c], 22%  **86b**	44
 **80c**	 **85c** $[\alpha]_{D}= +38^{o}$  **86c**  **81c'**  **81c** >98% ee[d], sum of **81**,**85** and **86** 31%	34
 **80d** R = OH **80e** R = TBDMS	 **81d** $[\alpha]_{D}= -26^{o}$ R = OH Ti/DET/TBHP 2:2.5:1.5 30% ee,25% Ti/DET/TBHP 1:1.25:1.5 >95% ee, 25% R = TBDMS 62% ee, 3%	48 58 41

[a] Conditions:$Ti(OiPr)_4$/(+)-DET/TBHP ratio 1:1.6:1.5; −20°C, 42h; reaction was quenched by adding citric acid in CH_2Cl_2-MeOH (9:1) for **80b** and **80e** or in acetone-ether(9:1) for **80c** and **80d**.

[b] Determined by HPLC using a chiral column (Daicel Chiralcel OD-H).

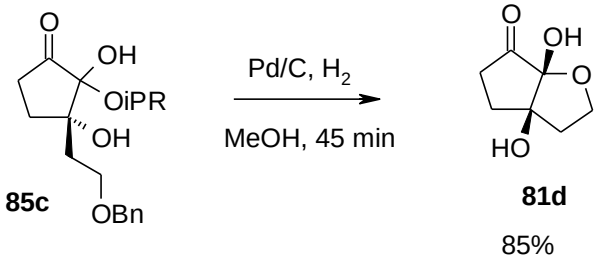
[c] Methyl acetal **84b** was converted to the corresponding isopropyl acetal **85b**.

[d] Isopropyl acetal **85c** was converted to intramolecular acetal **81d** (Scheme 58).

In the case of 3-ethyl-1,2-cyclopentanedione **80b** the initially formed methyl acetal **84b** in the course of quenching the reaction with methanol deacetalizes, resulting in the mixture of enol **81b** and hydrate **86b**. On the contrary, the α-hydroxy diketone **81b** was separated in its enol form as a stable crystalline solid. The oxidation of 3-(2-benzyloxyethyl)-1,2-cyclopentanedione **80c** gave after

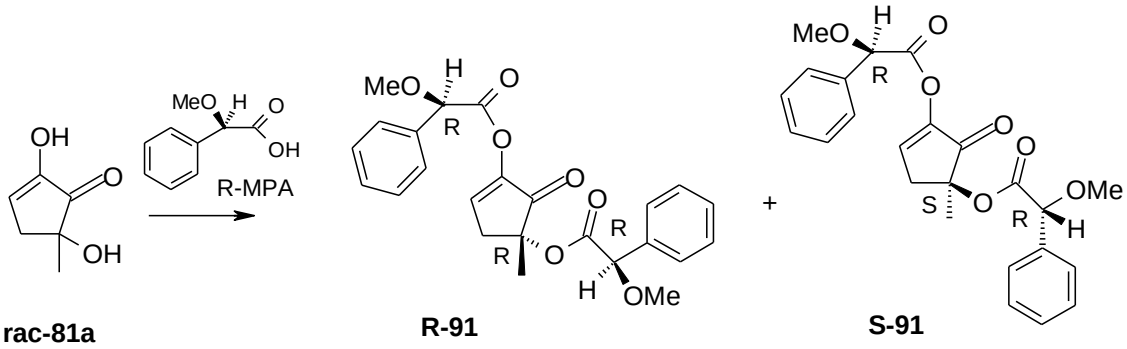
quenching the reaction and adding citric acid in the ether-acetone mixture (without using methanol) a crystalline isopropyl acetal **85c** as the primary hydroxylation product. It means that in the formation of the Sharpless complex when DET is added to Ti(O*i*Pr)$_4$ the isopropyl alcohol is released and, under the acidic reaction conditions, the intermediate epoxide **88** can be rearranged in isopropyl acetal **85c** only. However, purification on silica gel caused partial deacetalization of acetal to a mixture of hydrate **86c**, enol **81c** and diketone **81c'**.

In the case of hydroxyethyl substrate **80d** the primary oxidation product was separated as a stable intramolecular acetal **81d**. The enantiomeric purity of the product was low when 2 equivalents of the complex were used in the oxidation. This hints at the possibility that a complex with two chiral catalyst complexes attached is formed (one attached to the enol moiety and the other, to the primary alcohol moiety). Such a complex may have an opposite facial selectivity for the attached ligands. As a result, a lower enantioselectivity is observed. As the substrate exists predominantly in the enol form **80d** and, therefore, the hydroxyethyl substituent may be regarded as a homoallylic alcohol. The enantiofacial selectivity in the Sharpless asymmetric epoxidation is opposite for allylic and homoallylic alcohols.[25] The epoxidation of homoallylic alcohols proceeds with a moderate enantioselectivity and opposite absolute configuration. Indeed, when using 1 equivalent of the catalyst a cyclic acetal **81d** with a high enantiomeric purity is obtained (>95% *ee*; the same enantioselectivity that was observed in the oxidation of alkyl-substituted cyclopentanediones of **80a-c**). In the case of silyl protected substrate **80e** only 3% of intramolecular acetal **81d** with a moderate *ee* was isolated after chromatogaphy on silica gel. It may be suggested that the protecting group is cleaved during the process resulting in a complex mixture and not a definite product.



Scheme 58. Pd-catalyzed hydrogenolysis of the benzyl group in acetal **85c**.

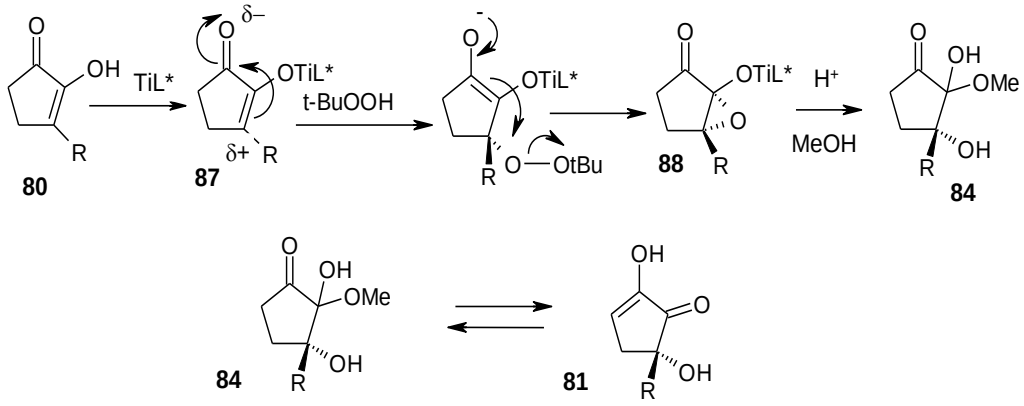
For the determination of an absolute configuration of product **81a** the di-(*R*)-MPA ester **91** from compound **81a** and the corresponding diastereomeric ester mixture from racemic **81a** with (*R*)-MPA was made (Scheme 59).



Scheme 59. Preparation of *R*-methoxyphenylacetic acid diesters from **81a**.

On the basis of ^{13}C NMR spectra of these compounds the *R* configuration is proposed for **81a** (III).

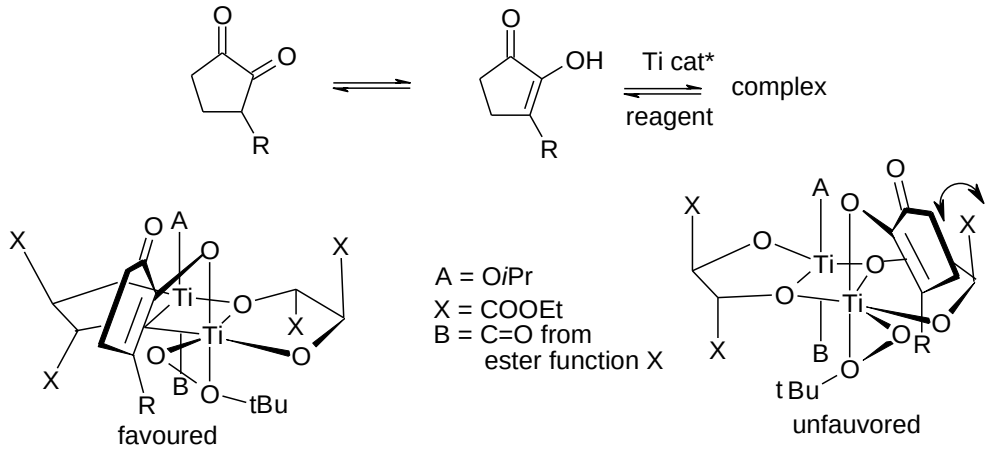
A possible simplified mechanistic pathway for the formation of 3-hydroxylated products from 3-alkyl-1,2-cyclopentanediones is rationalized in Scheme 60.



Scheme 60. Mechanistic pathway for the asymmetric 3-hydroxylation of cyclopentanediones.

It can be assumed that in the oxidation the Ti-catalyst affords first of all an enolate-type complex **87** with substrate **80**. This complex is responsible for the asymmetric induction and directs the facial selection. The reasons for such a high enantioselectivity may be described in terms of

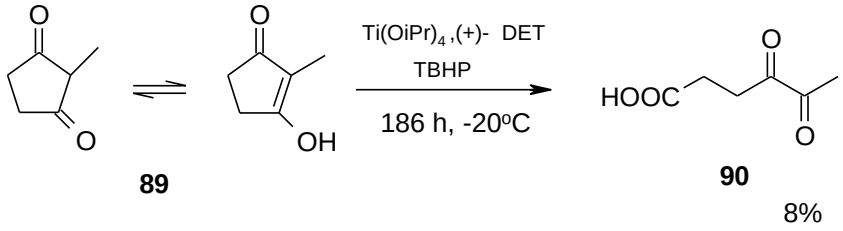
"favoured" and "unfavoured" conformations in the substrate-catalyst complex according to the simplified Sharpless oxidation model (Scheme 61).



Scheme 61. Enantioface selection. Formation of favoured and unfavoured intermediat complexes of the opposite face selection.

In the course of quenching of the reaction mixture with methanol, the intermediate epoxide **88** undergoes methanolysis resulting in the formation of acetal **84**.

An attempt was made to oxidize a cyclic 1,3- dione –2-methyl-1,3-cyclopentanedione **89** under the same reaction conditions. However, after a long incubation time (186 h) we were able to isolate 82% of the unreacted starting diketone and obtain 8% of 4,5-dioxohexanoic acid **90** as the only reaction product (Scheme 62).

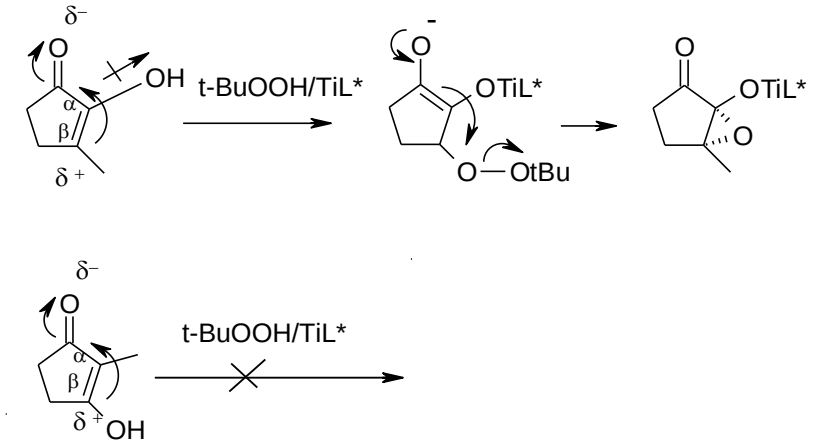


Scheme 62. Titanium-tartrate catalyzed oxidation of 1,3-cyclopentanedione.

Both the 3-methyl-1,2-cyclopentanedione and 2-methyl-1,3-cyclpentanedione investigated in this study exist mainly in the enolic form. Such enones are electron-deficient systems and their epoxidation is typically accomplished by the nucleophilic epoxidation. The epoxidation of electron-

deficient olefins such as α-hydroxyalkyl α,β-unsaturated ketones[84] and electrophilic cyanoallylic alcohols[85,86] using the Sharpless catalyst have also been described.

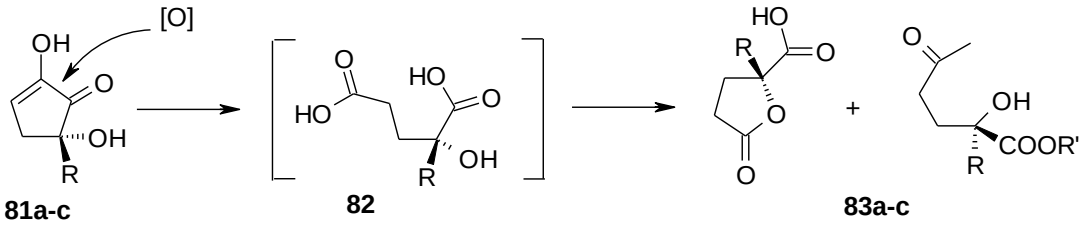
In our case, considering that peroxide reacts as nucleophile toward enone, the different behaviour of 1,2- and 1,3-cyclopentanediones in the oxidation is caused by the different nature of these substrates. If we assume that the first step of oxidation is the nucleophilic attack of *t* BuOOH (the O attached to the carbon) to the electrophilic carbon of the enone the results obtained can be rationalized as follows: in 3-methyl-1,2-cyclopentanedione the electrophilic properties of the β-carbon atom is increased by the inductive effect of the OH-group in the α-position (enol form). At the same time, in 2-methyl-1,3-cyclopentanedione the electrophilic properties are suppressed due to the +R effect of the OH-group in the β-position (enol form). As a result, the attack of *t*-BuOOH to the β-carbon atom in 2-methyl-1,3-cyclopentanedione is suppressed (Scheme 63).



Scheme 63. Comparison of mechanistic pathways of oxidation of 1,2-and 1,3-diketones.

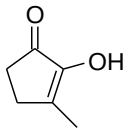
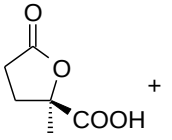
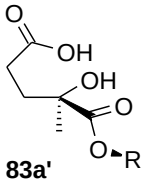
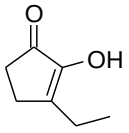
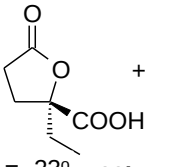
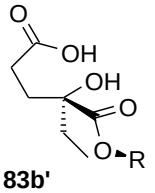
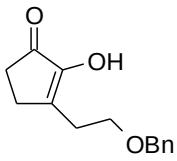
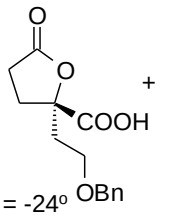
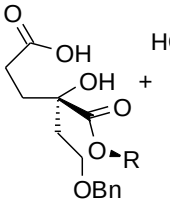
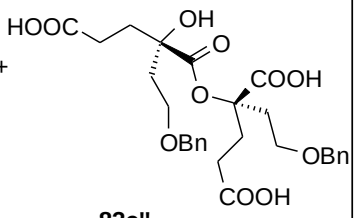
6.3.2. Ring cleavage of 3-alkyl-3-hydroxy-1,2-cyclopentanediones

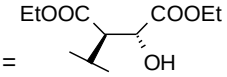
In the hydroxylation of 3-alkyl-1,2-cyclopentanediones more polar components always formed. We found that the first formation of enantiomeric 3-hydroxylated diketones **81a-c** is accompanied by the formation of the ring cleavage products, derivatives of the aliphatic diacids **82**, isolated as lactones and esters **83a-c**, respectively. It may be assumed that the 3-hydroxylated diketones undergo further oxidation according to Scheme 64.



Scheme 64. Ring cleavage of 3-alkyl-3-hydroxy-1,2-cyclopentanediones.

Table 9. Lactone-carboxylic acids and esters by the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones[a]

Cyclic dione	Ring cleavage oxidation products ee[b] %, yield %	Sum of 3-hydroxylated products
 **80a**	 $[\alpha]_D$ = -15° **83a** >95% ee[c], 44%  **83a'** >95% ee[e], 6%	15
 **80b**	 $[\alpha]_D$ = -23° **83b** >95% ee[c], 44%  **83b'** >95% ee[e], 7%	8
 **80c**	 $[\alpha]_D$ = -24° **83c** >98% ee[d], 28%  **83c'** >95% ee[e], 16%  **83c''** 9%	18

R = 

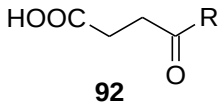
[a] Conditions: Ti(O*i*Pr)$_4$/(+)-DET/TBHP ratio 1:1.6:2.5; -20°C, 68h.
[b] Determined by HPLC using a chiral column (Daicel Chiralcel ODH).
[c] Determined by NMR from the (−) menthol esters of the corresponding acids.
[d] Lactone-acid **83c** was converted to spirodilactone **83d'** (Scheme 65).
[e] Determined by NMR, only one diastereomer was observed.

By choosing proper reaction conditions it is possible to obtain dominantly hydroxylated products **81** or, if needed, the ring cleavage products **83**. Using the excess of the oxidizing reagent the reaction can be directed toward the ring cleavage. In the case of 3-alkyl-1,2-cyclopentanediones lactones and esters **83a-c** in the combined isolated yield of up to 53% were obtained (Table 9).

The main ring cleavage products, lactone-acids **83a-c** formed by the cyclization of the corresponding hydroxy diacids were isolated after chromatography on silica gel. The esterification of diacids with diethyl tartrate, a component of the catalyst, was also observed (compounds **83a'-c'**, respectively). The amount of ester **83c'** was considerably larger in the case of substrate **80c**. A dimeric ester **83c''** formed by the cyclization of two hydroxy diacid molecules was obtained in the oxidation of compound **80c**.

The enantioselectivity (presented as *ee*) of the obtained ring cleavage oxidation reaction was high. Thus, the ring cleavage products with a high enantiomeric purity were obtained. The enantioselectivity of the ring cleavage products was as high as that of the corresponding 3-hydroxylated products. This means that the ring cleavage must proceed without any loss in optical purity.

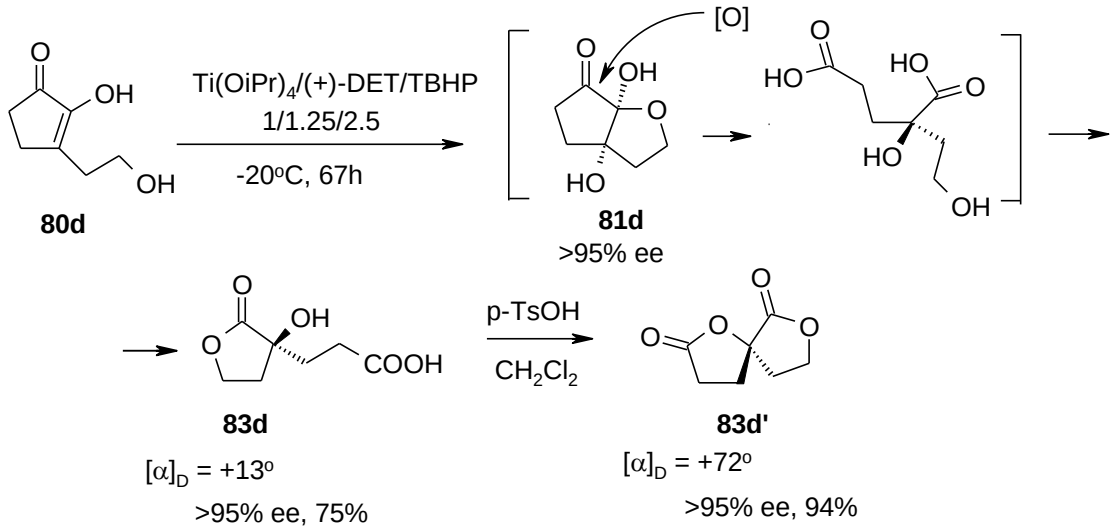
In all cases the formation of achiral side products, 4-oxocarboxylic acids **92**, was detected. However, the amount of these ring cleavage products was relatively low:



92

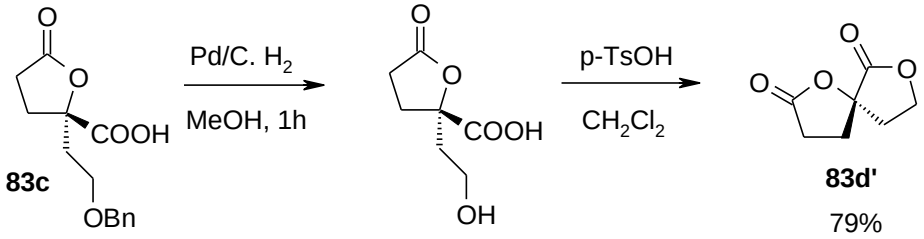
R = CH_3	amount of **92**	6%
R = C_2H_5	"	6%
R = CH_2CH_2OBn	"	9%

Similarly, when 3-hydroxyethyl-1,2-cyclopentanedione was oxidized lactone **83d** was obtained (presumably via the bicyclic acetal **81d**). In this case the formation of only one product, the lactone of dihydroxy-diacid, was observed. So, using the excess of the oxidizing reagent we obtained lactone-acid **83d** from **80d** in 75% isolated yield without loss of optical purity (*ee* for **81d** >95%; *ee* for **83d'** >95%; 11% of **81d** remained unreacted). This lactone can be converted into an interesting chiral spirodilactone **83d'** (Scheme 65).



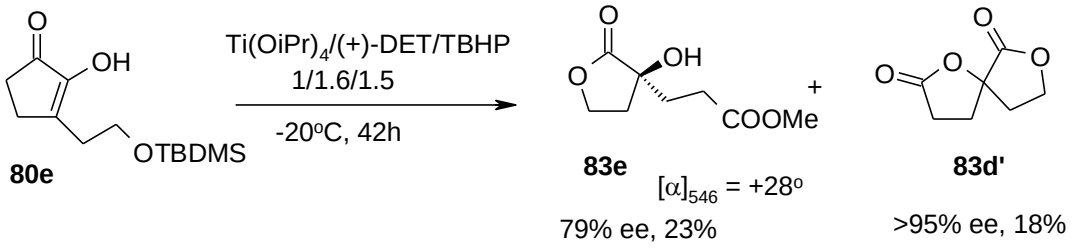
Scheme 66. Oxidation of **80d** followed by the ring cleavage of the bicyclic acetal **81d**.

The same spirodilactone **83d'** was obtained by hydrogenolisis of the benzyl group from lactone acid **83c** and subsequent cyclization of intermediate hydroxyl acid in 79% yield and a ee% >98% (Scheme 65.)



Scheme 65. Conversion of lactone-acid **83c** to spirodilactone.

In the case of the silyl protected substrate **80e**, the formation of two ring cleavage oxidation products, lactone-ester **83e** and spirodilactone **83d',** was observed (Scheme 67). It can be proposed that quenching the reaction by an acidic methanol solution caused the cleavage of the silyl group and esterification of the intermediate diacid. However, the unusually low *ee* value of the products obtained (*ee* for **83e** 79%; *ee* for the primary hydroxylation product **81d** 62%) indicated that the deprotection of **80e** may occur during the oxidation resulting in different species for oxidation.



Scheme 67. Asymmetric oxidation of the silyl protected substrate **80e**.

The asymmetric oxidation process developed enables to use 1,2-cyclopentanediones to prepare highly oxygenated carbocyclic and heterocyclic compounds. This reaction is potentially useful in the synthesis of γ-butyrolactones, which bear a functional group at the γ-position and would be amenable to a further elaboration, e.g., lactonic acid **83a** that was obtained by an optical resolution procedure has been used as starting material for the synthesis of biologically active compounds.[87,88] At present, there is also an extensive flow of reports where synthesis of spirolactones has been discussed because of their unique molecular structure and interesting biological activity. Among the compounds of synthetic interest several naturally occurring molecules bearing 1,7-dioxaspiro[4.4]nonane skeletons have been described.[89,90]

7. CONCLUSIONS

In this work, the utility of the Sharpless catalyst in the asymmetric oxidation of ketones has been demonstrated. The main results can be summarized as follows:

1. The scope of use of the Sharpless complex was extended. Ketones may be considered possible substrates for the asymmetric oxidation: several types of ketones were found to give different enantiomeric oxidation products.
2. Cyclobutanones undergo the asymmetric Baeyer-Villiger oxidation resulting in enantiomeric lactones with an enantioselectivity of up to 75% *ee* and with a good kinetic resolution of up to 40% yield in the case of bicyclic lactones.
3. A novel method for the direct α-hydroxylation of certain ketones was developed using the Sharpless catalyst. β-Hydroxy ketones undergo the asymmetric α-hydroxylation at the branched carbon resulting in α,β-dihydroxy ketones with a very high enantiomeric purity (86−97% *ee*) and in a satisfactory yield (37−58%).
4. 3-Alkyl 1,2-cyclopentanediones undergo the direct asymmetric oxidation resulting in two types of oxidation products – primary α-hydroxylation products and more oxygenated ring cleaved hydroxylation products:
   - The primary hydroxylation of 3-alkyl 1,2-cyclopentanediones enables to obtain the corresponding α-hydroxylated diketones with a high enantiomeric purity (>95% ee).
   - The further oxidation of 3-hydroxy-3-alkyl-1,2-cyclopentanediones causes the ring cleavage resulting in α-hydroxy diacids and the corresponding lactones in up to 75% isolated yield and with a high enantiomeric purity (>95% ee).
5. All the novel methods developed may have a preparative value for the synthesis of various chiral oxygenated compounds.

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(b) Aitken, R.A. In *Asymmetric Synthesis*; Chapman & Hall: London, **1995**, p. 2-5.
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APPENDIX

Experimental

^{1}H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker AMX-500 spectrometer. The solvent peaks $CHCl_3$ (δ 7.26 ppm), CH_3OH (δ 3.30 ppm), $(CH_3)_2SO$ (δ 2.50 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm), CD_3OD (δ 49.0 ppm) $(CD_3)_2SO$ (δ 39.50 ppm) for ^{13}C were used as internal references IR spectra were recorded on a Specord IR-75 spectrometer. Optical rotations were obtained using a Polamat A polarimeter or A. Krüss Optronic GmbH polarimeter P 3002. TLC was performed using DC-Alufolien Kieselgel 60 F_{254} (Merck) or Silufol® UV 254 silica gel plates. Merck Silica gel 60 (0.063-0.200 mm) or Chemapol silica gel L 40/100 was used for column chromatography. All reactions sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Commercial reagents were generally used as received. CH_2Cl_2 was distilled from CaH_2 and stored over 3Å molecular sieve pellets. THF and ether were distilled from $LiAlH_4$ before use, DMF and Et_3N from CaH_2.

2-*Exo*-iodo-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one 59

To a solution of bicyclo[3.2.0]hept-2-en-6-one (0.54 g, 5 mmol) in acetone/water 4:1 (18 mL) N-iodosuccinimide (1.41 g, 6.25 mmol) and a drop of acetic acid were added. After stirring at r.t. for 2 h, water (11 mL) was added to the reaction mixture and acetone evaporated under vacuum. The water phase was extracted 5 times with ether and the extract was washed with 5% $Na_2S_2O_3$ solution, 3 times with water, brine, dried (Na_2SO_4) and ether evaporated. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc 10:2) giving 0.88 g (71%) of iodohydrin **59**. ^{1}H and ^{13}C NMR ($CDCl_3$) from C_1 to C_7, $\delta^{1}H$: 3.44, 4.33, 4.73, 2.63(x)/2.22(n), 3.78, 3.12(x)/(n); $\delta^{13}C$: 40.61, 34.67, 83.22, 36.97, 63.28, 212.78, 55.09.

3-Hydroxymethylcyclobutanone 60

A mixture of diester **66** (487 mg, 1.87 mmol), NaCl (192 mg, 3.28 mmol) and water (0.09 mL, 5 mmol) in DMSO (3.7 mL) was heated at 160−170 ºC for 2 h and at 180−190 ºC for 2.5 h. After cooling, water was added and the product was extracted with ether. The combined extracts

were washed with brine, dried (Na_2SO_4) and the solvent evaporated. The reaction product and the unreacted diester were separated on silica gel (petrol ether/i-PrOH 80:1) giving 240 mg (68%) of ethyl 3,3-dimethoxycyclobutane-1-carboxylate; IR (film, cm^{-1}) 3060, 2900, 1760, 1460, 1290, 1050. ^1H and ^{13}C NMR ($CDCl_3$), from C-1 to C-5: δ^1H 2.80, 2.32/2.37, 2.32/2.37, OEt: 4.08, 1.20, OMe: 3.09 and 3.10; $\delta^{13}C$: 28.62, 35.28, 99.63, 35.28, 174.61, OEt: 60.47, 14.06, OMe: 48.23 and 48.50.

$LiAlH_4$ (386 mg, 10.16 mmol) in dry Et_2O (10.2 mL) was refluxed for 10 min, then cooled to 0°C. To this suspension ester (1.91 g, 10.16 mmol) in dry Et_2O (5.1 mL) was added dropwise and stirred at 0°C for 1h. Water (1.93 mL) was added dropwise at 0°C and the mixture was stirred at r.t. for 30 min. After filtration the precipitate was rinsed 6 times with Et_2O. The combined filtrates were dried (Na_2SO_4) and ether evaporated. The residue was purified by flash chromatography (silica gel, petrol ether/acetone 10:2) affording 1.29 g (87%) of pure product.

Acetal (1.29 g, 8.8 mmol) was stirred with 3% H_2SO_4 (v/v) (4.5 mL, 5 mmol) at r.t. for 1 h. The mixture was neutralized with $NaHCO_3$ (426 mg, 5 mmol) and extracted 8 times with small portions of EtOAc. The combined extracts were dried (Na_2SO_4), concentrated and purified by flash chromatography (silica gel, petrol ether/acetone 10:3) giving 0.83 g (95%) of 3-hydroxymethylcyclobutanone **60**; IR (film, cm^{-1}) 3500, 3000, 2950, 1790, 1400, 1220, 1110, 1040.

Typical procedure for asymmetric oxidation of cyclobutanones

To a solution of $Ti(OiPr)_4$ (0.45 mL, 1.5mmol) and 4Å powdered molecular sieves (100 mg) in CH_2Cl_2 (6 mL) L-(+)-diethyl tartrate (0.31 mL, 1.8 mmol) was added at –20 °C and the mixture was stirred for 15 min. After addition of cyclobutanone (1 mmol) in CH_2Cl_2 (2 mL) the mixture was stirred for additional 30 min. TBHP (0.44 mL, 1.5 mmol, 3.4M in toluene) was then added and the mixture was kept at –20 °C for 44 h. The reaction was quenched by stirring with a solution of citric acid monohydrate (315 mg, 1.5 mmol in a mixture of 10% acetone in ether, 30 mL) at r.t. for 1h. The reaction mixture was filtered through a path of Celite and purified by column chromatography on silica gel.

^1H and ^{13}C NMR ($CDCl_3$): **64**: from C-1 to C-8, δ^1H: 3.43, 4.11, 5.53, 2.64(x)/2.20(n), 5.14, 2.82(x)/2.61; $\delta^{13}C$: 49.52, 34.80, 80.71, 38.27, 84.29, 177.07, 36.47.

Preparation of (S)-(+)-α-methoxyphenyl acetic acid esters

To a stirred solution of lactone (0.086 mmol) in dry THF (1 mL) (*S*)-(+)-MPA (24 mg, 0.14 mmol), DCC (33 mg, 0.16 mmol) and DMAP (8 mg) were added. After stirring the reaction for 2 h at r.t. the mixture was diluted with ether (5 mL) and water (1 mL) was added. Then additional ether (25 mL) was added and the mixture was washed with 1M HCl solution, with saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel affording the diastereomeric *S*-MPA esters of the corresponding lactone.

2-Hydoxymethylcyclohexanone 68b

To a suspension of sodium hydride (5.1 g, 212.5 mmol) in benzene (100 mL) dimethyl carbonate (13.5 g, 150 mmol) was added and the mixture was heated to reflux. Then a solution of cyclohexanone (7.35 g, 75 mmol) in benzene (25 mL) was added dropwise over a period of 1 h and the mixture was heated for 20 min. After cooling to r.t. glacial acetic acid (15 mL) was added dropwise, followed by ice cold water (50 mL). The benzene layer was separated and the aqueous was extracted 3 times with benzene. The combined extracts were washed three times with cold water and dried (Na_2SO_4). The benzene was removed by distillation at atmospheric pressure, and the excess of dimethyl carbonate was removed under water-pump pressure. The residue was distilled at reduced pressure to give 6.5 g (56%) of methyl 2-oxocyclohexane-carboxylate, b.p. 85-90^oC (6 mm).

To above ketoester (4.68 g, 30 mmol) in benzene (250 mL) ethylene glycol (7.44 g, 120 mmol) and p-toluenesulfonic acid monohydrate (cat) were added. The mixture was heated to reflux for 40 h. After cooling the mixture was washed with 5% $NaHCO_3$ solution, brine, dried (Na_2SO_4) and benzene evaporated to give 5.94 g of ketalized product. The obtained crude ketal was reduced with $LiAlH_4$ followed by deketalization in aqueous H_2SO_4 according to the procedures described for the synthesis of 3-hydroxymethylcyclobutanone. Flash chromatography (silica gel, petrol ether/acetone 10:2) yielded 2.38 g (62% from methyl 2-oxocyclohexanecarboxylate) of 2-hydroxymethylcyclohexanone **68b**; IR (film cm^{-1}) 3500, 3000, 2920, 1720, 1460, 1140, 1030.

Typical procedure for asymmetric oxidation of β-hydroxy ketones

To a solution of $Ti(OiPr)_4$ (0.89 mL, 3 mmol) in CH_2Cl_2 (6 mL) (+)-DET (0.6 mL, 3.6 mmol) was added at –20 °C and the mixture was stirred for 15 min. After addition of β-hydroxy ketone (1 mmol) in CH_2Cl_2 (2 mL) the mixture was stirred for 30 min. Then TBHP (0.35 mL, 1.2 mmol, 3.4 M solution in toluene) was added and the mixture was kept at –20 °C for 46 h. The reaction was quenched by stirring with the solution of citric acid monohydrate (630 mg, 3 mmol in a mixture of 10% acetone in ether, 30 mL) at r.t. for 1h. The reaction mixture was filtered through a path of Celite, the Celite layer was washed with acetone and methanol. The solutes were concentrated and the residue was purified on silica gel.

^1H and ^{13}C NMR ($CDCl_3$): **79**: from C-1 to C-5, δ^1H: 2.42, 1.95, 2.56, 9.77; $\delta^{13}C$: 179.10, 32.79, 16.89, 42.66, 201.58.

Preparation of primary (R)-(-)-α-methoxyphenylacetic acid mono esters

To a mixture of (R)-(-)-MPA (21.6 mg, 0.13 mmol) and DCC (26.8 mg, 0.13 mmol) in dry THF (0.6 mL) α,β-dihydroxyketone (0.1 mmol) in THF (0.5mL) and DMAP (6.7 mg) were added. After stirring the mixture at r.t. for 2.5 h the workup was performed as described for derivatization of lactones with *S*-MPA. Flash chromatography on silica gel gave the primary *R*-MPA mono esters of the corresponding dihydroxy ketone.

2-Hydroxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-2-cyclopenten-1-one 80e

2-Cyclopentene-1-acetic acid (1.26 g, 10 mmol) was dissolved in MeOH (10 mL), followed by conc. HCl (0.1 mL). After stirring at r.t. for 24 h the mixture was diluted with ether (150 mL), washed with saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). The extract was then concentrated to ~5 mL and added at 0°C to a suspension of $LiAlH_4$ (380 mg, 10 mmol) in dry ether (10 mL). The mixture was stirred at 0°C for 1 h and water (1.9 mL) was added dropwise. After stirring at r.t. for 0.5 h and filtration with ether, the filtrate was dried ($MgSO_4$) and ether evaporated. The residue was purified by flash chromatography (silica gel, petrol ether/acetone 10:1) giving 0.94 g (84%) of 2-cyclopentene-1-ethanol.

The solution of above alcohol (0.94 g, 8.39 mmol), TBDMSCl (1.9 g, 12.58 mmol) and imidazole (1.14 g, 16.78 mmol) in dry DMF (37 mL) was stirred at r.t. for 20 h. Ether (200 mL) was

then added, the mixture was washed with water, with 5% $NaHCO_3$ solution, water, brine, dried (Na_2SO_4) and ether evaporated. The residue was purified by flash chromatography (silica gel, petrol ether/acetone 100:1) to give 1.642g (87%) of silyl protected 2-cyclopentene-1-ethanol.

To a stirred solution of this cyclopentene (1.642 g, 7.26 mmol) in *t*-BuOH (44 mL) and water (30 mL), cooled in an ice bath, was added over a 20-min period a cooled solution of $KMnO_4$ (1.264 g, 8 mmol) and NaOH (0.436 g, 10.9 mmol) in water (50 mL). After completion of the addition, the solution was stirred at 0ºC for 20 min, and then Na_2SO_3 (0.365 g, 2.9 mmol) in water (8 mL) was added. The reaction mixture was filtered and the filtrate was extracted 3 times with EtOAc. The combined extracts were washed with water, brine, dried (Na_2SO_4) and the solvents evaporated. Flash chromatography (silica gel, petrol ether/acetone 10:1) yielded 1.262 g (67%) of the diol.

To a solution of oxalyl chloride (1.27 mL, 14.55 mmol) in CH_2Cl_2 (33 mL) DMSO (2.25 mL, 31.8 mmol) in CH_2Cl_2 (7 mL) was dropwise added at –60 ºC. The mixture was stirred for 10 min, followed by addition of the above diol (1.262 g, 4.85 mmol) in CH_2Cl_2 (10 mL). After stirring at –60 ºC for 1 h, Et_3N (6.75 mL, 48.5 mmol) was added at –60ºC. The reaction mixture was then allowed to warm up to r.t., poured into a cold 1N HCl solution (100 mL) and extracted 2 times with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel, petrol ether/EtOAc 10:1 to 10:1.5) to give 594 mg (48%) of diketone **80e**.

2-Hydroxy-3-(2-hydroxyethyl)-2-cyclopenten-1-one 80d

To a solution of diketone **80e** (272 mg, 1.06 mmol) in THF (6 mL) 1.5 N HCl solution (2.4 mL) was added. After stirring at r.t. for 2 h the mixture was diluted with water (20 mL) and extracted 12 times with dry EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, petrol ether/acetone 10:5) yielding 132 mg (88%) of diketone **80d**. ^1H and ^{13}C NMR ($CDCl_3$+CD_3OD), from C-1 to C-5, C-1', C-2', δ^1H: 2.33, 2.24, 2.46, 3.69; $\delta^{13}C$: 204.01, 149.69, 145.73, 24.71, 31.96, 32.26, 59.13.

2-Hydroxy-3-(2-benzyloxyethyl)-2-cyclopenten-1-one 80c

To a solution of 2-cyclopentene-1-ethanol (0.906 g, 8.1 mmol) in DMF (12 mL) NaH (467 mg, 12.2 mmol, 60−65% in mineral oil) was added at 0 ºC. After the reaction subsided, benzyl chloride (1.7 mL, 14.6 mmol) was added. The reaction was stirred overnight, quenched then with water (5 mL) and extracted 3 times with CH_2Cl_2. The combined extracts were washed with water, brine, dried (Na_2SO_4) and the solvents evaporated. The residue was purified by flash chromatography (silica gel, petrol ether/acetone 100:1) affording 1.38 g (86%) of benzyl ether. This compound was dihydroxylated with $KMnO_4$ followed by Swern oxidation according to the procedures for synthesis of diketone **80e**. Chromatography (silica gel, petrol ether/EtOAc 10:2 to 10:2.5) gave 708 mg (31% from 2-(2-benzyloxyethyl)-1-cyclopentene) of diketone **80c**. ^{1}H and ^{13}C NMR ($CDCl_3$), from C-1 to C-5, C-1', C-2', δ^1H: 2.47, 2.40, 2.70, 3.74, Bn: 4.52 (OCH_2), 7.30-7.35 (Ph); δ^{13}C: 203.06, 149.67, 144.18, 25.89, 32.01, 29.47, 67.44, Bn: 73.02, 137.50(s), 127.75(o), 128.40(m), 127.78(p).

Typical procedure for asymmetric 3-hydroxylation of 3-alkyl-1.2-cyclopentanediones

To a solution of Ti(O*i*Pr)$_4$ (0.3 mL, 1mmol) and 4Å powdered molecular sieves (100 mg) in CH_2Cl_2 (6 mL) (+)-DET (0.27mL, 1.6 mmol) was added and the mixture was stirred for 15 min at −20 ºC. After addition of cyclopentanedione (1 mmol) in CH_2Cl_2 (2 mL) the mixture was stirred for 30 min. Then TBHP (0.44 mL, 1.5 mmol, 3.4 M solution in toluene) was added and the mixture was kept at –20 ºC for 42 h. The reaction was quenched by stirring with citric acid monohydrate solution (210 mg, 1 mmol in a mixture of 10% MeOH in CH_2Cl_2) at r.t. for 1 h. The reaction mixture was filtered through a path of Celite and purified by column chromatography on silica gel.

^{1}H and ^{13}C NMR ($CDCl_3$). **81c**: from C-1 to C-5, C-1', C-2', δ^1H: 6.45, 2.59/2.69, 1.92/2.06, 3.65/3.80; δ^{13}C: 204.08, 149.89, 127.79, 38.05, 75.45, 37.18, 66.38; **81c'**, δ^1H: 2.29, 2.65, 2.03/2.18, 3.63/3.78; δ^{13}C: 202.42, 202.49, 76.04, 30.00, 33.19, 36.43, 65.72; **85c**, δ^1H: 1.88/2.03, 2.37/2.39, 1.78/2.27, 3.74/3.80, i-Pr: 0.96, 1.04, 4.06, Bn: 4.51, 4.57 (OCH_2), 7.30-7.35 (Ph); δ^{13}C: 212.37, 97.94, 78.25, 30.30, 31.47, 32.50, 66.31, i-Pr: 23.10, 24.54, 65.84, Bn: 137.02, 127.95(o), 128.51(m), 128.00(p); **86b**, δ^1H: 1.95, 2.38, 1.68, 1.00; δ^{13}C: 215.07, 96.05, 78.84, 28.29, 31.04, 25.54, 6.87; **86c**, δ^1H: 1.98/2.04, 2.44/2.49, 1.97/2.20, 3.73/3.80; δ^{13}C: 213.19, 95.49, 78.23, 30.24, 31.28, 33.98, 65.98.

Preparation of (*R*)-(−)-α-methoxyphenylacetic acid diesters from 81 a

A mixture of **81a** (12.4 mg, 0.078 mmol), (*R*)-(−)-MPA (51.5 mg, 0.31 mmol), DCC (64 mg, 0.31 mmol) and DMAP (13 mg) in THF (1.5 mL) was stirred at r.t. for 2h. Then the workup was performed as described for derivatization of lactones with MPA. Flash chromatography (Chemapol silica gel L 40/100, benzene/acetone 30:1) afforded 32 mg of ***R*-91**. Analogously the corresponding diastereomeric esters mixture ***R*-91**+***S*-91** from racemic **81a** was prepared.

Typical procedure for synthesis of lactone-acids by asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones

The oxidation was performed as described for 3-hydroxylation of cyclopentanediones. In these cases in 8 mL of CH_2Cl_2 with 100 mg of 4Å powdered molecular sieves, 0.3 mL (1 mmol) of $Ti(OiPr)_4$, 0.27 mL (1.6 mmol) of (+)-DET, cyclopentanedione (1 mmol) and 0.4 mL (2.5 mmol) of a 6.25 M solution of TBHP in decane at –20 ºC for 68 h. After workup with citric acid the reaction mixture was purified on Chemapol silica gel L 40/100.

^1H and ^{13}C NMR. **83c** ($CDCl_3$): from C-2 to C-5, C-1',C-2', δ^1H: 2.31/2.47, 2.54/2.56, 2.12/2.46, 3.67; $\delta^{13}C$: 84.27, 31.80, 27.74, 176.08, 36.78, 64.10, 175.68 (2-COOH). **83a'** ($CDCl_3$): from C-1 to C-5, C-1' to C-4', δ^1H: 2.01/2.12, 2.29/2.52, 1.49 (2-CH_3), 5.51, 4.81, 4.28, 1.30 (1'-CH_2CH_3), 4.26 1.28 (4'-CH_2CH_3); $\delta^{13}C$: 174.88, 74.29, 33.93, 28.56, 178.24, 26.03 (2-CH_3), 166.10, 73.84, 70.53, 170.69, 62.46, 13.98 (1'-CH_2CH_3), 62.85, 14.03 (4'-CH_2CH_3); **83b'**($CDCl_3$), δ^1H: 2.03/2.04, 2.24/2.50, 1.71/1.86, 0.91 (2-CH_2CH_3), 5.50, 4.79, 4.27, 1.29 (1'-CH_2CH_3), 4.14/4.34, 1.27 (4'-CH_2CH_3); $\delta^{13}C$: 174.44, 77.59, 33.09, 28.48, 178.44, 32.14, 7.40 (2-CH_2CH_3), 166.06, 73.87, 70.60, 170.63, 62.40, 13.95 (1'-CH_2CH_3), 62.81, 13.95 (4'-CH_2CH_3); **83c'** ($CDCl_3$+CD_3OD), δ^1H: 1.92/2.04, 2.18/2.41, 1.96/2.12, 3.58/3.64 (2-CH_2CH_2O), 5.38, 4.64, 4.16, 1.19 (1'-CH_2CH_3), 4.16, 1.16 (4'-CH_2CH_3), Bn: 4.33, 4.38 (OCH_2), 7.17-7.24 (Ph); $\delta^{13}C$: 173.49, 76.62, 33.89, 28.01, 175.65, 37.61, 66.40 (2-CH_2CH_2O), 166.34, 73.84, 70.48, 170.15, 62.00, 13.65 (1'-CH_2CH_3), 62.01, 13.66 (4'-CH_2CH_3), Bn: 73.00 (OCH_2), 137.29, 127.54(o+p), 128.14(m) (Ph). **83c''**($CDCl_3$): from C-1 to C-14, δ^1H: 2.45/2.60, 2.30/2.35, 1.98/2.36, 2.43/2.59, 2.36/2.52, 3.20/3.50, 1.90/2.18, 3.47/3.57, Bn: 4.37, 4.33, 4.41 (OCH_2); $\delta^{13}C$: 179.73, 28.16, 30.44, 82.40, 176.59, 75.80, 33.51, 27.80, 179.54, 174.84, 32.03, 64.92, 38.44, 65.61, Bn: 73.46, 72.87, (OCH_2), 137.95, 137.58 (s), 128.38(m), 127.56, 128.01, (o), 127.66, 127.82 (p) (Ph). **92** (R=CH_3) ($CDCl_3$): from C-1 to C-5, δ^1H: 2.62, 2.76, 2.19;

δ^{13}C: 178.60, 27.78, 37.63, 206.77, 29.75. **92** (R=CH_2CH_2OBn) ($CDCl_3$): from C-1 to C-6, δ^1H: 2.64, 2.78, 2.75, 3.76, Bn: 4.52 (OCH_2), 7.29-7.35 (Ph); δ^{13}C: 178.34, 27.57, 37.39, 207.03, 42.80, 65.10, Bn: 73.22 (OCH_2), 137.91, 127.70(o), 128.38(m), 127.68(p) (Ph).

Preparation of (-) menthol esters of lactone-acids 83a and 83b

A mixture of **83** (0.1 mmol), (1*R*,2*S*,5*R*)-(−)-menthol (23.4 mg, 0.15 mmol), DCC (22.2 mg, 0.108 mmol) and DMAP (5.6 mg) in THF (1 mL) was stirred at r.t. for 3 h. The workup was performed as described for derivatization of lactones with MPA. Flash chromatography on silica gel yielded the (−)-menthol esters of the corresponding lactone acids. Analogously, the diastereomeric esters mixture from racemic **83a** and **83b** was prepared.

^{1}H and ^{13}C NMR ($CDCl_3$). (-) menthol esters of racemic **83a**: I*, from C-2 to C-5, δ^1H: 2.13/2.50, 2.58/2.63, 1.650 (2-CH_3), menthol: 4.74, 1.450, 1.051/1.702, 0.87/1.69, 1.496, 1.015/1.960, 1.793, 0.749, 0.894, 0.906; δ^{13}C: 83.86, 33.01, 28.46, 175.82, 23.61 (2-CH_3), 171.15 (2-COO), menthol: 76.27, 46.78, 23.09, 34.00, 31.32, 40.36, 26.29, 15.97, 20.74, 21.90; II, δ^1H: 2.13/2.49, 2.56/2.64, 1.646 (2-CH_3), menthol: 4.73, 1.445, 1.051/1.695, 0.87/1.69, 1.496, 1.000/1.963, 1.830, 0.749, 0.890, 0.906; δ^{13}C: 83.92, 33.10, 28.50, 175.89, 23.60 (2-CH_3), 171.15 (2-COO), menthol: 76.25, 46.81, 23.25, 34.02, 31.32, 40.45, 26.26, 16.10, 20.67, 21.90. Chemical shifts of diastereomeric ester I* were represented for **83a** obtained by asymmetric oxidation. **83b**: I*, from C-2 to C-5, δ^1H: 2.156/2.479, 2.56, 1.879/2.102, 1.001 (2-CH_2CH_3), menthol: 4.757, 1.477, 1.067/1.716, 0.893/1.707, 1.518, 1.037/1.997, 1.838, 0.765, 0.911, 0.923; δ^{13}C: 87.34, 31.19, 28.23, 175.77, 30.59, 8.11 (2-CH_2CH_3), 171.07 (2-COO), menthol: 76.40, 46.73, 23.06, 34.07, 31.38, 40.49, 26.22, 15.87, 20.75, 21.92; II, δ^1H: 2.163/2.446, 2.57, 1.851/2.126, 1.003 (2-CH_2CH_3), menthol: 4.769, 1.468, 1.068/1.711, 0.893/1.707, 1.518, 1.020/1.994, 1.856, 0.768, 0.909, 0.923; δ^{13}C: 87.38, 31.49, 28.27, 175.89, 30.54, 8.14 (2-CH_2CH_3), 170.96 (2-COO), menthol: 76.25, 46.78, 23.18, 34.07, 31.38, 40.53, 26.25, 15.98, 20.70, 21.92. Chemical shifts of diastereomeric ester I* were represented for **83b** obtained by asymmetric oxidation.

1,7-Dioxaspiro[4.4]nonane-2,6-dione 83d'

Method A. To a solution of lactone-acid **83d** (56 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) a crystal of p-TsOH was added. After stirring at r.t. for 3.5 h the mixture was washed with saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, petrol ether/acetone 10:3) giving 47 mg (94%) of spirodilactone **83d'**.

Method B. 10% Pd/C (10 mg) was added to a stirred solution of lactone-acid **83c** (20 mg, 0.076 mmol) in MeOH (2 mL) and the mixture was stirred under an atmospheric pressure of H_2 at r.t. for 1 h. After filtration and removing the solvents the residue was treated with p-TsOH and CH_2Cl_2 according to the above procedure A to give 9.4 mg (79%) of spirodilactone **83d'**.