N,N'-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride – the Jacobsen Catalyst

Timo Flessner and **Sven Doye***

Hannover, Institut für Organische Chemie der Universität

Received April 12th, 1999

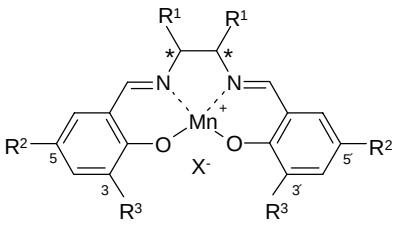
Keywords: Asymmetric catalysis, Asymmetric synthesis, Epoxidations, Manganese, Jacobsen catalyst

Abstract. The commercially available Jacobsen catalyst, N,N'-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride **2**, is the most enantioselective catalyst developed to date for the asymmetric epoxidation of a broad range of unfunctionalized olefins. After describing the synthesis of the title compound a brief discussion of the epoxidation mechanism is given. Afterwards several applications for the enantioselective epoxidation of unfunctionalized olefins are described. For each application the scope and limitations are discussed.

Contents

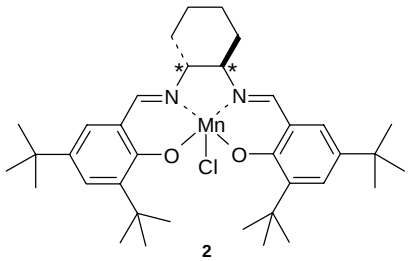
1. Introduction

Epoxidation of olefins is one of the most important processes for functional group manipulation in organic synthesis and the preparation of biologically active compounds [1]. The development of methods for asymmetric epoxidation (AE) has made this field even more attractive. In the 1980's Sharpless *et al*. have discovered an enantioselective titanium–tartrate-catalyzed epoxidation of a wide variety of allylic alcohols [2]. After first applications of porphyrine systems [3] and other more or less effective catalysts [4] or stoichiometrically used systems [5] as epoxidation agents for the formation of epoxides from unfunctionalized, prochiral olefins in the 1980's, this problem has been reinvestigated by Jacobsen [6] and Katsuki [7] in the 1990's. For this purpose both have used catalytic amounts of chiral, C_2-symmetric Mn(III)-salen complexes of general structure **1** in the presence of a stoichiometric oxidation agent continuing Kochi's work with achiral salen complexes [8]. Meanwhile over 100 complexes of this kind have been reported [9]. The most efficient and mostly used among them is *N,N'*-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride, the so-called Jacobsen catalyst **2**. This complex is stable to air and can be stored for long periods of time without decomposition [10].



1

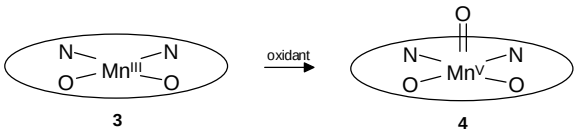
R^1, R^2, R^3 = variable
X^- = Cl^-, PF_6^-, AcO^-



2

  1436-9966/99/3410X-436 $ 17.50 + .50/0

The catalytically active species is represented by the oxygenated form, the Mn(V)-oxo-complex **4** which is easily formed from the Mn(III)-complex **3** in the presence of an oxidant (Scheme 1). Recently, this Mn(V)-oxo-intermediate could be detected for the first time *via* electrospray-tandem-mass spectroscopy by Plattner *et al*. [11].

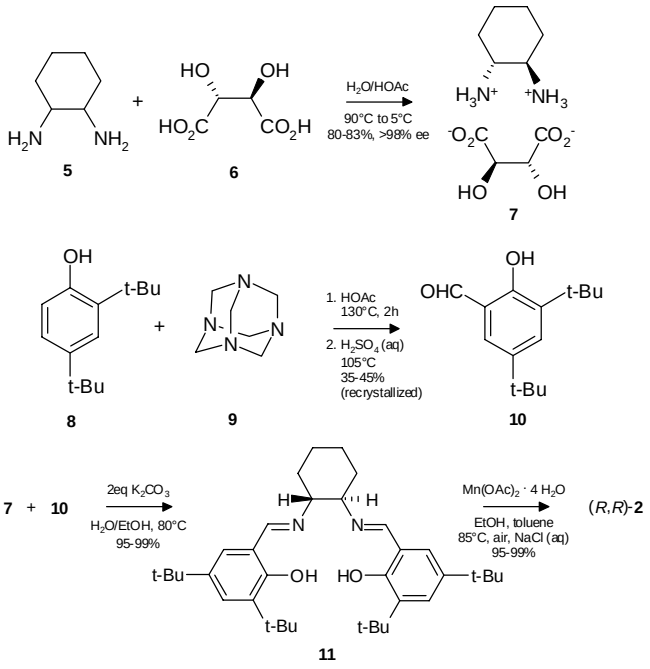


Scheme 1 Formation of Mn(V)-oxo-complex **4** from Mn(III) salen complex **3** in the presence of an oxidant.

As described in initial reports the epoxidation of olefins is performed using 1–8 mol% (Jacobsen) [6] or 9 mol% (Katsuki) [7] of different Mn(III)-salencomplexes together with stoichiometric amounts of iodosobenzene or -mesitylene as oxidants. Optimized procedures use a catalyst loading between 0.25 mol% and 5 mol% and sodium hypochlorite (bleach) as an inexpensive stoichiometric oxidant [9]. However, it should be noted that certain parameters of the reaction are dependent on the oxidant used (see below).

2. Preparation of Jacobsen Catalyst

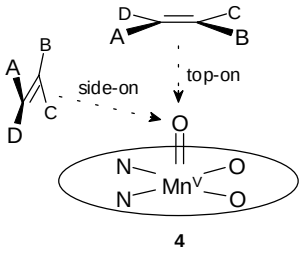
The Jacobsen catalyst is commercially available but can also be easily prepared from readily available and inexpensive starting materials. A detailed procedure for the convergent preparation has been published recently [12] (Scheme 2). The stereogenic centres are introduced *via* a resolution step using tartaric acid **6**. Formylation of 2,4-di-*t*-butyl-phenol **8** yields the appropriate salicylaldehyde derivative **10** as a crystalline solid. The chiral diimin **11**, prepared from **7** and **10**, can easily form the Jacobsen catalyst **2** by complexation with manganese acetate and oxidation on air.



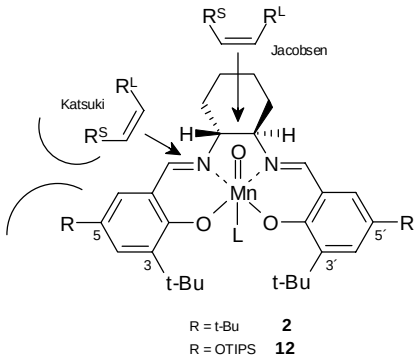
Scheme 2 Synthesis of the Jacobsen catalyst **2**.

3. Mechanism

A lot of attention has been put on the evaluation of the mechanism of the Jacobsen epoxidation [13]. Some of the examined salen-complexes could be crystallized, and the X-ray-structures are described [14]. Based upon these structures attempts to explain the dependence of the degree of enantioselectivity on the steric and electronic situation of the complexes have been made. Concerning the attack of the alkene to the chiral complex both Jacobsen and Katsuki propose a side-on mechanism.

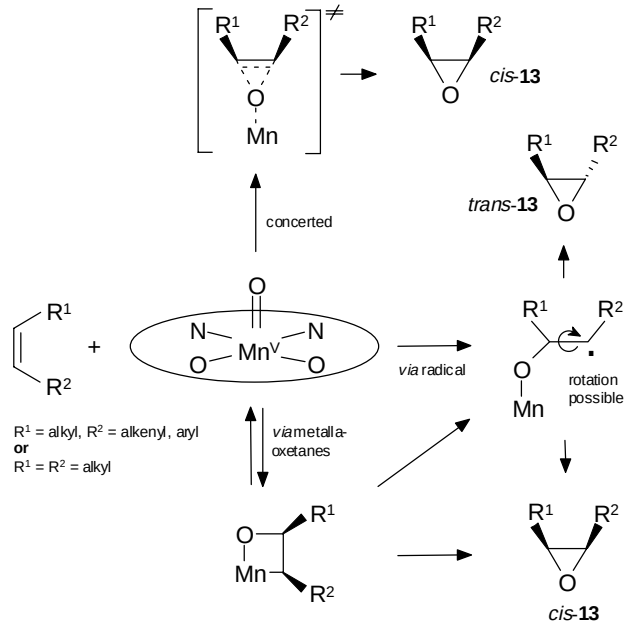


While Jacobsen postulates an attack *via* the diimine-bridge with the small alkene-substituent at the side of the axial H-atom at the chiral centre [9], Katsuki in his model suggests an attack via the imine moiety due to π,π-interactions between the incoming alkene and the imine group [15]. The regioselectivity in this case can be explained by the steric hindrance of the *t*-butyl-substituent. In spite of this discussion the preference for *cis*-olefins to be epoxidized by the catalytic species with high stereoselectivity can be undoubtedly explained with the side-on mechanism.



The question of oxygen transfer from the complex to the alkene is still not known in detail. At least three possible ways have been discussed mainly by Jacobsen [16], Katsuki [17] and Åkermark [18] (Scheme 3). A fourth approach *via* single electron transfer (SET) and the formation of radical cation intermediates was under investigation in order to explain the mechanism of other oxygen transfer reagents (*e.g.* Fe containing P-450 models) [19].

The concerted pathway is as useful as the metallaoxetane mechanism with a subsequent rearrangement in order to explain the *cis*-selectivity that can be observed in epoxidations of bis-alkylsubstituted *cis*-alkenes. But the resulting mixtures of *cis*- and *trans*-isomers in many mono-epoxidations of conjugated olefins need another explanation. A process *via* radicals that are able to perform the rotation around the former double bond seems likely. Experiments with vinylcyclopropanes as hypersensitive radical probes were conducted to "visualize" the potentially involved radicals by intramolecular trapping [18, 19]. In some cases open-chain products point out that radical species should be involved. But still the question remains if the radical is formed in the initial step or *via* metallaoxetanes.

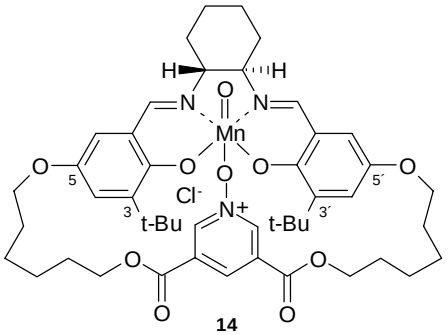


Scheme 3 Possible mechanism for the oxygen transfer from the catalyst to the alkene.

Additional efforts have been made in the field of stabilization effects of the reactive Mn(V)-oxo-complex. Stabilization can be achieved by electron-donating substituents in 5- and 5'-position [9, 14, 20] or the addition of donor ligands [9]. For example, the electronic properties of substituents in 5- and 5'-position of the salicylaldehyde moiety are reported to have a slight influence on the enantioselectivities obtained in the epoxidation of cyclic dienes to vinylepoxides (see 4.6.) [21]. The observed differences of enantiomeric excess were in between 2% and 15%. In this special case the triisopropylsilylether **12** was shown to contain the appropriate combination between electron-donating capacity and simple bulkiness. Corresponding observations have been made in asymmetric epoxidation of chromene-derivatives (see 4.2.) [22].

Another effective group of Mn(V)-oxo-complex stabilization agents is represented by amine-*N*-oxides. Several parameters of the reaction (*e.g.* yield, stereoselectivity, reaction rate) are dramatically influenced by the use of additives like 4-phenylpyridine-*N*-oxide (4-PPNO) or *N*-methylmorpholin-*N*-oxide (NMO) in usual amounts of 10 mol%. These promoters lead to slightly increased reaction rates and total catalyst turnover numbers [9, 23]. The role of these additives as co-ligands to manganese was manifested by the construction of a salen complex **14** with an intramolecular N-oxide linked *via* 5- and 5'-positions [16b]. No influence of further additives could be detected using this catalyst with intramolecular complexation.

NMO is also involved in an alternative anhydrous epoxidation protocol using *m*-chlorperbenzoic acid as stoichiometric oxidant. These conditions allow reduced temperatures (−78 °C) and quite often lead to higher enantioselectivities [24]. Using this procedure the first successful asymmetric epoxidation of a free carboxylic acid-bearing substrate (4-vinylbenzoic acid) could be achieved [24b].



14

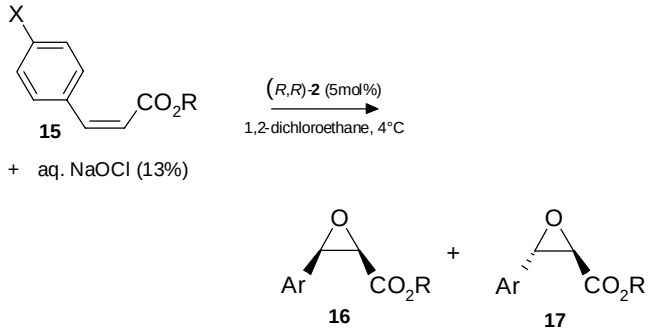
4. Applications

The steroechemical outcome of many epoxidations of conjugated and nonconjugated olefins can be effectively controlled by using the Jacobsen catalyst (*R*,*R*)-**2** and (*S*,*S*)-**2**, respectively. Most often an aqueous solution of bleach (pH > 9.5) is combined with an organic phase bearing the catalyst **2** and the substrate. As organic solvents for this two-phase system methylene chloride, *t*-butyl methyl ether and ethyl acetate find widest application. The reaction mixtures are usually stirred at 0 °C or room temperature for 1 to 12 hours [10].

With given pH-values between 9.5 and 11.5 no phase transfer catalyst is needed, because of sufficient equilibrium concentrations of HOCl (pK_a = 7.54). Below values of pH = 9.5 olefin chlorination might become a significant side reaction [25].

4.1. Epoxidation of cis*-Cinnamate Esters*

The first group of α,β-unsaturated esters that could be successfully epoxidized *via* oxo-transfer using the Jacobsen catalyst **2** is represented by *cis*-cinnamates [23]. In the epoxidation process of these relatively unreactive compounds (Scheme 4) a strong influence of additives like 4-PPNO was observed (Table 1). The yield and the catalytic turnover number could be dramatically increased, while the enantiomeric excess in this case was left unattended.



Scheme 4 Epoxidation of *cis*-cinnamate esters.

Table 1 Influence of additives on the epoxidation of *cis*-cinnamate esters.

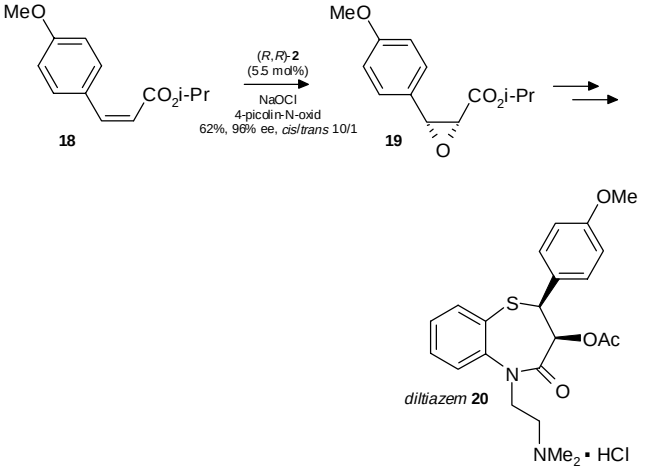
X=H, R = Et additive	turnover rate (min^{-1})	yield (%)	*ee* (%)	*cis*-epoxide/ *trans*-epoxide
none	2.3	67	93	4-5 : 1
4-PPNO (0.25 eq)	4.0	96	93	4-5 : 1
4-PPNO (1 eq)	7.6	>98	93	4-5 : 1

Very impressive experiments have been made on the effect of electronic variation of the cinnamate esters by aryl substitution (Table 2). A strong dependence of the *cis*/*trans*-ratio on the electronic properties of selected 4-substituents and a quite accurate correlation with their σ values could be observed. Electron-withdrawing substituents increase the formation of *trans*-epoxides, which is explained by their ability to stabilize a potentially involved radical species as shown in Scheme 3. In addition the enantiomeric excess obtained for the *cis*-epoxides are significantly higher than those for the *trans*-epoxides.

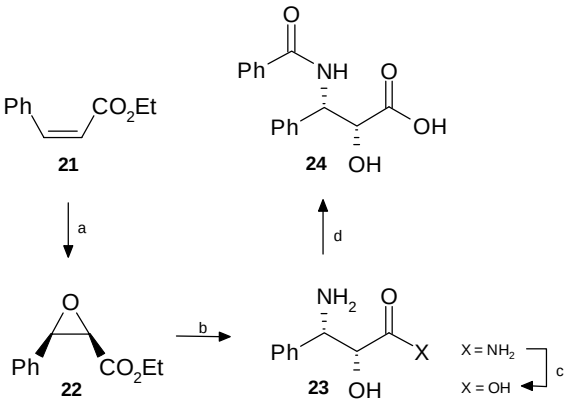
Table 2 Epoxidation of *cis*-cinnamate esters.

R = Me X	*cis*-epoxide/ *trans*-epoxide	ee_{cis} (%)	ee_{trans} (%)
OCH_3	11.7	72	66
CH_3	7.0	79	41
H	5.7	85	62
CF_3	0.80	79	55
NO_2	0.27	91	53

The group R also shows a significant influence on the stereochemical outcome of the epoxidation process, and especially the isopropyl ester **18** was used with great success. Therefore, a synthesis of the anti-hypertensive agent *diltiazem* **20** was established based on the enantioselective epoxidation of **18** (Scheme 5).



Scheme 5 Synthesis of *diltiazem* **20** based on the enantioselective epoxidation of *cis*-cinnamate ester **18**.



a) NaOCl, (*R*,*R*)-**2** (6 mol%), 4-PPNO (0.25eq), 56% (+13% *trans*-isomer), 95-97% ee; b) NH_3, EtOH, 65%; c) i: $Ba(OH)_2$, ii: H_2SO_4, 92%; d) i: PhCOCl, $NaHCO_3$, ii: HCl, 74%

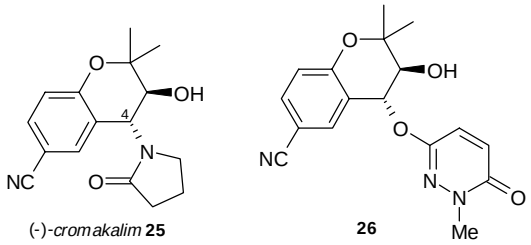
Scheme 6 Synthesis of the taxol side chain based on the enantioselective epoxidation of *cis*-cinnamate ethyl ester **21**.

Another very interesting application in stereoselective synthesis using cinnamate esters exists in the field of taxol side chain construction [26]. *N*-Benzoyl-(2*R*,3*S*)-3-phenylisoserine **24**, the acid ready for cou-

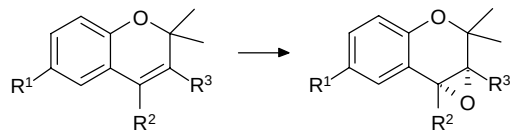
pling to *baccatin III* derivatives, can be prepared in 25% overall yield starting from the *cis*-cinnamate ethyl ester **21** (Scheme 6).

4.2. Epoxidation of Chromenes

Since dimethylchromene derivatives are biosynthetically formed by condensation of phenols with isoprene units, a lot of natural products and potential therapeutical agents like the potassium channel activator (–)-*cromakalim* **25** are based on this core structure [27]. The enantioselective epoxidation of prochiral chromenes plays an important role in the development of enantio- and diastereomerically pure target molecules. The nucleophilic ring opening of the formed epoxychromanes is highly regioselective due to steric and electronic factors (attack at 4-position).



Some representative examples of chromene epoxidation (Scheme 7) by using (*R*,*R*)-**2** as catalyst (2–4 mol%) and commercial bleach as oxygen-source are listed in Table 3 [28]. All products were obtained with absolute configuration (+)-(*R*,*R*).



27 R^1 = CN, R^2 = H, R^3 = H
28 R^1 = CN, R^2 = H, R^3 = Me
29 R^1 = NO_2, R^2 = H, R^3 = H
30 R^1 = H, R^2 = H, R^3 = H
31 R^1 = H, R^2 = Me, R^3 = H

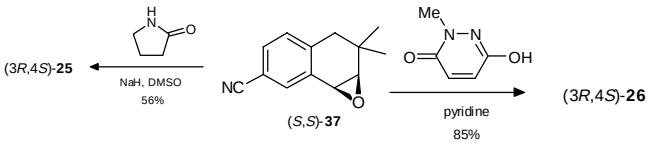
32 R^1 = CN, R^2 = H, R^3 = H
33 R^1 = CN, R^2 = H, R^3 = Me
34 R^1 = NO_2, R^2 = H, R^3 = H
35 R^1 = H, R^2 = H, R^3 = H
36 R^1 = H, R^2 = Me, R^3 = H

Scheme 7 Epoxidation of chromenes.

Table 3 Epoxidation of chromenes.

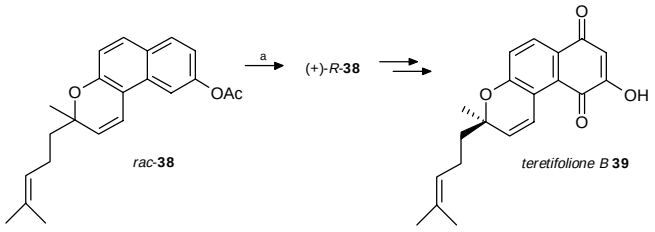
substrate	**27**	**28**	**29**	**30**	**31**
yield (%)	96	82	76	87	51
ee (%)	97	>98	94	98	97

Especially the (*S*,*S*)-nitril-epoxychroman **37**, that was obtained with (*S*,*S*)-**2** as catalyst, was shown to be an essential intermediate in the straightforward synthesis of (–)-(3*R*,4*S*)-**25** and (–)-(3*R*,4*S*)-**26** (Scheme 8).



Scheme 8 Regioselective nucleophilic opening of chromene epoxide (S,S)-**37**.

A kinetic resolution of racemic chromenes has been successfully used in the synthesis of (+)-*teretifolione B* **39**, the monomer component of the potent *anti*-HIV agent *conccurvone* (Scheme 9) [22]. For this purpose preliminary studies strongly recommended the use of salen-catalyst **12** instead of **2**. The differences of observed reaction rates in the epoxidation of the racemic mixtures in model studies went up to values around k_{rel} = 9 [29]. In the total synthesis of **39** no more than k_{rel} = 3.4 could be achieved. Nevertheless, this has been the first example for this methodology and the process was further improved with other substrates such as 1,2-dihydronaphthalenes [22b]. For these substrates good selectivities (k_{rel} = 6.3–9.1) were observed.



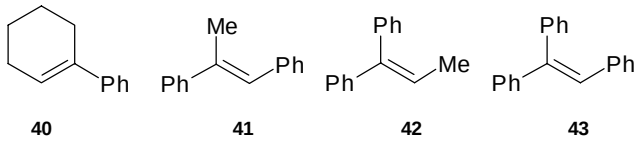
a) (*R*,*R*)-**12**, m-CPBA, NMO, dichloromethane, -78°C, 15%, 91% ee

Scheme 9 Kinetic resolution of racemic chromenes *via* enantioselective epoxidation.

4.3. Epoxidation of Trisubstituted Olefins

In spite of the fact that *trans*-alkenes were known to be poor substrates for asymmetric epoxidation (also see 4.7.) Jacobsen and Brandes in 1994 published their results concerning the epoxidation of trisubstituted olefins [30]. Surprisingly, alkenes like **40**–**43** could be shown to be excellent substrates for the epoxidation process using **2** and other Mn(III)-salencomplexes as catalysts. In Table 4 a representative choice of reactions with Jacobsen catalyst (*R*,*R*)-**2** (3 mol%) is summarized.

As can be seen good to excellent yields combined with high enantioselectivities could be obtained. Based on previous results with *cis*- and *trans*-alkenes the process with trisubstituted olefins has not been predicted to be that useful. Below the observations in three selected examples are compared. Jacobsen proposes a skewed side-on mechanism of the involved radical intermediate as an explanation for this unexpected phenomenon [30].



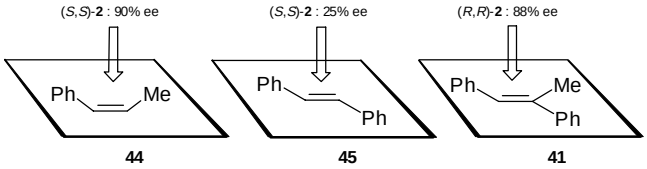
40 **41** **42** **43**

Table 4 Epoxidation of trisubstituted olefins.

substrate	yield (%)	*ee* (%), configuration
40	69	93, (–)-(*S*,*S*)
41	87	88, (–)-(*S*,*S*)
42	91	95, (–)-(*S*)
43	97	92, (+)-(*S*)

reaction conditions: solvent – dichloromethane; oxidant – buffered bleach (pH = 11.3); additive – 4-PPNO

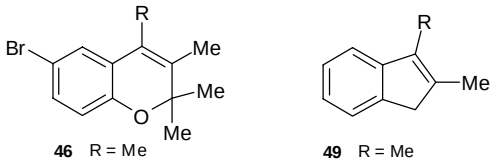
Though conjugated trisubstituted alkenes contain high synthetic utility, unconjugated trisubstituted alkenes are still very poor substrates for this process and other asymmetric epoxidations, respectively.



44 **45** **41**

4.4. Epoxidation of Tetrasubstituted Olefins

Further extension of the scope of asymmetric epoxidation was described in 1995 by the use of certain tetrasubstituted olefins as substrates [31]. Especially chromene and indene derivatives **46**–**50** were shown to undergo epoxidation with good to excellent enantioselectivities dependent on the catalyst used. In Table 5 some examples with Jacobsen catalyst **2** are listed. Enantiomeric excesses up to 97% could be obtained using different Mn(III)-salen catalysts with other steric and electronic properties. As can be seen from Table 5 the *ee's* vary from very low to excellent, although the variable substituent is the only site that has been changed. But the switch from simple alkyl-substitution to phenyl-substitution obviously causes a dramatic effect, that can not be explained only by steric or electronic interactions in the course of a side-on approach. In this context Jacobsen and Brandes postulate that the side-on approach at least in the case of tetrasubstituted olefins is unlikely. There is a need for further investigations and experiments on the mechanism of the oxygen atom transfer, which underlines the controversial discussion mentioned above.



46 R = Me
47 R = Et
48 R = Ph

49 R = Me
50 R = Ph

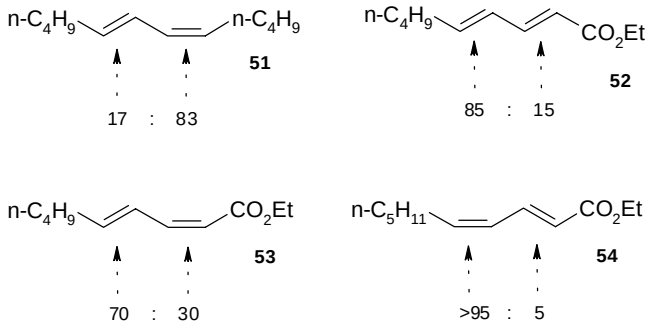
Table 5 Epoxidation of tetrasubstituted olefins.

substrate	**46**	**47**	**48**	**49**	**50**
ee (%)	85	87	4	15	86

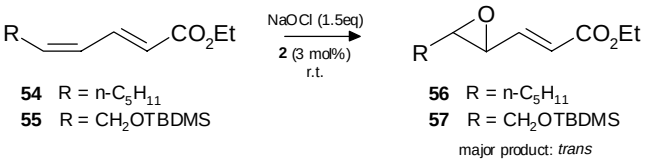
reaction conditions: **2** (3-5 mol%), 4-PPNO, dichloromethane, 0 °C

4.5. Epoxidation of Conjugated Polyenes

A very interesting field is opened by the application of the selective epoxidation to conjugated olefins with varying double bond configuration [32]. On the one hand regioselective mono-epoxidation has to be achieved, on the other hand the *cis*/*trans*-ratio of the outcoming epoxides has to be controlled. High regioselectivity can usually be observed in the epoxidation of *cis*,*trans*-dienes due to the much higher reactivity of the *cis*-double bond towards the salen-complex. Only very small amounts (< 5%) of bis-epoxides have been detected in addition to the desired vinyl epoxides even upon extended exposure to excess of oxidant.



The observed *cis*/*trans*-ratio cannot be generally controlled. However, with $\alpha,\beta-\gamma,\delta$-unsaturated esters useful selectivities in favour of the *trans*-products are obtained (Scheme 10, Table 6).



54 R = n-C_5H_{11}
55 R = $CH_2OTBDMS$

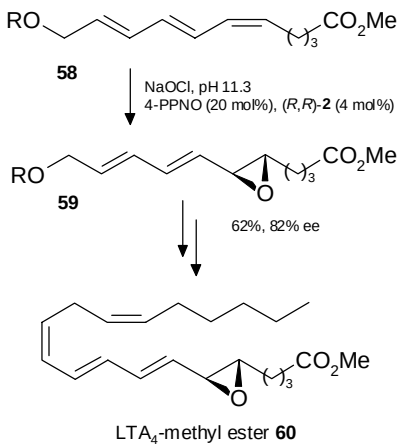
56 R = n-C_5H_{11}
57 R = $CH_2OTBDMS$
major product: *trans*

Scheme 10 Epoxidation of $\alpha,\beta-\gamma,\delta$-unsaturated esters.

Table 6 Epoxidation of $\alpha,\beta-\gamma,\delta$-unsaturated esters.

substrate	major product	isolated yield (%)	*ee* (%) of major product	*cis*/*trans*-ratio
54	**56**	81	87	1/9
55	**57**	58	83	1/7.3

This application has been used successfully in the formal total synthesis of the arachidonic acid metabolite *LTA*$_4$. The protected alcohol **58** underwent epoxidation dependent on the protecting group with moderately varying enantioselectivities (71–82%) and yields (62–74%). In Scheme 11 the example providing the highest *ee* (R = $COCH_2OPh$), and the subsequent pathway is presented.

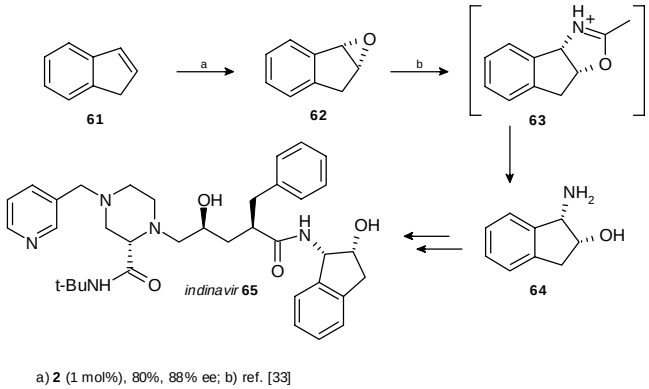


Scheme 11 Synthesis of the arachidonic acid metabolite *LTA*$_4$.

4.6. Miscellaneous Substrates for Epoxidation Reactions

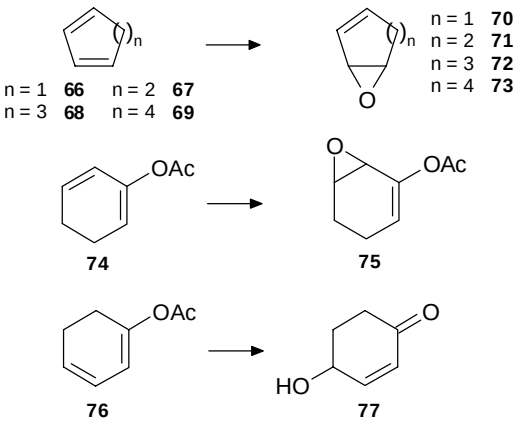
A very efficient pathway to the potent HIV protease inhibitor *indinavir* **65** has been developed based upon the enantioselective epoxidation of indene **61** [33]. With this substrate the dependence of the observed *ee*'s on the oxidant used was demonstrated impressively. Using bleach the maximum *ee* was 88% while a value of 96% was obtained with a combination of NMO and *meta*-chlorperbenzoic acid at low temperature. The *cis*-amino alcohol **64**, a key intermediate for the synthesis of indinavir **65** is prepared by an interesting modification of the known Ritter-reaction [34] (Scheme 12).

Cyclic dienes have also been studied concerning their application as substrates for asymmetric epoxidation [21]. Interesting experiments with both (*R*,*R*)-**2** and (*R*,*R*)-**12** have been conducted with various cyclic dienes **66**–**69**, **74** and **76** (Scheme 13). In all examples (*R*,*R*)-**12** was shown to give higher *ee*'s (up to 15% compared to (*R*,*R*)-**2**). The yields were reported to range mainly



Scheme 12 Synthesis of HIV protease inhibitor *indinavir* **65** based on the enantioselective epoxidation of indene **61**.

from 30% to 55% (Table 7). In the cases of cyclohexadiene derivatives up to equimolar amounts of products from aromatization could be observed.



Scheme 13 Epoxidation of cyclic dienes.

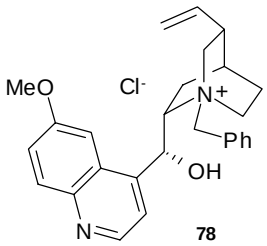
4.7. Epoxidations with Quaternary Ammonium Salts

Because of low enantioselectivities in the epoxidation of *trans*-alkenes, Jacobsen *et al*. in 1994 reported a versatile method to produce the desired *trans*-epoxide di-

Table 7 Epoxidation of cyclic dienes.

substrate	catalyst	yield (%)	*ee* (%)
66	(*R*,*R*)-**2**	40	63
	(*R*,*R*)-**12**	45	64
67	(*R*,*R*)-**2**	33	61
	(*R*,*R*)-**12**	30	65
68	(*R*,*R*)-**2**	73	64
	(*R*,*R*)-**12**	49	70
69	(*R*,*R*)-**2**	58	52
	(*R*,*R*)-**12**	55	57
74	(*R*,*R*)-**2**	30	85
	(*R*,*R*)-**12**	32	90
76	(*R*,*R*)-**2**	30	63
	(*R*,*R*)-**12**	47	68

rectly from *cis*-alkenes using the proposed radical pathway depicted in Scheme 3 [35]. The consequent investigation of unexpected observations led to a useful process for the synthesis of *trans*-epoxides from *cis*-alkenes using quaternary ammonium salts as very efficient additives. In first experiments the quaternary ammonium salt **78** was shown to be the most effective.



78

In all examples reported thus far, *cis*/*trans*-ratios between >99/1 and 3/1 have been observed. Therefore, the ratio of 4/>96 in the epoxidation of *cis*-stilbene in the presence of 20–25 mol% of a cinchona alkaloid derivative must be regarded as a very useful progress. In all cases providing high excess of *trans*-epoxide the TIPS-ether **12** was used as catalyst instead of **2** which was shown to be less effective in this special reaction.

5. Conclusion

Various salen-Mn(III)complexes were shown to be effective catalysts in the asymmetric epoxidation of a variety of olefins. Among them the commercially available Jacobsen catalyst **2** has found the widest application.

Conjugated *cis*-alkenes are very good substrates for epoxidation reactions giving high enantiomeric excess. Excellent results are also obtained with dimethylchromenes and special tri- and tetrasubstituted olefins. The regio- and diastereoselective epoxidation of conjugated polyenes is still limited to some $\alpha,\beta-\gamma,\delta$-unsaturated esters. Synthetically useful results have been detected in reactions employing *cis*,*trans*-diene esters like **54** in which the γ,δ-*cis*-double bond is far more reactive than the α,β-*trans*-double bond.

The asymmetric epoxidation of *trans*-alkenes in general remains an unsolved problem. Only special substrates may find useful applications. However, the epoxidation process in the presence of a quaternary ammonium salt seems to be an alternative procedure for the preparation of *trans*-epoxides exclusively. Differing amounts of *trans*-epoxides are also obtained in the epoxidation of dienes and enynes in many cases [36].

References

[1] Methods of Organic Chemistry, Houben-Weyl, Bd. E21e, Georg Thieme Verlag, Stuttgart **1995**, 4th Ed., 4599
[2] a) T. Katsuki, K. B. Sharpless, J. Am. Chem. Soc. **1980**, *102*, 5974; b) R. A. Johnson, K. B. Sharpless, Catalytic Asymmetric Synthesis (Ed. I. Ojima), VCH, Weinheim **1993**, 103
[3] a) J. T. Groves, R. S. Myers, J. Am. Chem. Soc. **1983**, *105*, 5791; b) J. T. Groves, P. J. Viski, J. Org. Chem. **1990**, *55*, 3628; c) R. L. Halterman, S.-T. Jan, J. Org. Chem. **1991**, *56*, 5253
[4] a) B.-H. Chang, R. H. Grubbs, C. H. Brubaker, Jr., J. Organomet. Chem. **1985**, *280*, 365; b) S. L. Coletti, R. L. Halterman, Tetrahedron Lett. **1992**, *33*, 1005
[5] a) R. C. Ewins, H. B. Henbest, M. A. McKervey, J. Chem. Soc., Chem. Commun. **1967**, 1085; b) F. Montanari, I. Moretti, G. Torre, J. Chem. Soc., Chem. Commun. **1969**, 135; c) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg, Tetrahedron Lett. **1976**, 1831; d) S. Yamada, T. Mashiko, S. Terashima, J. Am. Chem. Soc. **1977**, *99*, 1988; e) R. C. Michaelson, R. E. Palermo, K. B. Sharpless, J. Am. Chem. Soc. **1977**, *99*, 1990; f) H. B. Kagan, H. Mimoun, C. Mark, V. Schurig, Angew. Chem., Int Ed. Engl. **1979**, *18*, 485
[6] a)W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, J. Am. Chem. Soc. **1990**, *112*, 2801; b) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, J. Am. Chem. Soc. **1991**, *113*, 7063; c) W. Zhang, E. N. Jacobsen, J. Org. Chem. **1991**, *56*, 2296
[7] R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, Tetrahedron Lett. **1990**, *31*, 7345
[8] a) K. Srinivasan, P. Michaud, J. K. Kochi, J. Am. Chem. Soc. **1986**, *108*, 2309; b) K. Srinivasan, S. Perrier, J. K. Kochi, J. Mol. Cat. **1986**, *36*, 297
[9] E. N. Jacobsen, Catalytic Asymmetric Synthesis (Ed. I. Ojima), VCH, Weinheim 1993, 159
[10] Encyclopedia of Reagents for Organic Synthesis (Ed. L. A. Paquette), J. Wiley & sons **1995**, 4585
[11] D. Feichtinger, D. A. Plattner, Angew. Chem., Int. Ed. Engl. **1997**, *36*, 1718
[12] a) J. F. Larrow, E. N. Jacobsen, J. Org. Chem. **1994**, *59*, 1939; b) J. F. Larrow, E. N. Jacobsen, Organic Synthesis (Ed. A. B. Smith, III), **1997**, *74*, 1
[13] T. Linker, Angew. Chem., Int. Ed. Engl. **1997**, *36*, 2060
[14] P. J. Pospisil, D. H. Carsten, E. N. Jacobsen, Chem. Eur. J. **1996**, *2*, 974
[15] a) N. Hosoya, A. Hatayama, K. Yanai, H. Fujii, R. Irie, T. Katsuki, Synlett **1993**, 641; b) T. Hamada, R. Irie, T. Katsuki, Synlett **1994**, 479; c) T. Fukuda, R. Irie, T. Katsuki, Synlett **1995**, 197; d) T. Katsuki, J. Mol. Cat. **1996**, 87
[16] a) W. Zhang, N. H. Lee, E. N. Jacobsen, J. Am. Chem. Soc. **1994**, *116*, 425; b) N. S. Finney, P. J. Pospisil, S. Chang, M. Palucki, R. G. Konsler, K. B. Hansen, E. N. Jacobsen, Angew. Chem., Int. Ed. Engl. **1997**, *36*, 1720
[17] T. Hamada, T. Fukuda, H. Imanishi, T. Katsuki, Tetrahedron **1996**, *52*, 515
[18] a) P.-O. Norrby, C. Linde, B. Åkermark, J. Am. Chem. Soc. **1995**, *117*, 11035; b) C. Linde, M. Arnold, P.-O. Norrby, B. Åkermark, Angew. Chem., Int. Ed. Engl. **1997**, *36*, 1723
[19] H. Fu, G. C. Look, W. Zhang, E. N. Jacobsen, C.-H. Wong, J. Org. Chem. **1991**, *56*, 6497
[20] E. N. Jacobsen, W. Zhang, M. L. Güler, J. Am. Chem. Soc. **1991**, *113*, 6703
[21] S. Chang, R. M. Heid, E. N. Jacobsen, Tetrahedron. Lett **1994**, *35*, 669
[22] a) S. L. Vander Velde, E. N. Jacobsen, J. Org. Chem. **1995**, *60*, 5380; b) T. Linker, F. Rebien, G. Tóth, A. Simon, J. Kraus, G. Bringmann, Chem. Eur. J. **1998**, *4*, 1944

[23] E. N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martínez, Tetrahedron **1994**, *50*, 4323
[24] a) M. Palucki, P. J. Pospisil, W. Zhang, E. N. Jacobsen, J. Am. Chem. Soc. **1994**, *116*, 9333; b) M. Palucki, G. J. McCormick, E. N. Jacobsen, Tetrahedron Lett. **1995**, *36*, 5457
[25] S. Banfi, F. Montanari, S. Quici, J. Org. Chem. **1989**, *54*, 1850
[26] L. Deng, E. N. Jacobsen, J. Org. Chem. **1992**, *57*, 4320
[27] Chromenes, Chromanones, and Chromones, The Chemistry of Heterocyclic Compounds (Ed. G. P. Ellis), Wiley, New York 1977
[28] N. H. Lee, A. R. Muci, E. N. Jacobsen, Tetrahedron Lett. **1991**, *32*, 5055
[29] $k_{rel} = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$; c = concentration of remaining starting material
[30] B. D. Brandes, E. N. Jacobsen, J. Org. Chem. **1994**, *59*, 4378
[31] B. D. Brandes, E. N. Jacobsen, Tetrahedron Lett. **1995**, *36*, 5123
[32] S. Chang, N. H. Lee, E. N. Jacobsen, J. Org. Chem. **1993**, *58*, 6939
[33] C. H. Senanayake, F. E. Roberts, L. M. DiMichele, K. M. Ryan, J. Liu, L. E. Fredenburgh, B. S. Foster, A. W. Douglas, R. D. Larsen, T. R. Verhoeven, P. J. Reider, Tetrahedron Lett. **1995**, *36*, 3993
[34] J. J. Ritter, P. P. Minieri, J. Am. Chem. Soc. **1948**, *70*, 4045
[35] S. Chang, J. M. Galvin, E. N. Jacobsen, J. Am. Chem. Soc. **1994**, *116*, 6937
[36] N. H. Lee, E. N. Jacobsen, Tetrahedron Lett. **1991**, *32*, 6533

Address for correspondence:
Dr. Sven Doye
Institut für Organische Chemie
Universität Hannover
Schneiderberg 1B
D-30167 Hannover
Fax: Internat. code (0)511 762 30 11
E-mail: sven.doye@oci.uni-hannover.de